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Oral liquid antibiotic formulations with the focus on organoleptic properties that impact paediatric acceptability

Thesis presented by

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for the degree of

Doctor of Philosophy

University College Cork

School of Pharmacy

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Declaration

This is to certify that the work I am submitting is my own and has not been submitted for another degree, either at University College Cork or elsewhere. All external references and sources are clearly acknowledged and identified within the contents. I have read and understood the regulations of University College Cork concerning plagiarism and intellectual property.

The survey study in chapter 2 and the interview study in chapter 3 were conducted in collaboration with Dr. Joseph Ryan, and Prof. Colin Bradley, Department of General Practice, School of Medicine, University College Cork, Cork, Ireland. The human sensory study in chapter 4 was conducted in collaboration with Dr. Liz Sheehan, Ms. Margaret Shine, SRL Pharma, Cork, Ireland, Ms. Rehab El Hiny, Pharmaceutical Care Research Group, School of Pharmacy, University College Cork, Cork, Ireland, and Dr. Reda Mohamed, Cork University Hospital, Cork, Ireland. The GC-MS experimental work in Chapters 5 was designed and completed in collaboration with Dr. Anna Maria Hogan at the School of Chemistry, University College Cork, Ireland and with Ms. Iwona Skibinska and Prof. Kieran Kilcawley at the Food Quality and Sensory Science, Teagasc Food Research Centre, Fermoy, Ireland.

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Signed: _____Ayat Elgammal_____

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Publications and Presentations

Publications

Ayat Elgammal, Joseph Ryan, Colin Bradley, Abina Crean, Margaret Bermingham

The impact of drug palatability on prescribing and dispensing of antibiotic formulations for paediatric patients: a cross-sectional survey of general practitioners and pharmacists

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Challenges prescribing and dispensing oral antibiotics with poor palatability for paediatric patients: A qualitative interview study with GPs and pharmacists

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Ayat Elgammal, Liz Sheehan, Margaret Shine, Reda Mohamed, Kieran Kilcawley, Iwona Skibinska, Margaret Bermingham, Abina Crean

Flucloxacillin formulation odour acceptability: a human sensory assessment

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Oral Presentations

Ayat Elgammal, Joseph Ryan, Colin Bradley, Kieran Kilcawley, Iwona Skibinska, Margaret Bermingham, Abina Crean. *Role of odour in oral liquid antibiotic palatability*. Maynooth University World Antimicrobial Awareness Week Conference, Maynooth, Ireland, 2023

Ayat Elgammal, Liz Sheehan, Margaret Shine, Reda Mohamed, Margaret Bermingham, Abina Crean. *Odour assessment of flucloxacillin formulations using a human panel.* SSPC Symposium, University of Limerick, Ireland, 2024

Poster presentations

Ayat Elgammal, Liz Sheehan, Margaret Shine, Reda Mohamed, Margaret Bermingham, Abina Crean. *The odour acceptability of oral flucloxacillin formulations assessed using a human sensory panel*. 16th Annual Conference of the European Paediatric Formulation Initiative (EuPFI), Rotterdam, Netherlands, 2024.

Ayat Elgammal, Joseph Ryan, Colin Bradley, Abina Crean, Margaret Bermingham. *Attitudes and experiences of healthcare providers to prescribing and dispensing of oral liquid antibiotics for paediatric patients with a focus on palatability*. Prescribing Research in Medicines Management (PRIMM) 34th Annual Scientific Meeting, Manchester, UK, 2024

Ayat Elgammal, Joseph Ryan, Colin Bradley, Abina Crean, Margaret Bermingham. *Challenges Prescribing and Dispensing Oral Antibiotics with Poor Palatability for Paediatric Patients: A Qualitative Interview Study with GPs and Pharmacists*. Cork University Hospital - Child & Family Nursing Conference, Cork, Ireland, 2024

Ayat Elgammal, Joseph Ryan, Colin Bradley, Kieran Kilcawley, Iwona Skibinska, Margaret Bermingham, Abina Crean. *Role of Odour in Oral Liquid Antibiotic Palatability*. 15th Annual Conference of the European Paediatric Formulation Initiative (EuPFI), Glasgow, UK, 2023

Ayat Elgammal, Joseph Ryan, Colin Bradley, Kieran Kilcawley, Iwona Skibinska, Margaret Bermingham, Abina Crean. *Antibiotic palatability, A focus on the neglected role of drug odour*. 6th APV Winter Conference, Patient-centric drug product development acceptability across patient populations − science and evidence, Salzburg, Austria, 2023

Ayat Elgammal, Joseph Ryan, Colin Bradley, Abina Crean, Margaret Bermingham. *How patient acceptability influences prescribing and dispensing of oral liquid antibiotics to children: A survey of community pharmacists*. Prescribing Research in Medicines Management (PRIMM) 33rd Annual Scientific Meeting, Manchester, UK, Personomics: Putting the Patient at the Centre of Prescribing and Medicines Use, 2022

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Abbreviations

AED	Atomic Emission Detector
API	Active Pharmaceutical Ingredient
BNFC	British National Formulary for Children
CREC	Clinical Research Ethics Committee of the Cork Teaching Hospitals
DE	Dynamic Headspace Extraction
DVB/CAR/PDMS	Divinylbenzene/ Carboxen/Polydimethylsiloxane
EMA	European Medicine Agency
FPD	Flame Photometric Detector
GC–FID	Gas Chromatography with a Flame Ionization Detector
GC–MS	Gas Chromatography - Mass Spectrometry
GC-O	Gas Chromatography Olfactometry
GPs	General Practitioners
HS	Head Space
ID	Isotopic Dilution
ISO	International Organization for Standardization
MSD	Mass Spectrometry Mass Selective Detector
NHANES	National Health and Nutrition Examination Survey
PCA	Principal Component Analysis
PFPD	Pulsed Flame Photometric Detector
Ph	Pharmacist
SAFE	Solvent-Assisted Flavour Evaporation
SBSE	Stir Bar Sorptive Extraction

SCD	Sulfur Chemoluminescence Detector
SDE	Simultaneous Distillation Extraction
SmPC	Summary of Product Characteristics
SPME	Solid Phase Microextraction
SPSS	Statistical Package for the Social Sciences
SREC	Social Research Ethics Committee of University College Cork
TD	Thermal Desorption
UV	Ultraviolet
VAS	Visual Analog Scales
VOCs	Volatile Organic Compounds
VSCs	Volatile Sulfur Compounds
WHO	World Health Organization

Abstract

Palatability, 'the overall appreciation of a drug in relation to its smell, taste, aftertaste, texture and appearance', is a key element influencing paediatric medicine acceptability. Nonadherence to antibiotic treatment because of poor palatability can cause disease recurrence and may contribute to increasing rates of antimicrobial resistance. While the relationship between a medicine's acceptability and taste has been widely explored, the relationship between a medicine's odour and its acceptability has received less investigation.

Initially, a questionnaire study was conducted to explore General Practitioners' (GPs') and pharmacists' experiences of prescribing and dispensing oral liquid antibiotics for children respectively in Ireland. Study findings highlight that palatability issues caused GPs and pharmacists to switch oral liquid antibiotics to ensure treatment adherence despite their preference to follow the guidelines and select a first-choice antibiotic. Flucloxacillin was highlighted as the least palatable oral liquid antibiotic for children with a malodour.

Subsequently, an interview study was conducted to obtain a deeper and richer understanding of the experience, attitudes, and challenges faced by GPs and pharmacists. Both professions reported that in some circumstances such as the type of infection, lack of alternatives, and allergies they had to select an unpalatable antibiotic despite knowing that it has poor palatability. Both professions reported that they had never started the palatability discussion with parents to avoid negotiation because of the lack of alternatives. The study findings highlighted the importance of proactive dialogue discussing antibiotic palatability with parents and carers during prescribing and prior to dispensing.

A human sensory study was conducted to assess the odour acceptability of a range of oral flucloxacillin formulations by healthy adult volunteers. The odour of the commercial flucloxacillin solution and capsule formulations were rated acceptable. The commercial solution odour was described as fruity, and aromatic, while the commercial capsule was described as odourless. An unformulated flucloxacillin aqueous solution, and flucloxacillin formulated as minitablets, were deemed to have an unacceptable odour. Their odour was described as pungent, musty, plastic, and rotten. However, the odour of the flucloxacillin minitablet formulation, with silica incorporated as an odour suppressant, was described as odourless and deemed to be acceptable.

Finally, Gas chromatography - mass spectrometry (GC-MS) was used to identify the Volatile Organic Compounds (VOCs) associated with flucloxacillin's malodour. Two sampling techniques, Head Space (HS) and Solid Phase Microextraction (SPME), were investigated to detect VOCs in the headspace above flucloxacillin samples. The direct HS sampling detected two volatile compounds in flucloxacillin powder of which decane has a particular malodour that could contribute to the overall malodour of flucloxacillin. SPME analysis detected a greater number of VOCs of which octane, decane, undecane, toluene, and styrene are associated with a malodour that can contribute to the overall malodour of flucloxacillin. Interestingly, while the malodour of flucloxacillin was initially thought to be related to its sulfur content, dimethyl disulfide was the only volatile sulfur compound detected and only detected in the aqueous flucloxacillin solution headspace. Dimethyl disulfide can result from degradation of ethynthiol which is one of the flucloxacillin degradation-related VOC impurities.

In conclusion, poor palatability caused GPs and pharmacists to switch oral liquid antibiotics to ensure treatment adherence. Flucloxacillin was identified as a poorly palatable antibiotic with a malodour. Human volunteers associated the odour of unformulated aqueous flucloxacillin solution and minitablets with the descriptors musty, pungent, plastic, and rotten and unacceptable. The odour of a commercial solution was described as acceptable, fruity and aromatic whereas, commercial capsules and minitablets with silica were deemed acceptable and odourless. GC-MS using SPME analysis was used to identify the chemical origin of the malodour described in the human sensory study. A number of volatile compounds which could contribute to the overall flucloxacillin malodour were detected. However, future work is needed to quantify the volatile sulfur compounds (VSCs) associated with flucloxacillin's overall odour and inform an odour suppression formulation strategy based on component chemistry.

Chapter 1

General Introduction

1 Chapter 1

1.1 Introduction

Antibiotics are widely used in the treatment of bacterial infections. Children are prescribed antibiotic products more frequently than other patient groups (Bielicki et al., 2015; Versporten et al., 2013). The majority of preschool children are prescribed one or more medications each year, with antibiotics most frequently prescribed (Chai et al., 2012; Zhang et al., 2016). Antibiotics are often used to treat common childhood infectious diseases in the community, as well as life threating infections in hospitals (Hsia et al., 2019). However, inappropriate use of antibiotics can lead to the development of antimicrobial resistance a key threat to global health (WHO, 2015).

The commercially available oral antibiotic formulations for children are capsules and oral liquid formulations. The oral route is considered the most common route of medicine administration for children (Ali et al., 2014; Khan et al., 2022). Oral liquid formulations are reported as the preferred dosage form among children because of their ease in swallowing and dose adjustment (Ali et al., 2014; Nunn & Williams, 2005; Trofimiuk et al., 2019). Dose accuracy may be compromised when using very small volumes of oral liquid formulations. The ideal volume of liquid formulations should be swallowable in one unit. Therefore, the maximum volume should be adjusted to the swallow volume. However, use of liquid formulations is a challenge in the paediatric population because of concerns related to palatability, dose volume, and accurate dose measurement (Batchelor & Marriott, 2015a; Pawar & Kumar, 2002). Solid dosage forms have the advantage of better palatability and dose accuracy. However, fixed dose content and swallowing difficulties, due to tablet and capsule size, are challenging for paediatric patients (Khan et al., 2022). A study which assessed the available sizes of common paediatric antibiotics capsules (Jacobsen et al., 2016) revealed that

their sizes ranged from 8 to 25 mm in length with median 17 mm. The upper size limit of 25 mm would cause a challenge for children. Additionally, the shape (round, oval, or oblong) may influence a child's ability of swallowing a medication. The size and shape of a tablet were reported as fundamental to the ability of a child to swallow it by the European Medicines Agency (EMA) guideline on pharmaceutical development of medicines for paediatric use (EMA, 2013).

The acceptability of antibiotic products is a key aspect that needs to be considered to ensure an appropriate use of antibiotics particularly in paediatric patients (Klingmann et al., 2023). Acceptability is described by the EMA as an overall ability of the patient and caregiver to use a medicinal product as intended (EMA, 2013). It is considered a key aspect for compliance, *'the extent to which the patient's behaviour matches the prescriber's recommendations'* (Sackett, 1992) and adherence to treatment, *'the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider.'* (WHO, 2003). Palatability defined as the overall appreciation of a drug in relation to its appearance, taste, aftertaste, smell, and texture (Kozarewicz, 2014), is highlighted by the EMA paediatric use guideline as one of the key elements influencing paediatric acceptability of oral medicinal products (EMA, 2013). Palatability is mainly affected by the characteristics of drug substances and excipients included in the medicinal product formulation, as well as the formulation format. Poor palatability of antibiotics can cause non-compliance to treatment (Patel et al., 2022). Palatability needs to be considered in order to optimise effective prescribing, maximise adherence and therapeutic effect, and thereby reduce wastage (Baguley et al., 2012). Age-appropriate medicines are required to provide suitable dosage forms with an acceptable palatability for children (EMA, 2013).

1.2 Palatability issues of antibiotics

Antibiotics prescribed for the treatment of common paediatric illnesses, are noted for their poor palatability. In April 2025, a representative review of literature relating to the palatability of oral antibiotics was conducted using the PubMed database in order to inform this introduction. The search terms for PubMed were “antibiotics OR antimicrobials” AND “palatability OR acceptability” and “paediatrics OR children”. A specific antibiotic that is known to have palatability issues was also investigated, namely flucloxacillin. The titles and abstracts of the articles were screened to identify studies for full text review. A total of 14 studies were identified and discussed in this review. The characteristics of each study and the assessed antibiotics are outlined in **Table. 1**.

Table 1. Summary of key studies investigating the poor palatability of paediatric oral antibiotic formulations (n=14)

Author & Country	Participants	Aims	Methods	Dosage forms	Main findings
(Angelilli et al., 2000) United States	30 healthy children (aged 5-8 years)	Evaluating the palatability of 4 oral liquid formulations	The child was asked to rate the taste on a 10-cm visual analog scale incorporating a facial hedonic scale	Azithromycin, Cefprozil, Cefixime, Amoxicillin–clavulanic acid	Cefixime was selected as the best-tasting formulation. No differences between the other 3 preparations as either the best or worst tasting.
(Bergene et al. 2019) Norway	14 GPs, 1 intern, and 15 pharmacists from different chains	Investigating considerations of formulation characteristics by GPs and pharmacists when prescribing and dispensing medicines for children 0-6 years	Semi-structured focus groups interview, three focus groups were conducted with GPs and 3 focus groups with pharmacists	Oral prescription formulations of antibiotics (Range of antibiotics discussed identified in an open question)	Penicillin V described as challenging to administer because 'it tastes like mold' and requires frequent administration
(Bradshaw et al., 2016) United States	101 physicians (emergency, family medicine, and paediatric physicians)	Evaluating the palatability of commonly prescribed paediatric oral liquid antibiotics to determine if physicians would alter prescribing decisions after testing	Interventional study through conducting a taste testing, physicians completed a survey regarding their choice of paediatric oral liquid medication before and after the taste test	Amoxicillin, Cefdinir, Sulfamethoxazole-trimethoprim, Clindamycin, Metronidazole, Vancomycin, Azithromycin	Amoxicillin considered the most palatable. Vancomycin was considered the least palatable. Participants altered their prescribing preferences significantly from amoxicillin to cefdinir for otitis media and changed from azithromycin to amoxicillin for pneumonia
(Cohen et al., 2009) France	The parents of 953 children (aged 0.5 months to 14 years)	Evaluating the taste of oral liquid formulations (including generics)	Parents completed a questionnaire at the end of their child's treatment using five facial expressions tool	Amoxicillin–clavulanic acid reference products and generics, Amoxicillin reference product and generics	Amoxicillin–clavulanic acid princeps was more acceptable than its different generics. No significant differences between the amoxicillin reference product and the various generics

(Gee & Hagemann, 2007) United States	86 health-care professionals, pharmacy students (45%), physicians (30%), medical students (22%), pharmacists (2%)	Evaluating the palatability of 21 anti-infectives (including to inform paediatric healthcare practitioners about the issues associated with taste and compliance in paediatric patients.	Taste test evaluating the taste, texture, smell, and aftertaste using visual analog scale.	Amoxicillin (Amoxil®), Amoxicillin (Trimox®), Ampicillin (principen®), Amoxicillin/clavulanic acid (Augmentin®) Azithromycin (Zithromax®) Cefixime (Suprax®), Cefpodoxime (Vantin®), Cefuroxime axetil (Ceftin®), Cephalexin (generic), Clarithromycin (Biaxin®), Clindamycin (Cleocin Paediatric®), Dicloxacillin (Geneva®), Doxycycline (Vibramycin®), Erythromycin ethyl succinate (EES400®), Erythromycin sulfisoxazole (Pediazole®), Furandantin (generic), Loracarbef (Lorabid®), Metronidazole (Flagyl®), Penicillin VK (generic) Oxacillin (generic), Trimethoprim-sulfamethoxazole (generic)	Five highest ranked products included loracarbef (Lorabid), amoxicillin (Trimox), cefixime (Suprax), amoxicillin (Amoxil) and doxycycline (Vibramycin). The five lowest ranked products included clarithromycin (Biaxin), dicloxacillin (Geneva), oxacillin (Oxacillin generic), clindamycin (Cleocin paediatric) and metronidazole (Flagyl). Comments about the lowest ranked products included lingering aftertaste, bitter initial taste, gritty texture and unpleasant smell.
(Matsui et al., 1996) Canada	20 healthy volunteer children with a mean age of 9.2 +/- 2.0 SD years	Evaluating the palatability of four anti-staphylococcal oral liquid antibiotic formulations	A single-blind taste test using a 10-cm visual analog scale incorporating a facial hedonic scale	Cloxacillin, Cephalexin, Erythromycin, Fusidic acid,	Cloxacillin was selected as having the worst taste by most children. None of the antibiotics were clearly best tasting.
(Matsui et al., 1997) Canada	50 healthy children with a mean age 6.3 +/- 1.3 years and 20 adults.	Evaluating the palatability of 4 oral antibiotic suspensions effective against beta-	Taste test using a 10-cm visual analog scale incorporating a facial hedonic scale by both children and adults	Amoxicillin and clavulanic acid (banana flavour). Azithromycin (cherry flavour), Clarithromycin (wild fruit flavour),	Azithromycin was selected as best tasting by both children and adults.

		lactamase-producing bacteria		Erythromycin and sulfisoxazole (strawberry -banana flavour)	There was a significant difference between children and adults selecting the worst tasting antibiotics, with the children selecting clarithromycin and the adults selecting erythromycin-sulfisoxazole
(Powers et al., 2000) United States	715 children aged 4 to 8 years	Comparing palatability of oral liquid suspensions	A series of six randomized, single blind, crossover trials using a visual "smile-face" scale	Cefdinir, Amoxicillin/clavulanate potassium, Cefprozil, Azithromycin	Children preferred the taste and smell of cefdinir oral suspension compared to the other three antibiotics
(Rouse et al., 2017) United Kingdom	255 parent/ carers of children with cystic fibrosis	Obtaining parent/carer views on the administration of flucloxacillin oral liquid formulations	A mixed methods study which included a structured review of online forums and a survey of parent/carers of children with cystic fibrosis	Flucloxacillin (Medreich, Crescent, Actavis, Milpharm)	All flucloxacillin products in the study were reported to be poorly palatable with some brands more unpalatable than others.
(Soares et al., 2022) United States	43 paediatric prescribers	Evaluating the influence of taste on prescribing patterns of oral liquid antibiotic suspensions	Taste preferences were ranked on a 9-point scale. Then, an analysis of a 12-month retrospective and prospective of outpatient prescribing practices of the participants	Amoxicillin, Amoxicillin-clavulanate, Cefdinir, Azithromycin, Sulfamethoxazole + trimethoprim Cephalexin	Amoxicillin was the most preferable and amoxicillin-clavulanate was the least. There was a higher prescribing rate of cefdinir among the participants who had tasted it
(Steele et al., 1997) United States	26 health-care professionals adult volunteers	Evaluating the palatability of 22 oral liquid antibiotic suspensions	Each antibiotic was evaluated in appearance, smell, texture, taste, and aftertaste using scoring system on a scale of 1-10 with 1 indicating	Amoxicillin (Amoxil®) Amoxicillin/ clavulanate (Augmentin®), Ampicillin (Omnipon®, Principon®) Dicloxacillin (Dynapen®) Oxacillin (Prostaphlin®)	Reported unpalatable antibiotics were dicloxacillin (taste, aftertaste) oxacillin (smell, taste, aftertaste), erythromycin/ sulfisoxazole (taste, aftertaste), and cefpodoxime (taste, aftertaste).

			the lowest score and 10 the highest	Penicillin VK (Vveetids®) Cefaclor (Ceclor®) Cefadroxil (Duracef®) Cefixime (Suprax®) Cefpodoxime (Vantin®) Cefprozil (Cefzil®) Ceftibuten (Cedax®) Loracabef (Lorabid®) Azithromycin (Zithromax®) Clarithromycin (Biaxin®) Erythromycin (EES400®) Erythromycin and Sulfisoxazole (Pediazole®) Sulfisoxazole (Gantrisin®) Sulfamethoxazole and trimethoprim (Bactrim®)	The four highest ranked antibiotics were loracabef (Lorabid®), cefadroxil (Duracef®), cefprozil (Cefzil®), and cefixime (Suprax®).
(Steele et al., 2001) United States	86 physicians and health care personnel	Evaluating the palatability of 11 antimicrobial suspensions by using amoxicillin as a standard for comparison	Each antibiotic was evaluated in appearance, smell, texture, taste, and aftertaste	Amoxicillin, Amoxicillin/clavulanate, Clarithromycin, Azithromycin, Loracarbef, Cefpodoxime, Cefuroxime, Cefdinir, Cefixime, Ciprofloxacin, Trimethoprim, Trimethoprim-sulfamethoxazole	Antibiotics' overall palatability ranked from highest to lowest as follows: loracarbef, cefdinir, cefixime, azithromycin, ciprofloxacin, trimethoprim-sulfamethoxazole, clarithromycin, trimethoprim, amoxicillin/clavulanate, cefpodoxime and cefuroxime.
(Steele et al., 2006) United States	31 physicians and health care personnel	Evaluating the palatability of 7 oral liquid antibiotic suspensions that treat staphylococcal infections	Each antibiotic was evaluated in appearance, smell, texture, taste, and aftertaste on a scale of 0 to 5 with 1 indicating	Erythromycin ethyl succinate (EES®), Trimethoprim/sulfamethoxazole (Generic), Cephalexin (Generic), Rifampin (Generic),	Antibiotics were ranked highest to lowest as follows: rifampin, cephalexin, erythromycin (poor gelatinously thick texture), trimethoprim/sulfamethoxazol, clindamycin with flavorx(poor taste and aftertaste, unpleasant

			the lowest score and 5 the highest	Clindamycin with flavorx® as a flavouring agent (Cleocin®), Clindamycin without flavorx® (Cleocin®), Linezolid (Zyvox®)	odour), linezolid (poor taste and aftertaste), and clindamycin without flavorx (poor taste and aftertaste, unpleasant odour).
(Venables, Stirling, et al., 2015) United Kingdom	7 nurses, 8 medical practitioners and 6 pharmacists	Investigating the problems associated with prescribing, dispensing and administering oral medicines to children from the perspectives of medical practitioners, pharmacists and nurses.	Focus group qualitative study	Oral medicines prescribed to children (Range of antibiotics discussed identified in an open question)	Flucloxacillin solution was highlighted by all healthcare professional groups to be unpalatable for children due to its taste.

The identified studies reported the palatability issues of paediatric antibiotic formulations based on taste, aftertaste, smell, texture, and appearance **Table 1**. Taste was reported as the main category that differentiated between samples. Taste issues were reported for dicloxacillin and oxacillin (Steele et al., 1997), clindamycin and linezolid (Steele et al., 2006). Additionally, the taste assessment of four anti-staphylococcal antibiotic suspensions including cloxacillin, cephalexin, erythromycin, and fusidic acid, revealed that none of the assessed antibiotics were clearly identified as having a better taste compared to others investigated, with cloxacillin selected as having the worst taste by most children (Matsui et al., 1996). Penicillin V was identified as a poorly palatable antibiotic because it was described to taste like mold in a semi-structured focus groups interview conducted in Norway with GPs and pharmacists (Bergene et al., 2019). Similarly, all healthcare professional groups participating in a focus group study reported that flucloxacillin solution was poorly palatable to children due to its taste (Venables, Stirling, et al., 2015). All flucloxacillin products were reported as problematic in a survey study conducted by 255 parents/carers of children with cystic fibrosis in United Kingdom (Rouse et al., 2017). Some brands in the study were associated with fewer administration issues, however formulation characteristics associated with administration difficulties were not identified.

The taste assessment of generic and reference formulations of amoxicillin and amoxicillin–clavulanic acid was compared in a study conducted by Cohen et al. Parents completed a questionnaire at the end of their child's treatment using a five facial expressions tool. The study reported that amoxicillin–clavulanic acid reference product had better taste than its different generics whereas, there were no differences between amoxicillin reference product and the various generics. Additionally, Matsui

et al highlighted that there was a significant difference between the taste ratings of children and adults, with the children selecting clarithromycin and the adults selecting erythromycin-sulfisoxazole as the worst tasting antibiotics. The study evaluated the taste of beta-lactamase-resistant paediatric antibiotics by both children and adult healthy volunteers (Matsui et al., 1997).

Three studies conducted taste tests with paediatric healthcare practitioners to familiarize them with the issues associated with antibiotic palatability in paediatric patients. Bradshaw et al explored physicians' prescribing choices before and after a taste test of antibiotics commonly used in paediatric patients (Bradshaw et al., 2016). Most of the physicians who participated in the study changed their prescribing preferences significantly after the taste test - switching from amoxicillin to cefdinir for otitis media and changing from azithromycin to amoxicillin for pneumonia. Similarly, there was a significantly greater prescribing rate of cefdinir among paediatric prescribers who tasted this antibiotic in a study on the influence of a taste test on prescribing pattern before commonly prescribed paediatric antibiotics (Soares et al., 2022). Besides influencing the prescribers' choice of antibiotics for paediatric patients, taste tests can alter medication counselling habits of prescribers as reported in the taste test conducted by Gee et al (Gee & Hagemann, 2007). A majority of the prescribers participating in the study indicated after taking part in the taste test, they were more aware and more comfortable discussing the prescribed antibiotics and how to enhance paediatric compliance with the antibiotics with the patients and caregivers.

Two studies assessed the aftertaste of antibiotics. In both studies, aftertaste rating associated very closely with taste rating. Poor aftertaste was reported for oxacillin and dicloxacillin (Steele et al., 1997), clindamycin and linezolid (Steele et al., 2006). However, texture issues of thickness and grittiness were reported, with cefuroxime and

clarithromycin achieving the lowest texture scores (Steele et al., 1997). Similarly, Erythromycin was rated the lowest texture score and was noted to be gelatinously thick (Steele et al., 2006). Smell issues were reported for oxacillin (Steele et al., 1997). Most volunteers reported that they were able to detect oxacillin odour after tasting and was hardly detected prior to tasting. Clindamycin was ranked the lowest smell score and was reported to have unpleasant smell (Steele et al., 2006).

Colour preference varied among individual participants with the mean score for all pink medications higher than the mean score for white and cream products (Steele et al., 1997). However, white or clear antibiotic products were scored slightly higher than brightly coloured products in later study conducted in Steele et al in 2006. Cephalexin, which was formulated as a white medication, received the highest colour rating score in that study (Steele et al., 2006).

Healthcare professionals are aware of the challenges of administering unpalatable oral medicines for children (Bergene et al., 2017; Rautamo et al., 2020). The administration challenges were classified as either dosage form-related or patient-related ones in a focus group study conducted with 19 participants included physicians, nurses and clinical pharmacists (Rautamo et al., 2020). Dosage form-related challenges included unsuitable dose, dose volume, taste, texture, unsuitable dosage form, excipients, and drug manipulation. Patient-related challenges included swallowing, spitting, vomiting, age, and taste preferences. Bergene et al. reported that the three main strategies to give unpalatable oral medicine to children are: (i) open administration by giving medicine to the child knowingly by changing the palatability, (ii) hidden administration by giving medicine to the child unknowingly by camouflaging it in food, while sleeping or distracted by another activity, and (iii) forced administration by forcing children to take medicine with the use of restraint (Bergene et al., 2017). However, studies

investigating the influence of palatability on prescribing and dispensing practice in primary care by GPs and pharmacists respectively are limited. This thesis aims to addresses this research gap through conducting a cross-sectional survey of GPs and pharmacists in chapter 2 and to explore challenges related to prescribing or dispensing poorly palatable oral liquid antibiotics, and the impact of these challenges on both patients and the health system by conducting a semi-structured interview study with GPs and pharmacists in chapter 3.

1.3 Children are not small adults

Children cannot be considered small adults due to physiological variations in paediatrics compared with adults that can affect the drug concentration in the plasma or tissue (Krekels et al., 2019). The drug concentration in the plasma can be influenced by absorption, distribution, metabolism and excretion processes that differ in paediatrics compared with adults and have an influence on the pharmacokinetic profile of a drug (Batchelor & Marriott, 2015b). Additionally, the safety of excipients used in the formulations may differ with the physiological differences in paediatric populations and may lead to accumulation that may cause excipient toxicity (Rouaz et al., 2021). Therefore, careful dose adjustments need to be considered within paediatric populations to limit the incidence of any adverse effects. From a formulation perspective, paediatric populations needs to have dosage forms that can safely provide the required dose to the child in an easy and reliable way (Khan et al., 2022). This can improve and retain adherence and acceptability of the medicine. A range of factors can influence paediatric acceptability of a medicine including patient-related factors and medicine-related factors (Kozarewicz, 2014). In contrast to adults, patient factors in paediatric populations depends mainly on individual child characteristics including the

age of child, competency, and the child's cognitive development (Khan et al., 2022; Liu et al., 2014).

In 2010 the EMA published a survey reporting that 45–60% of all medicines given to paediatric patients in the European Union were used off-label (EMA, 2010). Off-label medicine indicates using a medicine prescribed outside of its marketing authorisation of age group, dosage, or route of administration. The EMA regulatory guideline on pharmaceutical development of medicines for paediatric use outlined the requirements for age-appropriate dosage forms with an acceptable palatability for children (EMA, 2013). The Paediatric Regulation encourages pharmaceutical manufacturers to provide a Paediatric Investigation Plan (PIP) prior to marketing authorisation of new drugs to investigate medicine development for children. A Paediatric Investigation Plan (PIP) is a development plan that aims to ensure that sufficient data are obtained through studies in paediatrics to support the development of marketing authorisation of medicines for children. Paediatric dosage forms can include oral liquids, chewable tablets, orodispersible tablets, and mini tablets. Minitablets, are a novel oral solid dosage form that have been developed for children to overcome the swallowability difficulties and palatability challenges through using odour and taste masking excipients (O'Brien et al., 2019). A minitablet is a tablet with a diameter equal to or less than 4 mm (van Riet-Nales et al., 2016). The swallowability of minitablets with a diameter of 2 mm was reported to be acceptable among children aged 6 months and above (Mitsui et al., 2022; Münch et al., 2023). In chapter 4, this thesis investigates minitablets as novel formulation approach that could enhance the overall paediatric acceptability of oral antibiotic formulations.

1.4 Contribution of Odour to Drug Palatability

An unpleasant odour is a key barrier to drug acceptability. Odour has a critical effect on drug palatability as flavour is defined as the combined perception of mouth-feel, texture, taste and smell (Hollowood et al., 2002). Smell not only influences a patient's perception of a medicine's acceptability prior to ingestion, it is also the main sense contributing to the determination of a substance's flavour (Rozin, 1982; Shepherd, 2006; Wilson, 2021). It was confirmed in a review conducted by Spence that between 75 and 95 % of what we think of as taste (i.e., as transduced by the gustatory receptors on the tongue), is caused by smell (i.e., information transduced by the nose) (Spence, 2015). However, research into the role that a medicine's odour plays in its patient acceptability has been limited to date.

The overall smell can be affected by drug concentration in the formulation. The smell of commercial oral liquid corticosteroid formulations (prednisolone 1 mg/mL; prednisolone sodium phosphate 1 mg/mL and dexamethasone 0.5 mg/5 mL) were compared and the dexamethasone formulation reported to have a better smell due to the lower drug concentration in the formulation (Mitchell, 2003). A study conducted with healthcare professionals (medical practitioners, pharmacists, and nurses) revealed that Klean-prep oral powder dissolved in liquid smells horrible and Abidec multivitamin drops also had a bad smell (Venables, 2014). Some terms used to describe the smell of medicines by 252 children receiving 524 oral formulations included 'sickly smell', 'strong aniseed smell', 'smells bad', 'smells horrible' and 'smells of acid'. Smell has also been reported as the reason for non-adherence to some topical treatment (Devaux et al., 2012). However, there are limited studies relating medication odour to compliance and adherence to treatment.

1.4.1 Chemical origin of odour

The sense of smell can differentiate between numerous odourants through approximately a thousand different odourant receptors in the nose **Figure 1.1** (Breer H., 2008). Olfaction has two pathways, orthonasal and retronasal, for the smell to reach the main olfactory epithelium in the nose **Figure 1.2** (Wilson, 2021). During orthonasal olfaction odours pass through the nostrils from the external environment to reach the olfactory epithelium as a result of inhalation. Orthonasal olfaction characterizes what we think of as our sense of smell. In retronasal olfaction, smells stimulate the olfactory epithelium from inside the mouth during consumption through exhalation via the back of the throat. Having arisen from inside the mouth, the retronasal experience is usually conflated with taste (Rozin, 1982).

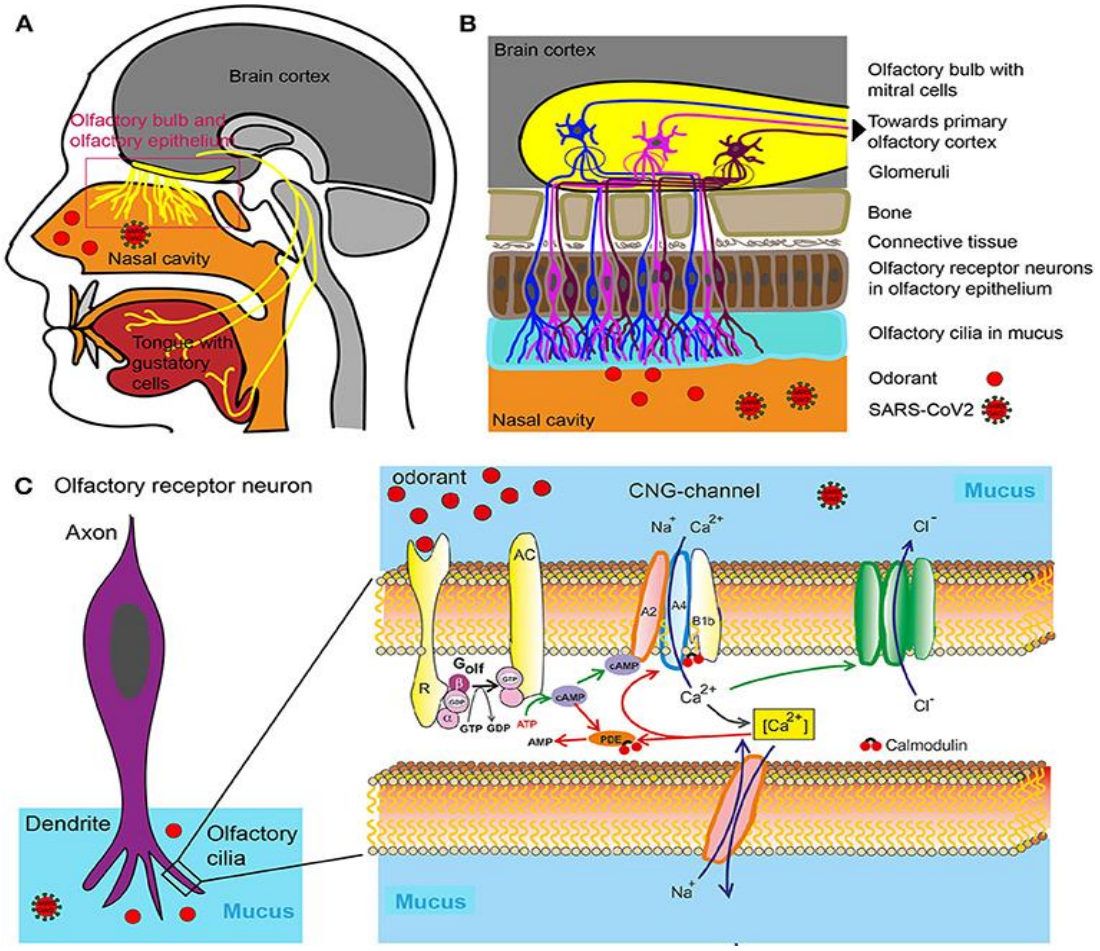

Figure 1.1. Olfactory system. (A) Head sagittal section showing the olfactory and gustatory systems. (B) Olfactory bulb, olfactory epithelium with olfactory receptor neurons. (C) Left: Olfactory receptor neuron with olfactory cilia and Right: Part of an isolated olfactory cilium illustrating processes upon odourant binding (Rebholz et al., 2020).

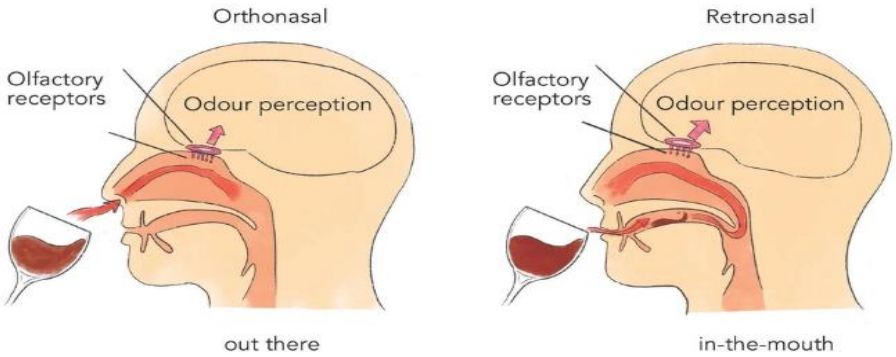

Figure 1.2. The two pathways of smelling: orthonasal olfaction and retronasal olfaction (Zhu, 2024).

Olfaction is triggered by a combination of volatile organic compounds (VOCs) emanating from a material (Spence, 2021). The presence of VOCs in the vapor phase stimulates both orthonasal and retronasal routes of olfaction (Pierce & Halpern, 1996; Sun & Halpern, 2005). VOCs are low-molecular-weight compounds with a molecular weight in the range of 50–200 Daltons. They evaporate easily at room temperature with a boiling point less than 250°C measured at a standard atmospheric pressure of 101.3 kPa (Anand et al., 2014). VOCs are subclassified into very volatile organic compounds with boiling points between 0 and 100°C, which are mainly gases, and volatile compounds with boiling points between 100 and 250°C, dispersed between air and liquid or solid surfaces (United States Environmental Protection Agency, 2011). VOCs are airborne compounds with variable lipophilicity and volatility. Their transfer to the body through the air from the emission source depends on their physical and chemical properties and mean lifetime in the atmosphere, which ranges from a few minutes to several months (Montero-Montoya et al., 2018).

VOCs interact with G protein–coupled odourant receptors in the olfactory epithelium of the nasal cavity (Breer et al., 2006; Dunkel et al., 2014). Active VOCs perceived in the orthonasal and/or retronasal cavity can interact synergistically or additively to produce the overall odour of a product. Their influence depends on their concentration and odour (Buttery, 1999; Leonardos et al., 1969). Although it is valuable to know which VOCs in a sample are odour active, the overall odour of a product is a combination of all active VOCs and can be different from that of each individual VOC (Garvey et al., 2021). Moreover, any change in the concentrations of some odourants can alter smell qualitatively (Malnic et al., 1999). Melnic and colleagues conducted a study using olfactory neurons from the dorsal region nasal septum of mice and a combination of calcium imaging and single-cell reverse

transcriptase–polymerase chain reaction to recognize odourant receptors for odourants with related structures but different odours. The study showed that one odourant receptor can identify multiple odourants, and that one odourant can be identified by multiple odourant receptors.

Odourant receptors are sensitive for diverse odourants depending on their chemical structure (Wackermannová et al., 2016). Minor differences in chemical nature and structure can change the odour threshold values significantly (Buttery, 1999). The olfactory system can detect some compounds, such as amines and thiols, with low odour threshold at very low concentrations as such compounds have strong metal-coordinating ligands (Zhang et al., 2018). Generally, compounds containing sulfur or nitrogen atoms in their structure have very low odour thresholds and can be recognized at the parts per billion level (Leonardos et al., 1969). The trace levels of VOCs with low perception threshold can be easily perceived during sensory analysis (Hummel et al., 1997).

1.4.2 Odour and flavour

Olfaction was highlighted as the main sense that contributes to flavour (Shepherd, 2006). while the term "taste" is commonly used to express the sense of flavour (Spence, 2013), food science tells us that the majority of the flavour comes from smell (Zampini M, 2012). Studies have revealed that individual presentation of a taste or an odourant creates overlapping stimulation in regions of the brain (Blankenship et al., 2019). Integration between odour and taste comes from cross-modal interactions between their modalities when they are present in mixture (Mizoguchi et al., 2016). This integration of odour and taste was reported previously as why some odours enhance or supress specific tastes such as sweetness and sourness (Patel & Pinto, 2014). For instance, strawberry odour was found to enhance sweetness taste of sucrose

solution (Frank & Byram, 1988). In a study conducted by Frank and Byram, 20 volunteers swallowed certain stimuli to study taste/smell interactions (Frank & Byram, 1988). Swallowing the stimuli stimulated both olfactory and gustatory systems in the same manner that occurs normally during the consumption of oral products. The tastants used in this study were sucrose for sweetness and sodium chloride for saltiness while the odourants were strawberry and peanut butter odours. While strawberry odour enhanced the sweetness of sucrose, peanut butter did not affect the sweetness. However, the saltiness of sodium chloride was not enhanced by strawberry odour, suggesting that this odour does not enhance taste in general (Frank & Byram, 1988). Likewise, a study conducted by Stevenson et al. revealed that caramel odour suppressed the sourness of citric acid and enhanced the sweetness of sucrose (Stevenson et al., 1999).

On the other hand, previous studies revealed that odour could be enhanced by a sweet taste (Arvisenet et al., 2019). A study was conducted on trained panellists to rate the intensity of the overall mint volatile release of two types of commercial chewing gum containing either sucrose or menthone as tastants (Davidson et al., 1999). Both types of gums showed that a sucrose sweet taste enhanced mint odour release intensity. Trained sensory panellists and wine experts showed how tartaric acid and sugar concentrations influenced the release of volatile compounds from four model wines (Arvisenet et al., 2019). Additionally, Welge-Lüssen *et al*. revealed that presenting odourants such as vanillin retronasally can enhance saliva swallowing reflex if combined with sweet taste (glucose) (Welge-Lüssen et al., 2009). Swallowing activity of saliva in the study was continuously monitored through recording ultrasound imaging of the mouth floor on videotape.

1.4.3 Patient factors that influence odour perception

The normal ability of smell is termed normosmia (Wrobel & Leopold, 2004a). Anosmia is the inability to smell, hyposmia is the decreased ability to smell, and dysosmia is altered perception of odour. Olfactory disorders can be a natural impairment of smell and taste ability that happen physiologically due to ageing (Bromley, 2000). Advanced age reduces chemosensory performance particularly the smell sense (Tuorila et al., 2001). The ability for olfactory recognition decreases sharply in a person's sixties and seventies. Likewise, the perception of bitter and sour tastes drops sharply with age. While taste loss is mostly partial only and people often explain a smell loss as a loss of taste (Wrobel & Leopold, 2004a). This confusion could be because olfactory dysfunction is usually associated with loss of flavour perception. Although, both taste and smell senses are affected adversely by aging, the sense of smell is affected by a higher degree than the taste sense (Bartoshuk, 1995).

Olfactory dysfunction can also be a consequence of a pathological event that causes conductive or sensory/neural losses (Wrobel & Leopold, 2004a). Conductive losses result from obstruction of the nasal airflow to the olfactory cleft and may be caused by chronic rhinosinusitis, allergic rhinitis, polyps, and tumors. Sensory/neural losses are derived from damage to, or dysfunction of, the olfactory nerves anywhere from the olfactory receptors through the olfactory bulbs to the processing centers in the brain involved loss of smell after upper respiratory infection. Sensory/neural losses may be caused by head trauma, toxins, congenital disorders, dementia, Alzheimer's disease, and multiple sclerosis (Wrobel & Leopold, 2004b). Complete obstruction of airflow from intranasal tumours can also cause smell loss. Olfactory dysfunction can also be congenital and in this case, patients usually have no memory associated with perception of flavour or smell during their lifetime (Wrobel & Leopold, 2004a).

Smell dysfunction has been shown to be a reliable marker of early stages of a number of neurodegenerative diseases such as Alzheimer's disease, Huntington's disease, and Parkinson's diseases and of schizophrenia (Olofsson & Freiherr, 2019). In Parkinson's disease, both retronasal and orthonasal olfactory function are severely impaired (Landis et al., 2009). Likewise, children with adenoid hypertrophy have a smell dysfunction, with both retronasal and orthonasal olfactory function being affected (Konstantinidis et al., 2005). Smell impairments have been reported with people who had a total laryngectomy (Leon et al., 2007). Smell dysfunctions have also been reported with diabetes mellitus (Catamo et al., 2021). The sudden loss of smell was recognized as a common symptom of COVID-19 infection (Cattaneo et al., 2022).

Medication can affect smell senses causing smell alteration (Ackerman & Kasbekar, 1997; Henkin, 1994), with medications such as chemotherapeutic agents, antibiotics, statins, diuretics, tricyclic antidepressants, anti-inflammatory agents, and many other classes being implicated (Amézaga et al., 2018; Sevryugin et al., 2021). Kan *et al*. assessed the effect of eight antibiotics on smell disorders, of which six were associated with antibiotic-induced smell disorders (Kan et al., 2021). These were azithromycin, clarithromycin, doxycycline, levofloxacin, and moxifloxacin hydrochloride.

1.4.4 Drug product factors that influence odour perception

As outlined, olfaction is triggered by a combination of VOCs (Bertuzzi et al., 2018; Cheng, 2010; Ianni et al., 2020; Spence, 2021). Generally, VOCs are responsible for characteristic odours and play an important role in determining the palatability of medicinal products (Pennerman et al., 2016). VOCs can be impurities found in drug substances (Jain & Basniwal, 2013). These include remnants of solvents that were used during the synthesis of the drug or excipients used in the manufacture of drug formulations (Argentine et al., 2007; Camarasu et al., 2006). They may also arise due

to degradation related products (Baertschi, 2006). Barbarin *et al*. showed that VOCs were responsible for the malodour of cefotaxime and that these VOCs originated from the degradation of the cefotaxime during radiation sterilization and from residual solvent impurities (Barbarin et al., 1999). The study revealed that VOCs such as carbon oxide sulfide and carbon disulfide released from the degradation of the drug itself. However, others came from the presence of residual solvents which are volatile impurities already present before irradiation. The formation of esters and acetaldehyde O-methyloxime was due to interaction between the solvents and the drug. Examples of VOCs identified in pharmaceutical medicines are presented in **Table 1.2**.

Table 1.2. Examples of volatile organic compounds identified in pharmaceutical medicines and method of determination.

Name of drug	Matrix	Determined substances	Method	Ref
Methamphetamine (psychostimulant)	Drug substance	29 Impurities	GC–FID[1] & GC-MS[2]	(Zhang et al., 2008)
Ketoprofen (nonsteroidal anti-inflammatory drug)	Drug substance and capsule	2 Residual solvents (Cyclohexane and toluene)	GC– ID[3]	(Coran et al., 2001)
Drug substances dissolved in dimethyl sulfoxide and water	Standard solution prepared in dimethyl sulfoxide and water	Separation of 13 solvents	GC with HS- SPME[4]	(Raghani, 2002)
Pharmaceutical product denoted drug A	Drug powder dissolved in water resulted in weakly acidic solution	4 Residual solvents (ethanol, cyclohexane, triethylamine, and pyridine)	Fast GC coupled with EZFlash™ using two different fibers in the SPME extraction technique	(Legrand et al., 2003)
Pharmaceutical Packaged tablets (active and placebo)	Drug formulation and its packaging material	Compound responsible for the packaging off-odour (ethyl-2-mercaptoacetate)	GC–FID	(Sides et al., 2001)
Water soluble pharmaceutical drug	API sample dissolved in aqueous buffer	Impurities (methyl and ethyl esters of various sulfonic acids)	using five kinds of SPME fibers	(Colón & Richoll, 2005)
Peppermint taste-masked tablets	Tablet formulation	Components of peppermint flavor loss (menthone and menthol)	GC–MS using SPME extraction technique	(Yeung et al., 2003)
Isoniazid (antibacterial drug)	commercial isoniazid syrup	Degradant (hydrazine)	GC/MS using SPME extraction technique	(Carlin et al., 1998)
β-lactam (antibiotic)	Drug substance	Impurity of an alkylating reagent (carbonic acid chloromethyl tetrahydro-pyran-4-yl ester)	GC–FID using SPME extraction technique	(H. Li & Sluggett, 2005)
Diclofenac, piroxicam (non-steroidal anti-inflammatory drugs), and Vitamin B-complex	Injectable formulations	Benzaldehyde, the toxic oxidation product, results from use of co-solvent benzyl alcohol	GC with electron capture detection	(Kazemifard et al., 2003)

DPI 201-106 (a positive inotropic agent used in the treatment of heart failure)	Free base and bismesylate salt of DPI 201-106	Methyl methanesulfonate and ethyl methanesulfonate	GC–MS with SIM	(Ramjit et al., 1996)
Drug substance not disclosed	Drug substance	Mesylate esters (methyl methanesulfonate, ethyl methanesulfonate, and isopropyl methanesulfonate)	GC–FID	(W. Li, 2004)
Drug substance not disclosed	Drug substance	Alkyl mesylates (Methyl, ethyl and isopropyl mesylates)	GC–MS	(C. R. Lee et al., 2003)
Drug substance not disclosed	Drug substance	Residual solvent (ethanol, tetra-hydrofurane and toluene)	GC–FID	(Otero et al., 2004)
Flucloxacillin (Antibiotic)	Drug substance	Residual solvent (methanol, ethyl acetate and toluene)	Derivatization with thiocyanate followed by GC–MS	(Haque, 2014)

[1] GC–FID: gas chromatography with a flame ionization detector

[2] GC–MS: gas chromatography–mass spectrometry

[3] ID: isotopic dilution

[4] HS: Head space & SPME: Solid phase microextraction

1.4.5 Tools to measure the smell

A range of tools can be used in general for odour and odourant assessment including olfactory analysis to measure a human's subjective perception of odour and analytical instrumental techniques to measure the odour composition (Bax et al., 2020; Muñoz et al., 2010; Wang et al., 2023). Odour is the experience and sensation of smell whereas odourant is the chemical substance that creates a smell.

1.4.5.1 Olfactory techniques

Olfactory techniques involve a sensory evaluation (quantitative and qualitative) of odours using the human nose as the detector (Muñoz et al., 2010). Quantitative evaluation includes discrimination tests differentiating between products, and descriptive tests describing the sensory attributes of product odours. Examples of discrimination tests comprise duo-trio tests, triangle tests, and paired comparison tests (Wang et al., 2023). Qualitative evaluation aims to get an in-depth understanding of odour intensity and odour profile through focus groups and/ or one-on-one interviews (Muñoz et al., 2010). Children can be observed by the primary caregiver to evaluate odours by conducting ranking tests using observation-based methods of child's reaction or facial expression (Moniot-Ville et al., 1998; Verrotti et al., 2012). Additionally, children aged from 4 years and above can carry out more complex scaling tests themselves through using 3, 5 or 7-point hedonic scales anchored with appropriate words for children (Mistry & Batchelor, 2017). However, descriptive tests are challenging for children because of their limited verbal skills, and short span of concentration (Guinard, 2000). Adults can differentiate more accurately between odour sensory attributes and are therefore preferred to conduct the descriptive testing than children (Guinard, 2000). Olfactory techniques provide insight into human perception and preferences for product odour. However, the accuracy of these

techniques can be reduced because of subjectivity and sensory variations based on cultural and geographical differentiations (Muñoz et al., 2010). In chapter 4 of this thesis the odour of flucloxacillin oral formulations will be assessed by olfactory technique using human adult volunteers.

1.4.5.2 Instrumental techniques

Analytical instrumental techniques are used to identify and quantify chemical compounds causing malodours. Advantages of these techniques are objectivity, repeatability and accuracy (Bax et al., 2020). The commonly used techniques are gas chromatography (GC) and electronic nose. The electronic nose is an instrument designed to mimic human sensory capabilities in the detection of volatile compounds (Ghasemi-Varnamkhasti et al., 2018). The electronic nose consists of an electrochemical sensor array sensitive and partially selective for volatile compounds that give a physical change based on the chemical input (Mohd Ali et al., 2023). The physical changes are transferred into electric signals, with a particular pattern-recognition system identifying a chemical analyte or chemical mixture that representing simple or complex odours (Ghosh et al., 2021). However, the limitations of this technique are the limited sensitivity of the sensors with the requirement of altering the selective sensors for particular analytes (Lu et al., 2022).

GC techniques are sensitive with high efficiency to detect trace levels of volatile compounds that contribute to odour composition (Bertuzzi et al., 2018). VOCs are the chemical origin of odour (Bertuzzi et al., 2018; Cheng, 2010; Ianni et al., 2020; Spence, 2021). During analysis, volatile organic components of a sample mixture are separated in a column and identified when they reach the detector for identification and quantification. Different detection methodology can be used in combination with GC including Mass Spectrometry (GC-MS), Flame Ionised Detector (GC-FID), Time

of Flight-MS (CG-ToF-MS), and Olfactometry Mass spectrometry (GC-O-MS) (Bertuzzi et al., 2018; Clarke et al., 2021). The MS detector identifies and measures the separated compounds by their mass-to-charge ratio. In FID, the compounds separated by the GC enter the combustion chamber of the FID. Within this chamber, the sample is combined with a hydrogen fuel-rich gas and an oxidant such as air. Subsequently, the mixture is ignited to generate a flame. The ions and electrons generated during the combustion process are attracted to the collector electrode. Then, the detector signal undergoes processing, generating a chromatogram that displays peaks related to the separated components in the sample. A ToF MS detector measures the time it takes for ions of different masses to travel through a flight tube, enabling accurate mass-to-charge ratio determination. GC-O-MS is a combination of both human olfaction that detects the odour activity of each eluting compound from the GC and MS detector that quantify the eluted compounds. Olfactometric detection can be used to assess odour qualitatively by determining whether a compound has odour activity or through describing the odour or quantitatively by evaluating the odour intensity or the duration of the odour activity. The olfactometric detection of compounds has the advantage of assessing the relationship between the quantified compound and the human odour perception.

VOCs can be analysed utilising different volatile extraction methods in combination with GC technique (Cheng et al., 2022; Clarke et al., 2021; Hummel et al., 1997). Volatile extraction techniques are used to isolate and concentrate VOCs from products. Examples of the extraction techniques that will be used in chapter 5 are Head Space (HS) and solid-phase microextraction (SPME) (Cheng et al., 2022; Clarke et al., 2021). Head Space sampling technique involves heating the sample in a sealed vial to allow volatile compounds to evaporate into the headspace. Then, the gas in the vial

headspace is injected into a GC-MS **Figure 1.3**. SPME is a solvent-free sample preparation technique that employs a coated fiber that extract, isolate and concentrate volatile organic compounds from different sample matrices **Figure 1.4**. Chapter 5 will explore the capability of gas chromatography methodology to identify and quantify VOCs related to the malodour of flucloxacillin.

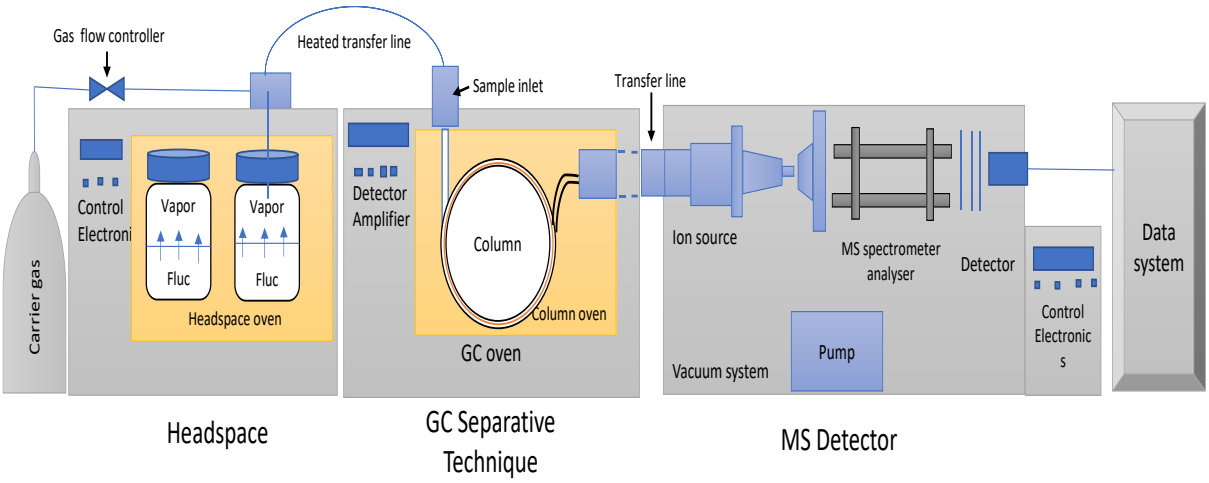

Figure 1.3. Diagram of Headspace GC-MS

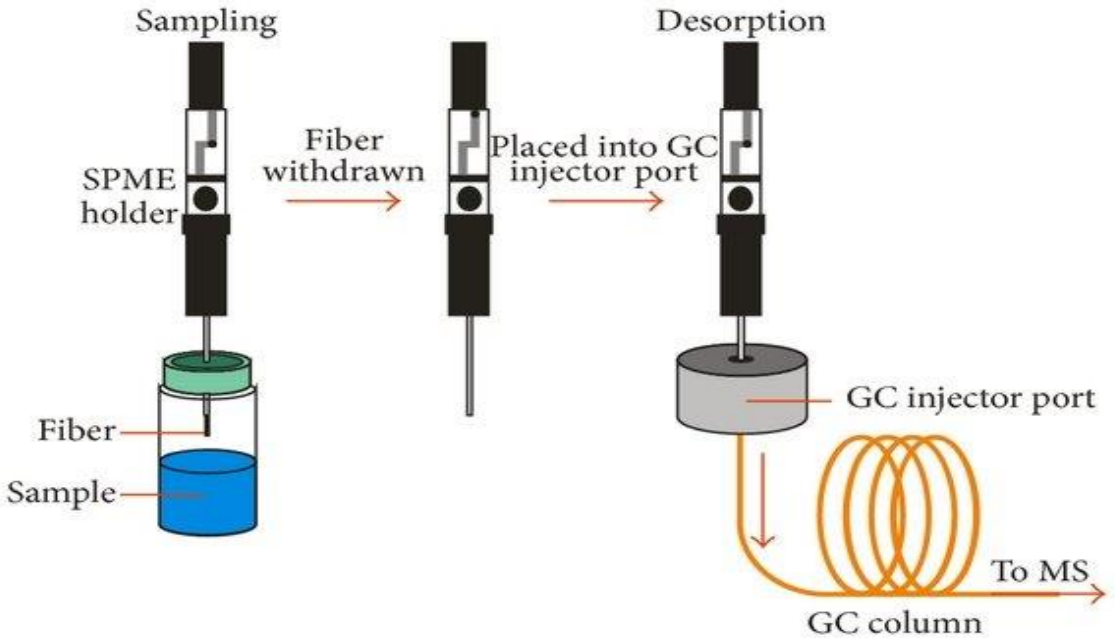

Figure 1.4. Solid-phase microextraction (Schmidt & Podmore, 2015)

1.5 Thesis aims and objectives

The overall aim of this thesis was to define the organoleptic properties associated with the poor palatability of oral liquid antibiotics that impact paediatric acceptability. The first aim was to investigate the impact of poor palatability on primary care clinical practice using survey and interview studies. The second aim was to explore the impact of oral flucloxacillin formulations on odour profile and odour acceptability. The aims were achieved by the research approach outlined in the following thesis chapters.

Chapter 2:

- To explore the influence of palatability on prescribing and dispensing practices of oral liquid antibiotics for children in primary care through conducting a cross-sectional survey of GPs and pharmacists.

Chapter 3:

- To explore challenges related to prescribing or dispensing poorly palatable oral liquid antibiotics, and the impact of these challenges on both patients and the health system by conducting a semi-structured interview study with GPs and pharmacists.

Chapter 4:

- To evaluate the odour acceptability of commercial flucloxacillin oral formulations, and a novel flucloxacillin minitablet formulation, via a sensory study using human volunteers.

Chapter 5:

- To explore the capability of gas chromatography methodology to identify and quantify VOCs related to the malodour of flucloxacillin.

Thesis outline

Title: Oral liquid antibiotic formulations with the focus on organoleptic properties that impact paediatric acceptability

Chapter One: General Introduction

Thesis Aim: To define the organoleptic properties associated with the poor palatability of oral liquid antibiotics that impact paediatric acceptability

Aim One:
To investigate the impact of poor palatability on clinical practice using survey and interview studies

Aim Two:
To explore the impact of formulations on odour profile and assess the odour acceptability of flucloxacillin formulations

Objective One:
To explore the influence of palatability on prescribing and dispensing practices of oral liquid antibiotics for children in primary care.

Objective Two:
To explore challenges related to prescribing or dispensing poorly palatable oral liquid antibiotics, and the impact of these challenges on patients and health system.

Objective Three:
To evaluate the odour acceptability of commercial flucloxacillin formulations through sensory study using a human panel.

Objective Four:
To establish a gas chromatography methodology to identify and quantify the volatile components related to the malodour of flucloxacillin.

Chapter Two:
The impact of drug palatability on prescribing and dispensing of antibiotic formulations for paediatric patients: a cross-sectional survey of general practitioners and pharmacists

Chapter Three:
Challenges Prescribing and Dispensing Oral Antibiotics with Poor Palatability for Paediatric Patients: A Qualitative Interview Study with GPs and Pharmacists

Chapter Four:
The odour acceptability of oral flucloxacillin formulations assessed using a human sensory panel

Chapter Five:
Establish a gas chromatography method to quantify the volatile components related to the malodour of flucloxacillin formulations

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Chapter Six: Discussion, Conclusions & Future Work

Chapter 2

The impact of drug palatability on prescribing and dispensing of antibiotic formulations for paediatric patients: a cross-sectional survey of general practitioners and pharmacists

Authors: Ayat Elgammal, Joseph Ryan, Colin Bradley, Abina Crean, Margaret Bermingham.

Journal: Family Practice, Volume 41, Issue 6, Pages 962–969.

Publication Date: December 2024.

DOI: 10.1093/fampra/cmad071

Contribution: As lead author, I applied for the ethical approval to conduct the study. I was responsible for writing the paper and developing the draft questionnaire that was finalized with the co-authors. I collected and analysed the data that was subsequently revised and finalised with the co-authors.

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The section numbers, figures, tables, references style has been adapted to conform to the style and numbering of the thesis.

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2 Chapter 2

2.1 Introduction

Antibiotics prescribed for the treatment of common paediatric illnesses, are noted for their poor palatability (Angelilli et al., 2000; Demers et al., 1994; Werk & Bauchner, 1998). The palatability of these oral antibiotic products is a key consideration to ensure compliance, adherence and effective treatment (Baguley et al., 2012). Poor palatability, leading to incomplete antibiotic treatment, can result in disease recurrence and can lead to the use of broad-spectrum antibiotics which is discouraged because it may then cause antimicrobial resistance and rising rates of resistance in the general population (Bosley et al., 2018; Laxminarayan et al., 2013; WHO, 2015).

Prescribing the most suitable antibiotic for children is a challenging process even with an obvious diagnosis (Bergene et al., 2019). General practitioners' (GPs) considerations when prescribing antibiotics for children in a community setting are multi-faceted (Biezen et al., 2019; Bosley et al., 2018; Cabral et al., 2015; Lucas et al., 2015). After clinical indication and compliance with prescribing guidelines, palatability is a secondary factor that can influence the prescribing of oral antibiotics for children. Poor palatability of antibiotic formulations was also noted during a study exploring how formulation factors are considered by Norwegian GPs when prescribing medicines for children. The GPs expressed their preference to prescribe first choice antibiotics according to clinical guidelines. However, when patient adherence was undermined by antibiotic palatability, it presented them with 'two suboptimal alternatives'; prescribing a second-choice antibiotic course that the child may adhere to, or the first choice course that might not be completed (Bergene et al., 2019). The antibiotic example highlighted in this study was Penicillin V (phenoxymethylpenicillin), which was the first-choice antibiotic for common

respiratory infections. However, in the study this agent was reported to have poor acceptability and to be challenging to administered to children.

Bergene and colleagues also explored the consideration of formulation factors by pharmacists dispensing medicines for children (Bergene et al., 2019). Pharmacists reported it was common to have questions from parents related to the taste of medicines prescribed for children. They reported that sometimes they dispensed a different formulation of an antibiotic prescribed if a patient indicated an inability to administer a specific formulation to their child. However, the antibiotic type was only changed after consulting the prescriber. Both GPs and pharmacists engage with the challenges of paediatric acceptability of oral liquid antibiotics. The use of medications in paediatric patients can be enhanced through an appropriate support from healthcare professionals. They can support parents/ caregivers by counselling on the importance of the treatment, and how to administer the medication to the child (Bergene et al., 2017). While GPs and pharmacists are not the medicine takers, both professions receive feedback, in particular from parents/caregivers, about the acceptability and palatability of oral liquid antibiotics (Bergene et al., 2019). Pharmacists have a unique perspective on the texture and smell as they are responsible for reconstituting oral liquid antibiotics from the dry powder state.

GPs and pharmacists are aware of the challenges of administering unpalatable oral medicines for children (Bergene et al., 2017; Rautamo et al., 2020; Trofimiuk et al., 2019; Venables, Batchelor, et al., 2015; Venables, Stirling, et al., 2015). However, studies investigating the influence of palatability on their prescribing and dispensing practice are limited. Previous studies of this topic have focussed on specific medicines (Bergene et al., 2019) or on specific infections (Biezen et al., 2019; Cabral et al., 2015), have not included pharmacists (Biezen et al., 2019; Cabral et al., 2015)

and have not focussed in detail on palatability. The aim of this study was to explore GPs' experiences of prescribing oral liquid antibiotics for children and pharmacists' experiences of dispensing oral liquid antibiotics for children.

2.2 Methods

2.2.1 Ethical approval

Ethical approval was granted by the Social Research Ethics Committee of University College Cork (SREC), Log no 2021-138.

2.2.2 Study design

A survey was developed to maximise the reach of the study and obtain the views of a large sample of GPs and pharmacists. The draft questions were developed with reference to literature review specifically studies conducted by Bergene and colleagues, Venables et al., and Bradshaw H et al. (Bergene et al., 2019; Bradshaw et al., 2016; Venables, Batchelor, et al., 2015) and the professional experience of the research team members. The research team consisted of two GPs and three pharmacists. All questions used in the survey are novel questions developed for this study by the research team. The draft questionnaire was piloted electronically. It was shared by email with an independent convenience sample of four GPs and four pharmacists. The responses to the survey and qualitative feedback from this sample were used to refine the survey and finalise the questions. These responses were not included in the final analysis. The final questionnaire (**Supplemental Material 7.1.1**) was agreed by all research team members. The survey was hosted in Google Forms and consisted of a participant information sheet, consent form and questionnaire.

2.2.3 Questionnaire composition

The questionnaire consisted of 20 questions for GP and 23 questions for pharmacist participants. The initial sections collected demographic data. The GP branch of questions focused on factors that influence the prescribing of oral liquid antibiotics, whereas the pharmacist branch focused on factors that influence the dispensing of oral liquid antibiotics. The final sections, for GPs and pharmacists, contained questions

about palatability of oral liquid antibiotics. To explore the antibiotics most associated with general palatability issues in children, all participants were asked to select from a given list of the oral liquid antibiotics. As pharmacists reconstitute oral liquid antibiotic products prior to dispensing they are exposed to their aroma. Some antibiotics have been reported to have a foul smell (Kardas, 2005; Ruff et al., 1991; Steele et al., 1997). To explore this further, pharmacists were asked to state oral liquid antibiotic products with smell issues that they had encountered during their preparation. Pharmacists were also asked to state the oral liquid antibiotic products with texture issues they had encountered during their preparation. Survey questions 11,12,15,16 used a four-item ranking scale from frequently to never. Questions 9 for GPs and question 10 for pharmacists ranked the factors considered when prescribing or dispensing an oral liquid antibiotic product for children. Respondents were asked to rank 1 for the factor considered most important, 2 for next most important and so on.

Most of the survey questions were not compulsory and respondents had the option to skip these questions. For some questions one or more answers could be chosen by respondents. The only compulsory questions were questions 9,12,13, 17-19 in the GP survey and questions 10,13, 15-17 in the pharmacist survey. The research team limited the number of compulsory questions to ensure that participants answered only the questions of which they had knowledge or experience. A child, for the purposes of this study, was considered to be aged birth to 12 years. This age profile was selected as children older than 12 years are less likely to require liquid medicines than children 12 years and under. In Ireland, a pharmacist can switch brand of a medicine dispensed unless the prescriber specified otherwise, and can change the strength of a formulation

dispended, but they cannot change the type of antibiotic dispensed without contacting the prescriber.

2.2.4 Sample characteristics

The inclusion criteria were GPs and trainee GPs registered with the Medical Council of Ireland, and pharmacists registered with the Pharmaceutical Society of Ireland, who selected community pharmacy as their area of professional practice.

2.2.5 Data collection methods

Permission was granted by the Pharmaceutical Society of Ireland to use their community pharmacist email contact list. The questionnaire was emailed to 3943 community pharmacists inviting them to take part in the study. The research team did not have access to a national database of GP email addresses. Therefore, the questionnaire was disseminated to GPs and trainee GPs in the Cork region of Ireland using the Cork GP training scheme e-mail list which includes 64 GPs and GP trainees. A link to the online questionnaire was included in the email. To maximise study's reach and participation, a link to the questionnaire was posted by members of the study team and related institutional accounts on Twitter and LinkedIn and via relevant professional discussion groups on WhatsApp. The questionnaire was available from November 2021 to March 2022.

2.2.6 Data analysis

The responses from the online questionnaire were analysed in Microsoft Excel. Categorical variables were presented as frequencies (%) and responses to free text questions were explored using Braun & Clarke's thematic analysis (Braun & Clarke, 2019). The codes for each question were generated using the QSR International NVivo Qualitative Data Analysis Software (V.12). The codes were reviewed, categorized, and themes related to the study topic were generated for each free text question. As

each survey item was not compulsory, percentage responses were calculated based on the number of responses to that individual survey item.

2.3 Results

2.3.1 Participant Demographics

A total of 244 participants completed the questionnaire and key demographic details are outlined in **Supplementary Table 2.1**. Fifty-nine respondents were GPs (24.2%), and the remaining 185 participants were pharmacists (75.8%). As the survey was distributed via social networking sites, a final response rate could not be determined. One hundred and seventy-three of the participants were female (70.9%). Twenty-nine GPs (49.2%) and 134 pharmacists (72.4%) had >10 year's professional experience. Thirty-seven GPs (64.9%) and 141 pharmacists (77.5%) reported that ≤20% of their prescription patients were children.

2.3.2 General factors that influence the antibiotic prescribing and dispensing

When asked to rank factors they considered when prescribing or dispensing an oral liquid antibiotic product for children, clinical guidelines and availability of supply were ranked as the most important factors by the majority of GP and pharmacist respondents respectively (**Table 2.1**). While a minority of respondents ranked palatability as the most important factor, 38% of each profession listed it as the 2nd important factor from the choices provided.

Table 2.1. Factors that influence prescribing of oral liquid antibiotic by GP and dispensing of oral liquid antibiotics by pharmacist respondents respectively.

Rank	GPs (n=59)			Pharmacists (n=185)		
	Clinical guidelines	**Dosage regime**	**Palatability**	**Availability of supply**	**Product cost**	**palatability**
Most important factor	79.7% (n=47)	6.8% (n=4)	13.6% (n=8)	66.5% (n=123)	13.5% (n= 25)	20% (n= 37)
2nd important factor	16.9% (n=10)	45.8% (n=27)	37.3% (n=22)	16.2% (n= 30)	45.9% (n= 85)	37.8% (n= 70)
Least important factor	3.4% (n=2)	47.5% (n=28)	49.2% (n=29)	17.3% (n= 32)	40.5% (n= 75)	42.2% (n= 78)

Participants then listed any other factors they consider when prescribing or dispensing an oral liquid antibiotic product for children. The question was answered by 76 pharmacists (41.1%) and 20 GPs (33.9%) and a wide range of factors were noted. The 144 factors mentioned were categorised into factors associated with patient and product. While patient factors were listed by both GPs and pharmacists, they featured more predominantly by GPs. A number of responses were similar across both professions, including allergy, age appropriateness, antimicrobial history, customer preference and patient feedback. However, other patient factors reported by GPs and not by pharmacists included parental attitude and education, child's weight, compliance, and illness. In contrast product factors were more frequently listed by pharmacists. Product factors noted by both professions included duration of therapy and route of administration. However, dose volume was the main product factor identified by 21.3% of pharmacists. More details are outlined in **Supplementary Table 2.2**.

2.3.3 Palatability of oral antibiotic type

Flucloxacillin and clarithromycin were identified as the most unpalatable antibiotics by both professions (***Figure 2.1***).

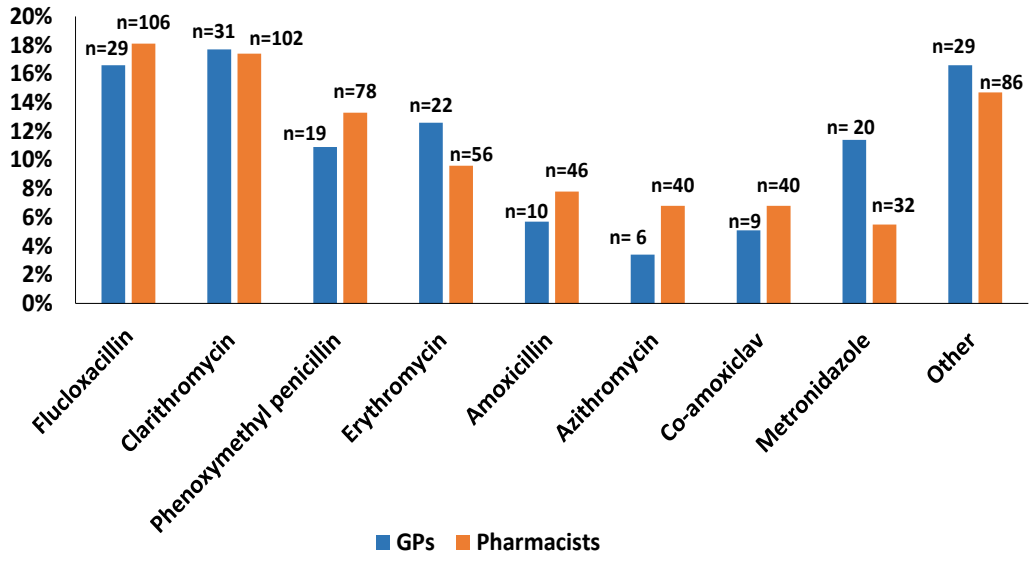

Figure 2.1. Percentages of antibiotics with palatability issues (e.g., smell, taste, aftertaste, and texture) reported by the survey participants with a total of 175 responses from GPs and 587 responses from pharmacists were received for this question.

When pharmacists were asked to state oral liquid antibiotic products with smell issues, one-hundred and twelve responses were received. The antibiotics reported with the worst smell were flucloxacillin (n = 41, 36.6%), and phenoxymethylpenicillin (n = 37, 33.0%). When the pharmacists then asked to state oral liquid antibiotic products with texture issues, one-hundred and forty-five responses were received from 135 respondents. Clarithromycin was most frequently identified as an antibiotic with texture issues (n = 65, 44.8%). Azithromycin (n = 18, 12.4%) and cefuroxime (n = 14, 9.7%) were also reported to have texture issues (***Figure 2.2***).

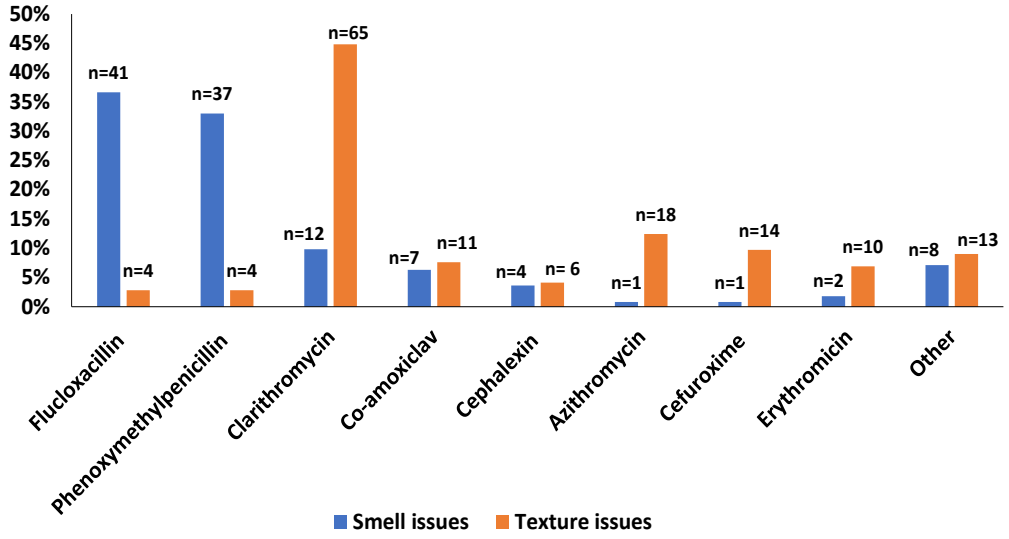

Figure 2.2. Percentages of antibiotics with smell and texture issues (i.e., feeling in the mouth) that pharmacist respondents had encountered during their preparation. 112 responses were received for the smell issue and 145 responses were received for the texture.

Amoxicillin was reported as the most palatable antibiotic for children by 58.1% of GP respondents and 49.7% of pharmacist respondents. Cefaclor was identified as the most palatable oral liquid antibiotic by 19.4% of GP respondents and 25.1% of pharmacist respondents.

2.3.4 Palatability impact on clinical practice

Of the pharmacists surveyed, 31.3% frequently and 40.7% occasionally discussed antibiotic palatability with parents/caregivers. However, 46.6 % of GPs indicated that they rarely or never discussed the palatability with parents/caregivers (***Figure 2.3***). Among GP respondents (n=59), 62.7% reported never and 32.2% reported rarely writing "*Do not substitute*" on a prescription for an oral liquid antibiotic for a child (***Figure 2.3***). Among both GPs and pharmacists, 11.9% indicated that they never deviated from clinical guideline or changed dispensing choice because of palatability issues respectively. However, occasional (approximately monthly) deviation from

clinical guidelines was reported by 35.6% GPs and occasional switching was reported by 26.5% of pharmacists (***Figure 2.3***).

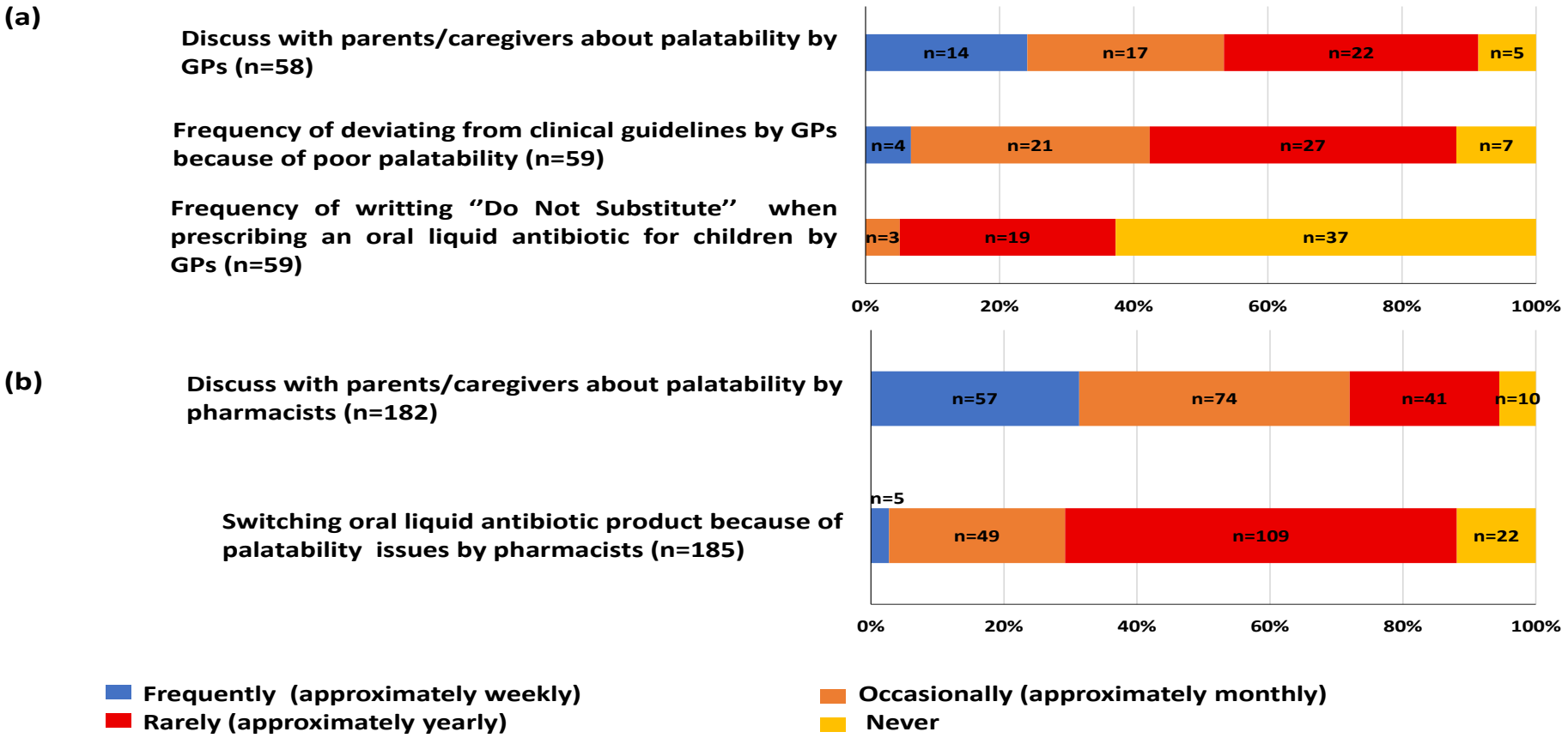

Figure 2.3. Discussion about palatability (e.g., smell, taste, aftertaste, and texture) with parents/caregivers and frequency of deviating from clinical guidelines and switching oral liquid antibiotics for children reported by (a) GPs and (b) pharmacists' respondents respectively.

GP respondents who had deviated from clinical guidelines, were asked to rank the palatability-related reasons causing them to deviate from clinical guidelines (**Table 2**). Of the 52 respondents, 40 (76.9%) reported that ensuring adherence to treatment was the most common reason to deviate from clinical guidelines. Maintaining a good physician-patient relationship was ranked as the 2nd common reason by 50% of GP respondents. GP participants were then asked a free text question to list any other reasons which cause them to deviate from clinical guidelines because of poor palatability. One respondent stated that oral liquid antibiotics dosed four times a day are very awkward for school-going children.

Table 2.2. Reasons which cause GPs to deviate from clinical guidelines because of poor palatability (n=52).

Rank	Ensure compliance and adherence to treatment	Maintain a good physician-patient relationship	Parental/ caregiver pressure
The most common reason	76.90% (n=40)	7.70% (n=4)	15.40% (n=8)
The 2nd common reason	13.50% (n=7)	50.00% (n=26)	36.50% (n=19)
The least common reason	9.60% (n=5)	42.30% (n=22)	48.10% (n=25)

2.3.5 Switching antibiotic products by pharmacists because of palatability issues

Pharmacists who reported that they had switched an oral liquid antibiotic product because of palatability issues were asked to indicate which products they had switched from and to. The question was answered by 113 pharmacists answered this question with 143 individual responses. Switching from one brand to another brand of the same antibiotic was reported by 30.8% of respondents. This included switching brand of phenoxymethylpenicillin (n=24), flucloxacillin (n=7), amoxicillin (n=6), and other (n=7). A further 44.8% of the respondents reported switching from an antibiotic to a different antibiotic after consulting the prescriber. Respondents reported contacting the prescriber for alternative prescriptions after parents had complained of non-compliance. Most of the participants reported that they switched from clarithromycin (n=17), flucloxacillin (n=13), and phenoxymethylpenicillin (n=12). These antibiotics were switched mainly to either amoxicillin (n=12) or cefaclor (n=11). Twenty-six participants identified which antibiotic they had switched from without specifying which product they had switched to. Examples of switching are outlined in **Supplementary Table S2.3 & S2.4.**

2.3.6 Advice to administer an unpalatable oral liquid antibiotic to a child.

Pharmacists were asked how they would identify an oral liquid antibiotic product that may have poor palatability. Of the total responses (n=379), 47% identified through parent/caregiver feedback. Palatability issues were also identified through drug smell during preparation (20.6%), drug texture during preparation (16.4%), parents/caregiver unwilling to administer the drug to the children (14.0%), and 2.1% stated their own personal experience.

Pharmacists were then asked about the advice they would give to a parent/caregiver who is unable to administer an unpalatable oral liquid antibiotic to a child. Of the 289 responses, 52% reported advising a parent/caregiver to manipulate the required doses, such as by mixing with food or diluting the antibiotic in a flavoured liquid; 21.8% advised to promise a reward to the child after taking the dose; and 14.2% recommended dividing the required dose into smaller portions. Other advice reported by pharmacists is outlined in **Supplementary Table 2.5.**

2.4 Discussion

This study has identified palatability issues associated with prescribing and dispensing oral liquid antibiotics for paediatric patients reported by GPs and pharmacists. Among GPs and pharmacists, 88.1% of each profession reported that they have deviated from clinical guidelines or changed dispensing choice because of palatability issues. Among GPs who have deviated from clinical guidelines, 77% reported this was in order to ensure compliance and adherence to treatment. Among pharmacists who have changed dispensing choice due to palatability issues, 31% report that they switch from one brand to a more palatable brand of the same antibiotic and 45% switch the type of the antibiotic after consulting the GP. In some cases, where a parent/caregiver is unable to administer an unpalatable oral liquid antibiotic to a child, pharmacists advised to manipulate the required doses by mixing with food or diluting in a flavoured liquid. Flucloxacillin and clarithromycin were reported as the least palatable oral liquid antibiotics for children. Flucloxacillin was highlighted as the antibiotic with the worst smell whilst clarithromycin was the antibiotic with the most textural issues. Amoxicillin and cefaclor were identified as the most palatable oral liquid antibiotics for a paediatric population.

In the current study, 80% of GPs identified clinical guidelines as the most important factor they considered when prescribing an oral liquid antibiotic for children. However, 88% of them reported that they might need to deviate from clinical guidelines because of poor palatability, an issue that was also reported in Norway by Bergene *et al*. who found that GPs preferred to follow the guidelines and prescribe first-choice antibiotics. However, poor palatability could lead to prescribing of second-choice agents (Bergene et al., 2019). Additionally, previous studies showed that poor palatability is a main reason for prescribing second-choice, broad-spectrum

antibiotics for paediatric patients (Dekker et al., 2017; Fossum et al., 2013; Pottegård et al., 2015). In the present study, GPs reported that their primary reason for deviating from clinical guidelines was to ensure adherence to treatment. The second most common reason was to maintain a good physician-patient relationship. It has previously been reported that sub-optimal adherence to treatment might cause complications in the physician-patient relationship (Winnick et al., 2005).

Among pharmacists in the present study, 67% identified availability of supply as the most important factor they considered when dispensing an oral liquid antibiotic for children. However, 88% reported that they would switch antibiotic products because of poor palatability. Pharmacists reported switching from a less palatable brand to a more palatable brand of the same antibiotic or switching the type of the antibiotic, based on parent/caregiver feedback. This was done after consulting with the prescribing GP. These results are similar to those reported by Bergene *et al*., who found that pharmacists might need to switch the prescribed antibiotic product at parents' request or change the type of antibiotic after contacting the prescriber (Bergene et al., 2019). Pharmacists in the current study reported that they had contacted the prescriber for alternative prescriptions after parents had complained of non-adherence. Pharmacists revealed that where a parent/caregiver is unable to administer an unpalatable oral liquid antibiotic to a child, the pharmacist might advise to manipulate the required doses or promise a reward to the child after taking the dose. However, Venables *et al.* have reported that unnecessary manipulation should be avoided as such manipulation can alter therapeutic response and decrease drug bioavailability (Venables, Batchelor, et al., 2015). Similarly, a previous study reported that parents/caregiver might need to manipulate the oral dosage form to achieve better

palatability (van der Vossen et al., 2019). The study reported the need to develop more palatable formulations in order to reduce drug manipulation.

Palatability is discussed with parents/caregivers by 91% of GPs and 95% of pharmacists when prescribing or dispensing oral liquid antibiotics for children. Such discussion is essential to ensure successful treatment (Baguley et al., 2012). An effective collaboration between GP, pharmacist, parent, and child can enhance the appropriate selection of antibiotic, adherence to treatment and hence decrease the risk of antimicrobial resistance (Baguley et al., 2012; Bergene et al., 2019). Baguley and colleagues suggest that GPs need to be more aware of the importance of palatability when prescribing oral liquid antibiotics for children to ensure effective prescribing (Baguley et al., 2012). Bergene and colleagues recommend that pharmacists could integrate shared decision-making into their practice and that they could discuss the availability of different formulations with a parent/caregiver in order to dispense the best choice oral liquid antibiotic for every child (Bergene et al., 2019). The three strategies of drug administration of an oral liquid antibiotic are open administration, hidden administration, and forced administration. It is essential that both GPs and pharmacists discuss these three strategies with the parent/caregiver and identify their preferences when prescribing or dispensing an oral liquid antibiotic (Bergene et al., 2017).

The most palatable oral liquid antibiotics for children were reported in the current study to be amoxicillin and cefaclor. However, cefaclor a cephalosporin broad-spectrum antibiotic, should not be used as a first-line choice when a narrow spectrum antibiotic is effective in primary care, according to the current clinical guidelines in Ireland and the United Kingdom (*Antibiotic Prescribing - HSE.Ie, Preferred Antibiotics in Primary Care*, 2019; *Antimicrobial Prescribing Guidelines - NHS.UK*,

2021). Nevertheless, 18% of pharmacists in the present study highlighted that cefaclor was one of the antibiotics that they had frequently switched to after contacting the GP because of its preferred palatability.

In the current study, flucloxacillin and clarithromycin were reported to be the least palatable oral liquid antibiotics for children. A number of previous studies have reported the unpalatability of clarithromycin to paediatric patients (Blasi & Tarsia, 2005; Powers, 1996; Steele et al., 2001). Steele *et al*. reported in a study conducted in the United States that the texture and acceptability of clarithromycin can be improved by decreasing the grittiness of the product in pharmaceutical processing (Steele et al., 1997). However, the findings of the current study suggest that the texture of clarithromycin is still problematic to children. Flucloxacillin has been identified as an unpalatable oral liquid antibiotic for children in studies conducted in the United Kingdom (Baguley et al., 2012; Rouse et al., 2017; Venables, Stirling, et al., 2015). However, unlike Venables *et al*., who reported that the unpalatability of flucloxacillin relates to its taste (Venables, Stirling, et al., 2015), the findings of the present study indicate that the poor palatability of flucloxacillin relates to its smell. Smell is considered to be the main sense that contributes to flavour (Rozin, 1982; Shepherd, 2006). It was confirmed in a review conducted by Spence that between 75% and 95% of what we think of as taste is actually caused by the smell sense (Spence, 2015). Indeed, olfaction was agreed by most researchers in the review to be the dominant sense in tasting. However, there is ongoing confusion with using the term "taste" to express the sense of flavour.

These findings highlight the importance of developing more palatable oral liquid formulations of the first-line antibiotics for paediatric population to avoid using broad spectrum antibiotics and to ensure better adherence to the clinical guidelines.

Availability of such improved formulations has the potential to improve patient adherence, reduce antimicrobial treatment failure, and improve the care of paediatric patients.

2.5 Strengths and limitations

This study included both GPs and pharmacists to provide a comprehensive explanation of the impact of drug palatability on prescribing and dispensing processes of oral liquid antibiotics. Additionally, the respondents are very experienced with at least half of respondents in each profession having >10 years' experience in their discipline. However, there are limitations to this study. The number of GP respondents was relatively small as the survey was disseminated by email to GPs and trainee GPs in the Cork region only. The survey was distributed in November 2021, during the Covid-19 pandemic, when all healthcare services including GPs and pharmacists, were under pressure. This may account for the small sample size. The survey was also circulated on social media to ensure a broader recruitment of eligible participants. There is a risk that in circulating the survey on social media, it could reach people who are not eligible to participate in the study. However, this topic is very specific and needed someone in clinical practice to answer the questions. To moderate this risk, the public social media posts specified that Irish-based participants were sought for the study and specified the two professions targeted. The WhatsApp messages were sent to groups that were specifically for Irish-based GPs and pharmacists. The relatively small sample size and limited demographic diversity of the participants may limit the generalisability of the study. Future studies are suggested to investigate the impact of palatability on prescribing and dispensing paediatric oral antibiotics in different social and cultural contexts. The survey instrument used in the study was novel and has not been used in

any population outside of this study. However, the results align with those of studies that have been conducted in Norway, the United Kingdom, and the United States.

2.6 Conclusion

This study has identified palatability issues associated with prescribing and dispensing oral liquid antibiotics for paediatric patients reported by GPs and pharmacists. A majority of GP respondents reported that they have deviated from clinical guidelines because of palatability issues. The need to ensuring adherence to treatment was the main palatability-related reason causing GPs to deviate from clinical guidelines. Similarly, most pharmacists reported that they have switched an antibiotic due to palatability issues reported by a parent/caregiver. Pharmacists reported switching from one brand to a more palatable brand of the same antibiotic based on parents/caregiver feedback or switching the type of the antibiotic after consulting the GP. In some cases, where a parent/caregiver is unable to administer an unpalatable oral liquid antibiotic to a child, pharmacists advised to manipulate the required doses by mixing with food or diluting in a flavoured liquid. Amoxicillin and cefaclor were identified as the most palatable oral liquid antibiotics while flucloxacillin and clarithromycin were reported as antibiotics with poor palatability. There is a need to develop pharmaceutical approaches to adapt oral liquid formulations of flucloxacillin and clarithromycin antibiotics to improve palatability and thus paediatric patient acceptability.

Chapter 3

Challenges prescribing and dispensing oral antibiotics with poor palatability for paediatric patients: a qualitative interview study with GPs and pharmacists

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Contribution: As lead author, I applied for the ethical approval to conduct the study. I was responsible for writing the paper and developing the draft topic guide for the interviews that was finalized afterwards with the co-authors. I conducted the interviews with all GP participants and six pharmacist participants. I also collected, transcribed, coded and analysed the data that was subsequently revised and finalised with the co-authors.

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The section numbers, figures, tables, and references style has been adapted to conform to the style and numbering of the thesis.

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3 Chapter 3

3.1 Introduction

Children's age, weight and potential allergies can influence choice of medicines for this patient group. However, children can also experience sensory-related problems such as issues with taste, smell, and texture when administered oral prescription medicines (Rautamo et al., 2020; Venables, Stirling, et al., 2015). Poor palatability, based on smell, taste, aftertaste, and texture of antibiotics is one of the key causes for non-adherence to antibiotic treatment among paediatric patients (Baguley et al., 2012; Kardas et al., 2005; Winnick et al., 2005). Failure to complete antibiotic treatment because of poor palatability can cause disease recurrence and can result in switching to a more palatable antibiotic which is typically a more broad-spectrum antibiotic (Ramgoolam & Steele, 2002). This can lead to the development of antimicrobial resistance and may play a role in expanding rates of antimicrobial resistance in the general population (WHO, 2015).

Young children may experience difficulties in swallowing oral solid dosage forms such as tablets and capsules (Batchelor & Marriott, 2015a). Therefore, a liquid antibiotic formulation is the most common dosage form among children (Lajoinie et al., 2016). A study by Li et al. revealed that two-thirds of the global sales of paediatric antibiotic formulations were in the form of a liquid (Li et al., 2020). Nevertheless, administration of liquid formulations with poor palatability is a challenge for children where the dissolved drug is in direct contact with the taste buds and olfactory receptors that are more sensitive in children compared with adults (Pawar & Kumar, 2002). A study conducted by Venables et al. revealed that several medicines with unacceptable palatability were refused by children or manipulated by parents (Venables, Batchelor, et al., 2015). Children's refusal of medicines resulted in spitting out the dose or closing

their mouth prohibiting administration. Manipulation through mixing drugs with different foodstuffs or diluting the recommended dose with a flavoured liquid to aid medicines administration, has been suggested as a solution. However, this action can alter the therapeutic response and drug bioavailability (Venables, Batchelor, et al., 2015).

The clinical guidelines and availability of supply were ranked as the most important factors affecting the selection of antibiotics by the majority of GP and pharmacist respondents respectively in a recent survey conducted by the research team members. The survey revealed that a majority of GPs had at times deviated from clinical guidelines, and that the majority pharmacists had changed antibiotic dispensing choice because of palatability issues to ensure treatment adherence. Almost half of respondents of each profession indicated that they rarely or never discussed the palatability with a child's parents or caregivers in chapter 2. The current study presented builds on the results of this prior survey providing a deeper and richer understanding of the survey outcomes. The experience, attitudes, and challenges faced by GPs and pharmacists in primary care regarding prescribing and dispensing poorly palatable oral liquid antibiotics for paediatric patients are investigated and the impact of this issue on patients and health systems.

3.2 Methods

3.2.1 Ethical approval

Ethical approval was granted by the Social Research Ethics Committee of University College Cork, Log no 2021-138A2.

3.2.2 Study design

A topic guide for the semi-structured interviews was developed based on the prior survey responses in chapter 2 and associated research literature (Bergene et al., 2019). It was further developed through group discussions by the research team members. Separate topic guides were used for each profession though the topic guides were broadly aligned. The key difference was that the topic guide for GPs referred to prescribing and the topic guide for pharmacists referred to dispensing oral liquid antibiotics. The topic guide was piloted independently with one GP and one pharmacist in one-to-one interviews. The pilot interviews were conducted to check for length, suitability of the language and potential causes of bias such as leading questions. The pilot interviews were transcribed to check that they have produced enough data related to the research question. Qualitative feedback from the pilot interview were used to refine and finalise the topic guide questions. The pilot interviews were not included as part of the main analysis. The topic guide was agreed by all research team members. The topic guide is available as Supplementary Material 7.2.1.

For contextual background, the study presented was conducted in Ireland where antibiotics are prescribed by GPs and dispensed by pharmacists in Ireland. It is also of note that an Irish pharmacist can switch the medicine brand dispensed (unless the prescriber specifies otherwise on the prescription) and change the strength of a formulation dispensed. Pharmacists cannot change the type of antibiotic dispensed without contacting the prescriber. For oral liquid antibiotic products which require reconstitution, they are reconstituted in the pharmacy prior to dispensing.

3.2.3 Sample characteristics

The inclusion criteria were GPs and trainee GPs registered with the Irish Medical Council; and pharmacists registered with the Pharmaceutical Society of Ireland, who selected community pharmacy as their area of professional practice. Selection of participants was based on obtaining a diverse representation of practitioners such as years of experience, and roles in primary care practice.

3.2.4 Data collection methods

The final survey question in the prior survey of 59 GPs and 185 pharmacists, on the impact of drug palatability on prescribing and dispensing of antibiotic formulations for paediatric patients in chapter 2, asked participants if they were interested in taking part in a follow-up semi-structured interview. Survey participants who were interested were asked to provide their contact details and were invited to take part in this interview study. The survey and the interview studies were conducted separately to permit in-depth quantitative and qualitative data analysis of the data set obtained from each study. The research team also invoked their professional networks to identify potential participants. These additional participants were invited by email or WhatsApp to take part in the study. A WhatsApp message was sent to professional WhatsApp groups including groups of GP trainees and GP trainers and pharmacist special interest groups of which the research team have membership. Additionally, snowball sampling was invoked, and interview participants were invited to suggest colleagues who might be interested in participating in the study. An information sheet and consent form were sent by email to individuals who indicated an interest in taking part in the study. Participants provided signed, informed consent prior to their interview. Verbal consent was also obtained before starting interviews. One-to-one video-conferencing interviews were conducted using a closed channel of the online

meeting platform Microsoft Teams. Each interviewee was provided with a meeting code to guarantee data protection. The semi-structured interviews were conducted by two members of the research team (AE and JR) between December 2022 and December 2023. All GP participants were interviewed by a pharmacist (AE). Pharmacist participants were interviewed by a pharmacist (AE) or a GP (JR).

3.2.5 Data analysis

All interviews were recorded using Microsoft Teams and a transcript was created. The interviews were anonymised and transcribed by AE using Microsoft Word and checked for accuracy by MB and AC. The interviews were then saved in the QSR International NVivo Qualitative Data Analysis Software (V.12) for analysis. Data were analysed using Braun & Clarke's reflexive thematic analysis (Braun & Clarke, 2019). The research team reviewed and familiarised themselves with the interview response data through multiple reading of each manuscript. Elements of interest in the data was inductively coded by AE. To better ensure reliability of coding, samples of transcripts were independently reviewed and coded by MB and AC. Codes were then finalised and grouped into categories related to the study topic. Initial themes representing a number of codes were generated and discussed between all research team members. Themes were subsequently refined, and the final themes were agreed by all research team members.

3.2.6 Reporting

This study was reported corresponding to the SRQR (Standards for Reporting Qualitative Research) guidelines (O'Brien et al., 2014).

3.2.7 Research team and reflexivity

AE is a pharmacist and PhD researcher. AC, and MB are academic pharmacists in the School of Pharmacy, University College Cork. JR is a GP and CB is an academic GP. All pharmacists and GPs of the research team have experience of dispensing and prescribing oral liquid antibiotics, respectively.

The use of the term parents in this study included caregivers and people who administer antibiotic to children at home.

3.3 Results

3.3.1 Participants

Twenty participants were interviewed, of which seven were GPs, and thirteen were pharmacists. Six participants, three of each profession, were parents themselves. Mean length of interviews was 14 minutes with a range from 7 to 33 minutes. The variation in the length of the interviews was related to variability in the style of verbal communication and extent of the detailed responses provided by participants. Sixteen of the participants were female and 4 were male. Both genders were invited to participate in the study. However, a greater number of females agreed to participate. The disparity in gender may somewhat reflect the gender breakdown amongst registered Irish pharmacists and GPs. The Pharmaceutical Society of Ireland (PSI) and Irish College of General Practitioners (ICGP) annual report reported that 64% and 56% of Irish pharmacists and GPs are females respectively. Median years of participants' experience was 11 years with an interquartile range of 2 – 27 years of practice. The key demographic details are outlined in **Supplementary Table S3.1**.

3.3.2 Themes and Subthemes

Data analysis revealed three main themes and eight sub-themes (**Figure 1**). The main themes identified were (i) the challenges reported by GPs and pharmacists on prescribing and dispensing oral liquid antibiotic for paediatric patients, (ii) the impact of prescribing or dispensing poorly palatable oral liquid antibiotics, and (iii) suggestions to overcome these challenges.

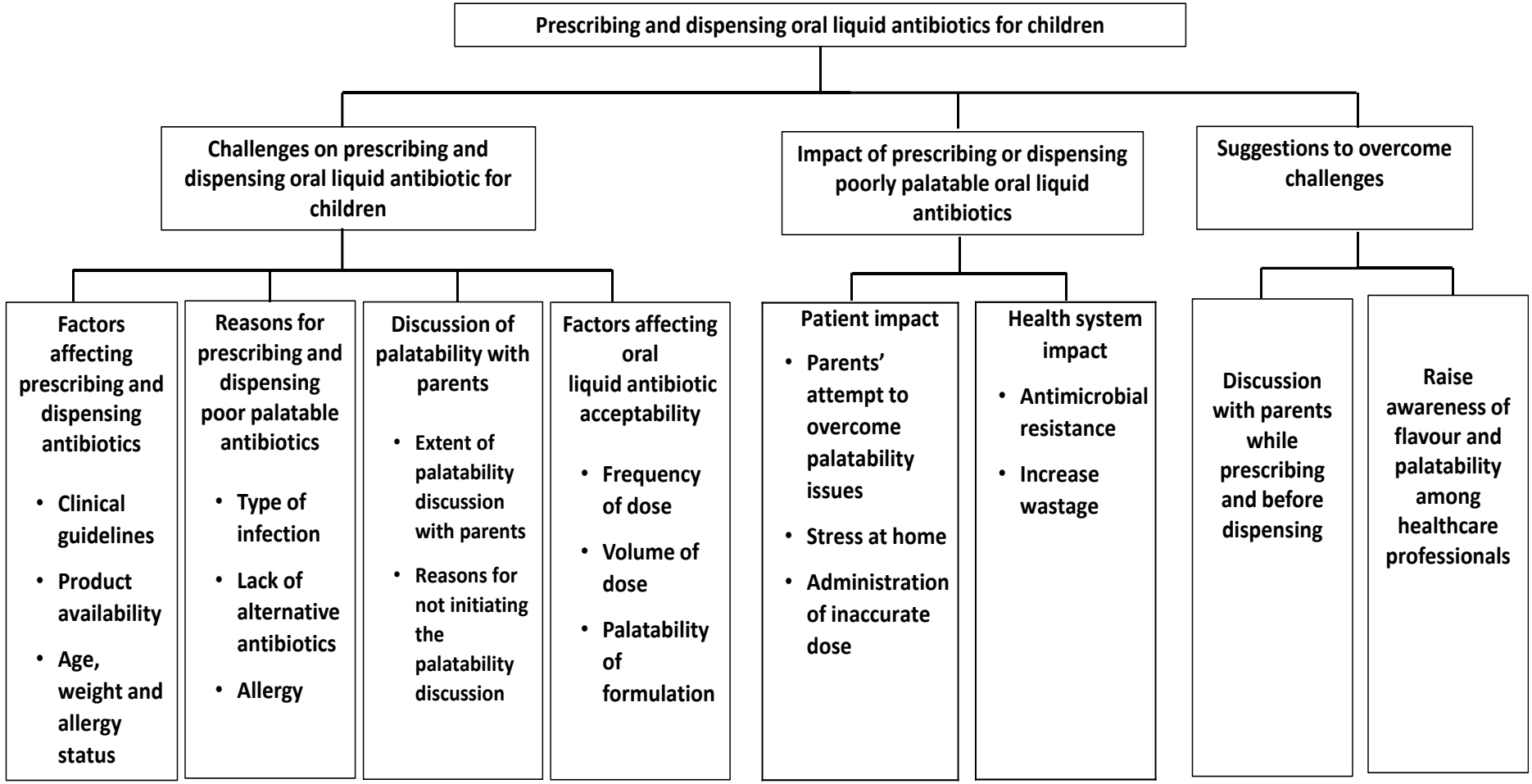

Figure 3.1. Schematic outlines the identified themes and sub-themes.

3.3.3 Theme 1: Challenges associated with prescribing and dispensing oral liquid antibiotic for children

The theme of challenges of prescribing and dispensing oral liquid antibiotic for paediatric patients included the factors affecting prescribing and dispensing antibiotics, reasons to prescribe or dispense poorly palatable antibiotics, palatability discussions with parents, and factors affecting oral liquid antibiotic administration.

3.3.3.1 Subtheme: factors affecting prescribing and dispensing antibiotics

Identified factors included clinical guidelines, availability of antibiotics, and age, weight and allergy status of the child. Clinical guidelines were considered mainly by GPs as they make the initial decision to select an antibiotic for a paediatric patient. Availability of antibiotics was highlighted by both professions as a recent challenge that they had to consider. Pharmacists reported that shortage of antibiotics caused them to manipulate solid dosage forms into liquid. Age and weight were factors that both professions considered to calculate the antibiotic dose. Both professions considered allergy status of the child before prescribing or dispensing an oral liquid antibiotic.

"First of all, when I prescribe for children, the first questions I should ask the parents about is allergy. If the child is allergic to penicillin, so I have to prescribe something of [a] different family such as clarithromycin and my first choice in this case is usually Klacid® [clarithromycin]." (GP5)

"*Because of the shortage with antibiotics at the moment, there is a leaflet going around with how to make the solid dosage forms into liquid format, but It's just that's effort in trying to make sure that you're getting the right dose [and] you're open to error then."* (Ph1)

3.3.3.2 Subtheme: reasons for prescribing and dispensing poorly palatable antibiotics

All participants reported that in some circumstances they had to select an unpalatable antibiotic even though they know that it has poor palatability. The main reasons reported were the type of infection, lack of alternatives, and allergy.

"*If I had a swab or culture back with a specific sensitivity, then I really would try to encourage them to find some way that they can get the child to take it.*" (GP3)

"*I'm more confined in terms of the lack of alternatives, so I would just have to go with what we have in stock.*" (Ph10)

"*If there is a penicillin allergy, I have to prescribe macrolide, so I prescribe Klacid® [clarithromycin] though I know it is unpalatable but unfortunately you are limited.*" (GP5)

3.3.3.3 Subtheme: discussion of palatability with the parents

This subtheme encompasses the extent of antibiotic palatability is discussed with parents, and reasons for not initiating a discussion about palatability with parents.

3.3.3.3.1 Extent of palatability discussion with parents

All participants reported that they only consider discussing oral liquid antibiotic palatability if a parent raises the issue. They all stated that they never initiate the palatability conversation with parents. However, participants reported that parents often negotiated about antibiotic palatability with both professions such as asking for alternative if they struggled to administer a previous antibiotic to the child. The parent might also ask for an alternative antibiotic even before completing the original antibiotic course.

"*I wouldn't discuss palatability unless the parents specifically asked, I would just say the label directions."* (Ph2)

"I suppose I changed when the parent, a day or two later, were saying, look, we've tried and get however many doses in, and it hasn't happened. So, could we try [an] alternative?" (GP1)

3.3.3.3.2 Reasons for not initiating the discussion about palatability with parents

Participants reported different reasons for not starting the palatability discussion with parents. The main reasons were to avoid negotiation because they do not have alternatives; they avoid raising the potential issue until the child tries to take the

antibiotic. They also avoid raising palatability issues with parents in case parents pass this fact to the child who will then be primed to refuse the antibiotic.

"I think if you warn the parent that it's not nice, they're going to probably pass that on to the child before they've even started. Just try and give it [antibiotic] to them." (Ph9)

3.3.3.4 Subtheme: formulation factors affecting oral liquid antibiotic acceptability

Participants reported that the factors affecting oral liquid antibiotic administration by parents were frequency, volume, and palatability. Palatability factors included taste, smell, and texture. Texture involved grittiness and viscosity. Participants stated that it is a challenge for the parents to give antibiotics to children, in particular if it required a high number of doses per day, a large volume, or poor palatability. Participants reported the poor acceptability of flucloxacillin formulations due to their poor taste, unpleasant smell and four times a day dosing schedule. The clarithromycin product Klacid® was also reported as poorly palatable due to grainy texture. A list of formulation acceptability issues associated with the poorly palatable oral liquid antibiotics reported by the participants are outlined in **Table 3.1**.

"It depends on how many times per day, some antibiotics has the advantage that it can be taken twice per day, parents forget about the doses if it is more than that." (GP5)

Table 3.1. Reported antibiotic acceptability issues detailing antibiotics and brands where mentioned.

Antibiotic	**Brands Mentioned**	**Acceptability issues**
Flucloxacillin	No brand mentioned	Taste, smell, frequency
Clarithromycin	Klacid®	Texture
Phenoxymethylpenicillin	Calvapen®	Flavour*, texture
Trimethoprim	No brand mentioned	Taste
Co-amoxiclav	Augmentin®	Flavour
Azithromycin	Zithromax®	Flavour, texture
Cephalexin	Keflex®	Taste
Amoxicillin	Pinamox®	Flavour

* Flavour is the combined perception of mouthfeel, texture, taste and smell.

3.3.4 Theme 2: Impact of prescribing or dispensing poorly palatable oral liquid antibiotics

The second main theme was the impact of prescribing or dispensing poorly palatable oral liquid antibiotics. This encompassed two sub-themes: patient impact, and health system impact.

3.3.4.1 Subtheme: Patient impact

The patient impact subtheme explored the impact on children and their parents of prescribing and dispensing practices relating to unpalatable oral liquid antibiotics. This included parents' attempt to overcome palatability issues, administration of inaccurate doses, and stress at home.

3.3.4.1.1 Parents' attempt to overcome palatability issues

Lack of parent counselling about how to administer a poorly palatable antibiotic to their child in a safe manner can cause the parents to use unlicensed dose manipulation practices. Participants reported that poor palatability can lead to unlicensed manipulation of the antibiotic by parents by mixing the dose with food or drink. Examples were given by participants of particularly challenging situations that they encountered. Examples include a participant who reported that a grandmother intended to use nebulizers to give an oral antibiotic formulation to a child because of its poor palatability. Another example was participant who stated that a parent misled her by saying that their child had a penicillin allergy in order to avoid taking an unpalatable antibiotic they have been dispensed before. Participants believed that it is important to discuss palatability with parents to build a trust relationship with the parents as these examples show.

"I had a scary thing recently actually, that there was a grandmother of the child. She was looking at nebulizers and it turned out when I was talking to her then that she was going to try and put the liquid

antibiotic into the nebulizer and see if she could give the antibiotic to the child that way, because the child just wouldn't take the antibiotic..” (Ph10)

“The mom also told me she had a penicillin allergy. So, the choice is then very limited, and then the doctor said oh no, they [the child] actually don't have penicillin allergy, they just don't like the taste of all the penicillin ones. …. then I told the mom that there's almost nothing left on the shelf besides penicillin antibiotics. Then the mom was like, well, she's not really allergic. She's …. got the pink one last time and the pink one was just horrible. She doesn't want the pink one again, do you have another colour? So, I just went to the shelf and looked at the colours of them and I was like, yeah, I have a yellow and a white one and the doctor on the phone said, yeah, perfect one of them. This is just such a bad way of deciding what antibiotic to give someone, but they were happy.” (Ph12)

3.3.4.1.2 Inaccurate dose

Participants reported that parents manipulating antibiotics because of poor palatability could lead to administration of an underdose. Parents try to disguise either the consistency or the flavour of the original product. They thought it is better to try and give the child part of the dose rather than taking nothing at all.

“I suppose if the parent is mixing it with a bit of whatever it might be, you kind of feel they would take little. They might not get the full dose.” (Ph3)

3.3.4.1.3 Stress at home

Participants reported that parents sometimes want to give their child the antibiotic by forcing it into the child. Forcing a child to take a poorly palatable oral liquid antibiotic can cause stress at home. Participants described that a parent’s job is so much more difficult when the antibiotic is unpalatable. A pharmacist reported that her own children have to be held down by her husband in order to give them some of the antibiotic dose.

“I've just finished a course of Pinamox® [amoxicillin] with them, where they roared and screamed no for the yellow one and for the course of the antibiotic. I've had to get my husband to catch and hold of

one of them and it's like trying to dose a calf. So yeah, it's not easy. I think from a psychological point of view for kids, it's not great that they have to be held down nearly to have an antibiotic." (Ph1)

3.3.4.2 Subtheme: Health system impact

This subtheme explored the influence of prescribing and dispensing unpalatable oral liquid antibiotics on the health system. This comprised antimicrobial resistance and increased wastage.

3.3.4.2.1 Antimicrobial resistance

Participants reported that they are trying to follow the clinical guidelines to avoid contributing to antimicrobial resistance. However, poor palatability can cause them to select a non-first line antibiotic to make sure that the child will take it.

"Kids especially kids who'd have special needs, their parent would want daily dosing antibiotic. I do have a patient where the doctor will give Klacid® [clarithromycin] because it will be a smaller quantity and you'll be able to get it into them easier which isn't great for antibiotic resistance, but it just comes down to palatability. You just have to stand your ground when it comes to that situation with the way that everything is coming now with antibiotic resistance and that it's going to come to the stage where nothing is going to work if we give in to my patients. It's not a sweet chocolate. You go with the guidelines for a reason." (Ph1)

3.3.4.2.2 Increased wastage

Participants informed that poor palatability of oral liquid antibiotics can increase wastage when the parents asked for a different antibiotic. Parents would recognize the antibiotic once reconstituted based on their previous experience. However, sometimes they ask for alternative after trying it and before completing the antibiotic course. In all cases, the unused antibiotic has to be disposed of in the pharmacy.

"You'd have something to dispense, and then you bring it out to the parents, they would then tell you we don't want this one because the child doesn't like the taste. That is something that happened. Maybe it's something we should consider earlier on in the process of dispensing rather than later, so

that it doesn't come to the point where the antibiotic is made-up ready to go on the fridge. It might need to be a little bit earlier rather than one of the last things I would consider." (Ph4)

3.3.5 Theme 3: Suggestions to overcome challenges

The third theme was suggestions to overcome challenges. This included two sub-themes: counselling parents while prescribing and before dispensing the antibiotic and increasing awareness of antibiotic palatability among health care professionals.

3.3.5.1 Subtheme: Discussion with parents while prescribing and before dispensing

Participants highlighted the importance of increasing parental awareness about the reasons for selecting the first line antibiotic and encourage the parent to attempt to administer it to the child. They emphasised that it is crucial to discuss palatability issues with parents during prescribing and before dispensing to avoid non-disclosure and unlicensed manipulation practices by parents. This could be accomplished by counselling parents and supporting them through the provision of advice about safe and effective methods of administration. Pharmacists reported that they provide syringes to place the dose into the side of the child's mouth to get rid of the dose very quickly instead of a spoon that washes the dose around the mouth. Some participants reported that they advise parents to bribe the children and give them a reward after taking a dose. However, participants preferred provision of approved information on manipulation techniques by including such information in the patient information leaflet. Participants would also welcome guidelines on counselling parents on administering unpalatable oral liquid antibiotics. Furthermore, many participants reported that parents referred to an antibiotic by its colour, rather than by the drug or product name, a practice that can create a barrier to effective communication about the antibiotic.

"Parents associate antibiotics with the colour to find out if what they're getting this time is the same as what they got last time." (Ph7)

"At least knowing what the flavour is of an oral liquid antibiotic for a child and knowing the colour and knowing the consistency of it and perhaps before reconstituting the antibiotic to ask the parents or the person collecting the medicine, you know, this is the one we have in stock, it's a suspension, it's yellow in colour, it is lemon flavoured. Is that OK to dispense for the child. So, they perhaps will be additional questions to be added to the checklist before dispensing." (Ph11)

3.3.5.2 Subtheme: Increasing awareness of palatability among healthcare professionals

Many participants reported that they have never tasted an oral liquid antibiotic themselves. There is a lack of knowledge about antibiotic palatability issues in both professions, in particular a lack of flavour awareness among GPs. Therefore, it important to increase their awareness about this issue to be able to support parents.

"I have no idea what it tastes like" (Ph12)

"I don't know what is the pink one. What is the yellow one? What is the white one? I'm not really familiar with them" (GP6)

3.4 Discussion

Through qualitative interviews with pharmacists and GPs, the key findings of this study identify specific challenges related to prescribing and dispensing poorly palatable oral liquid antibiotics, and the impact of these challenges on both patients and the healthcare system. The study findings also provide healthcare professionals suggestions for overcoming these challenges. These findings build upon earlier studies focused on physicians' perceptions of prescribing inappropriate antibiotics based on parents' expectations (Barden et al., 1998; Biezen et al., 2019; Mangione-Smith et al., 2006) by focusing on the impact of antibiotic poor palatability. The findings also expand on prior studies which identified antibiotics with poor palatability (Klingmann

et al., 2023; Steele et al., 1997) exploring the impact of poor palatability on prescribing or dispensing practices, and related patient and health system impacts.

Clinical guidelines, availability of antibiotics, and age, weight, and allergy status of the child were the main factors affecting the choice of antibiotics for children by both professions. However, the type of infection, lack of alternatives, and allergy influence healthcare professionals to select an oral liquid antibiotic with poor palatability. In the present study penicillin allergy was highlighted as a factor that could limit choice of antibiotics. It was reported in previous studies that patients, both adults and children, with a medical history of penicillin allergy had increased risk of receiving broad-spectrum antibiotics compared to non-penicillin allergic patients (Dijk et al., 2014; Lee et al., 2000; Sade et al., 2003). In the current study, clarithromycin was reported as an appropriate alternative antibiotic in the case of penicillin allergy. However, the study also revealed that some oral liquid formulations of clarithromycin are unpalatable for children because of a grainy texture. This issue was reported in a previous study (Steele et al., 1997).

Formulation factors that affect paediatric acceptability of oral liquid antibiotics identified in this study were reported to be frequency of administration, dose volume, and palatability. Likewise, Liu at al. reported that the acceptability of oral liquid formulations was directly influenced by the same factors (Liu et al., 2014). Flucloxacillin was highlighted as an unacceptable oral liquid antibiotic in the present study because of its poor taste, unpleasant smell, and high dose frequency. Likewise, Venables *et al*. reported the unacceptable taste and smell of flucloxacillin (Venables, Stirling, et al., 2015). Lack of palatable oral liquid antibiotic alternatives confined healthcare professionals' selection of antibiotics. Although oral liquid dosage form is the preferred formulation among young children, there is a lack of availability of

palatable options (Matsui, 2007). Klingmann et al. reported the lack of appropriate antibiotic formulations for use in hospitalised children (Klingmann et al., 2023) and Ventola has highlighted that the lack new antibiotics developed in recent years has limited the antibiotic options available to treat bacterial infection (Ventola, 2015). However, the current study highlights how the shortage of paediatric antibiotic formulations leads to manipulating solid dosage form into liquid dosage form for children. This manipulation can affect dose accuracy (Richey et al., 2013). The European Medicines Agency highlighted the need for age-appropriate medicines for children (Dunne, 2007).

This study highlights the differences between GPs, pharmacists, and parents' experiences regarding oral liquid antibiotics knowledge. Parents often associate antibiotics by the colour of the formulation. However, GPs reported that they are unfamiliar with antibiotic product colour or are only aware through parent comments. Although pharmacists know the colour of different antibiotics, both professions reported that they have never tasted the antibiotic formulations. Similarly, Peña et al reported that prescribers hav limited knowledge regarding paediatric liquid medications with bad tasting (Peña et al., 2024). Additionally, Bradshaw *et al*. reported that a tasting test of liquid formulations changed physicians' prescribing preferences for some infectious conditions (Bradshaw et al., 2016). The physicians in that study switched from prescribing amoxicillin to cefdinir for otitis media and from azithromycin to amoxicillin for pneumonia. Raising awareness of formulation characteristics such as taste, smell, texture, and colour of different antibiotic formulations is needed among healthcare professionals to be able to select the most appropriate formulation for each child. The current study emphasizes the need of updates in prescribing and dispensing guidelines as well as including training

programmes for both GPs and pharmacists with a particular focus on understanding the challenges around oral liquid antibiotic palatability for paediatric patients. Training provision can highlight how poor palatability can influence treatment adherence and the potential clinical repercussions of non-completion of treatments, including antimicrobial resistance.

Non-adherence to antibiotic treatment because of poor palatability can lead to switching to a more palatable antibiotic which is typically a more broad-spectrum antibiotic (Ramgoolam & Steele, 2002).The findings of this study highlight that the poor palatability of oral liquid antibiotics can lead to prescribing a non-first line antibiotic which could contribute to antimicrobial resistance. Additionally, non-adherence to antibiotic treatment due palatability could also lead to an increase in the development of antimicrobial-resistance (Alexander et al., 2008; Kandrotaite et al., 2013; Segador et al., 2005). Antimicrobial resistance is a global problem that threatens global public population (Mendelson & Matsoso, 2015; Shallcross & Davies, 2014; WHO, 2015). Therefore, there is a need to improve adherence to regimes of oral first-line antibiotic formulations by improving their palatability.

The study findings revealed that oral liquid antibiotics poor palatability can lead to unlicensed manipulation by parents and the administration of inaccurate dose. Participants in this study reported that parents manipulate poorly palatable antibiotics through mixing the required dose with food or drink. However, unlicensed manipulation can affect stability, efficacy and bioavailability of medicines and should be avoided (Venables, Batchelor, et al., 2015). The current study identified the need for pharmacists to discuss and give suitable administration advice to parents based on the specific characteristics of each dispensed antibiotic formulation, its palatability and its associated challenges prior to dispensing. This may help to avoid manipulation

of doses and non-disclosure of unlicenced dosing practices by parents. The current study asserted the need for the development of manipulation guidelines for paediatric medicines by authorities such as medicines and healthcare regulators. This finding aligns with earlier research (Richey et al., 2013).

The current study highlighted that GPs and pharmacists avoid discussion with parents about oral liquid antibiotic palatability. Such lack of discussion with parents was similarly highlighted in previous studies (Barden et al., 1998; Biezen et al., 2019). Barden et al. conducted a focus group study with parents and physicians to study their perceptions about antibiotic use (Barden et al., 1998). The study reported that lack of discussion with parents was a reason for antibiotic overuse. The physicians in the study reported that prescribing antibiotics was influenced by their perception that parents expected to receive an antibiotic prescription during the medical visit. However, parents revealed that they would be satisfied if the physician explained the reasons for not prescribing an antibiotic. Similarly, Mangione et al.'s cross-sectional study to examine the relationships between physician and parents revealed that a communication gap between physicians and parents increases physicians' perceptions that antibiotics are expected by parents and leads to inappropriate antibiotic prescribing (Mangione-Smith et al., 2006). Counselling guidelines are needed to improve communication between healthcare professionals and parents about antibiotic usage and in particular about include information regarding oral liquid antibiotic palatability.

Conversation with parents about palatability, as well as the importance of receiving the first-choice antibiotic during prescribing and before dispensing, were identified as approaches that may improve adherence to the antibiotic treatment. Participants reported parents negotiate regarding palatability with both professions by asking for

an alternative antibiotic if they struggled to administer a previous antibiotic to the child. They might also ask for an alternative even before completing the antibiotic course. Previous studies report that deviation from clinical guidelines by GPs or switching between antibiotic brands by pharmacists because of poor palatability was often based on parents' requests (Bergene et al., 2019). Incomplete antibiotic treatment because of poor palatability increases medicines wastage. The current study revealed that providing parent with information regarding the colour and flavour of the selected antibiotic before reconstitution could decrease wastage by avoiding switching antibiotic brands after the initial formulation being reconstituted. Bergene and colleagues have previously recommended that discussion with parents about availability of different formulations would lead to dispensing the most suitable antibiotic product for every child (Bergene et al., 2019). Proactive dialogue discussing antibiotic palatability with parents and carers during the prescribing process and prior to dispensing can reinforce parents and carers' understanding of the importance of following the prescribed treatment, despite potential palatability issues, and minimise switching from first choice antibiotics treatments.

In summary study findings highlight a need to develop more palatable oral liquid formulations of the first-line antibiotics. It is envisaged that developing more palatable oral liquid antibiotics, either through flavouring, texture enhancement or innovative formulation approaches such as minitablets, will contribute significantly to improving paediatric treatment adherence. Future studies are suggested to investigate the acceptability of different formulation approaches, as well as the evaluation of education and training strategies to overcome barriers related to palatability in different social and cultural contexts.

3.5 Strengths and limitations

This qualitative study included interviews with both GPs and pharmacists. The research team included members of both professions. Six participants were parents themselves who provided their experience as healthcare professionals as well as parents. A strength of the study was the broad range of years of experience of participants, ranging from 2 to 27 years with an average experience of 11 years, which provided the views and experiences of a diverse representation of practitioners. While the participants with more years of experience have more experience of this topic, those with less experience brought a fresh perspective to the problem. The study was limited to exploring palatability issues from the experience of GPs and pharmacists. Based on the findings of this study, a follow on study with other primary and secondary care health professionals, parents, and children would be worthwhile to determine how the themes identified relate to their experiences.

A limitation of the study was the lower number of GP participants, almost half the number of pharmacists. The reason for the lower GP number can be related to the overall difficulty in engaging GPs in research internationally despite their critical role in extending knowledge and translating new information into practice (Hummers-Pradier et al., 2008; Sahin et al., 2014; Salmon et al., 2007). Despite the relatively small GP sample size, a range of clear views were obtained from which it was possible to identify valuable themes. After 18 interviews, two further interviews were conducted. The data saturation was reached when no new themes emerged. There may a perceived element of potential bias amongst volunteers recruited by research team's professional networks. However, as healthcare professionals describing experiences and challenges faced during routine practice this was not considered a significant limitation. Conducting the interviews via Microsoft Teams may have limited potential

participants from participating in the research. Limitations such as technical issues, planning, privacy and rapport related to the use of online video conferencing for conducting qualitative studies has been recently reported (Boland et al., 2022). However, for this study interviews were conducted via videoconferencing due to the advantages it offers in terms of convenience and time flexibility for the interviewees, with the ability to conduct interviews outside normal business hours. In general, interview studies may be subject to interviewer or social desirability biases. The study comprised semi-structured interviews to ensure adequate predictive validity. In addition, participants' willingness to share their experiences or perspectives can be impacted by the interviewer's communication style. To minimise these biases, the interviews were conducted by two members of the research team and samples of transcripts were independently reviewed and coded by three members of the research team.

Most of the participants were recruited by the research team's professional networks in the Cork region, which may limit the generalizability of the study, however many findings are supported by the broader literature.

3.6 Conclusion

There is a need to increase palatability awareness among healthcare professionals and parents of children prescribed oral liquid antibiotics. Raising palatability awareness among healthcare professionals will enable them to deliver appropriate counselling to parents. Discussion with parents about palatability and the importance of receiving the first-choice antibiotic should occur during prescribing and before dispensing. This may decrease the wastage through avoiding switching antibiotic brands after reconstitution. The development of more palatable antibiotic formulations, either

through flavour or texture enhancement or innovative formulations such as minitablets, may play a role in improving medicine taking practices in children.

Chapter 4
Flucloxacillin formulation odour acceptability: a human sensory assessment

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Contribution: As lead author, I applied for the ethical approval to conduct the study. I was responsible for writing the paper and developing the draft protocol that was finalized afterwards with the co-authors. I recruited all the volunteer participants for the study, prepared the samples that were assessed, and organized the study steps. The study was then conducted in collaboration with the co-authors. I collected and analysed the data that was subsequently revised and finalised with the co-authors.

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The section numbers, figures, tables,and references style has been adapted to conform to the style and numbering of the thesis.

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4 Chapter 4

4.1 Introduction

Palatability is a key element influencing paediatric medicine acceptability as highlighted in the European Medicine Agency's guideline on pharmaceutical medicines for paediatric use (EMA, 2013). Palatability is a key consideration to ensure medication adherence and effective treatment when prescribing oral antibiotics for children (Baguley et al., 2012). Poor palatability was reported as one of the main reasons for non-adherence in an interview study conducted with 815 carers of children aged less than 18 years prescribed oral antibiotics (Patel et al., 2022).

Flucloxacillin, a widely prescribed oral antibiotic for paediatric indications, is reported as an unpalatable antibiotic for paediatric patients. Rouse et al. investigated difficulties associated with administration of different brands of oral liquid flucloxacillin to children because of their poor palatability (Rouse et al., 2017). The study reported a significant relationship between the concentration of flucloxacillin and the number of doses administered successfully. All flucloxacillin products in the study were reported as problematic, with some brands associated with fewer administration issues, however formulation characteristics associated with administration difficulties were not identified. A review by Baguley et al. identified flucloxacillin's poor palatability and recommended it should not be prescribed as oral liquid formulation without prior 'taste testing' by the child (Baguley et al., 2012).

Flucloxacillin's poor palatability was related to its taste in a focus group study conducted by Venables et al. with nurses, medical practitioners and pharmacists (Venables, Stirling, et al., 2015). However, pharmacists and primary care doctors reported that flucloxacillin's malodour was also a contributing factor to its poor palatability in chapter 2 and 3 herein. To our knowledge, studies in chapter 2 and 3

were the first studies to report the malodour of flucloxacillin, despite this being known anecdotally for some time. Odour not only influences a patient's perception of a medicine's acceptability prior to ingestion, it is also the main contributing sense to the determination of a substance's flavour (Spence, 2015). Despite, the contributary role odour can play in a medicine's overall palatability and acceptability, research into the role drug product odour plays in drug product acceptability has been somewhat neglected to date.

Flucloxacillin is an isoxazolyl semi-synthetic penicillin of the β -lactam group of antibiotics (Figure 4.1). Oral liquid flucloxacillin can be formulated as either powder for oral solution that contains flucloxacillin as flucloxacillin sodium or powder for oral suspension that contains flucloxacillin as flucloxacillin magnesium. According to the European Pharmacopoeia, flucloxacillin sodium is freely soluble in water whereas flucloxacillin magnesium is slightly soluble in water (Pharmacopoeia Eur, 2022). The aim of this study was to evaluate the influence of formulation approaches on odour acceptability using human adult volunteers. The initial aim was to assess the odour of flucloxacillin solution compared to flucloxacillin suspension. However, there was a shortage of flucloxacillin suspension and its salt in Ireland and UK. Therefore, the study assessed commercially available formulations and novel flucloxacillin formulations. The commercial flucloxacillin formulations assessed included an oral liquid solution and a hard gelatin capsule. Oral liquid formulations are reported as the most preferred dosage form among children because of their ease in swallowing and dose adjustment (Ali et al., 2014; Nunn & Williams, 2005). However, use of liquid formulations in paediatric populations can be challenging due to concerns related to palatability, dose volume, and the accurate dose measurement (Batchelor & Marriott, 2015a). Hard gelatin capsule formulations have the advantage of having better

palatability and dose accuracy. However, the fixed dose content and swallowing difficulty due to capsule size and format are challenging for paediatric patients (Khan et al., 2022). Novel minitablet flucloxacillin formulations were also assessed in this study.

A minitablet is a tablet with a diameter equal to or less than 4 mm (van Riet-Nales et al., 2016). The minitablets format has the advantages of both liquid and solid dosage forms with dose flexibility, and better swallowability for paediatric populations (O'Brien et al., 2019). The swallowability of minitablets was reported to be acceptable among children aged 6 months and above (Mitsui et al., 2022; Münch et al., 2023). Mesoporous silica was added as an excipient to the minitablets to investigate its potential to suppress flucloxacillin's malodour because of its high adsorptive capacity. Silica has the capability to adsorb volatile compounds because of large surface area and pores (Hou et al., 2004). This adsorption is based on the amount of volatile compounds entering the pores of silica particle (Cosseron et al., 2013; Ncube & Su, 2012). Silica is widely used in pharmaceutical formulations mainly as a flow aid (*Pharmaceutical Excipients, Mesoporous Silica (MPS)*, 2024). However, to our knowledge this is the first reported inclusion of silica in pharmaceutical formulations specifically as an odour suppressant.

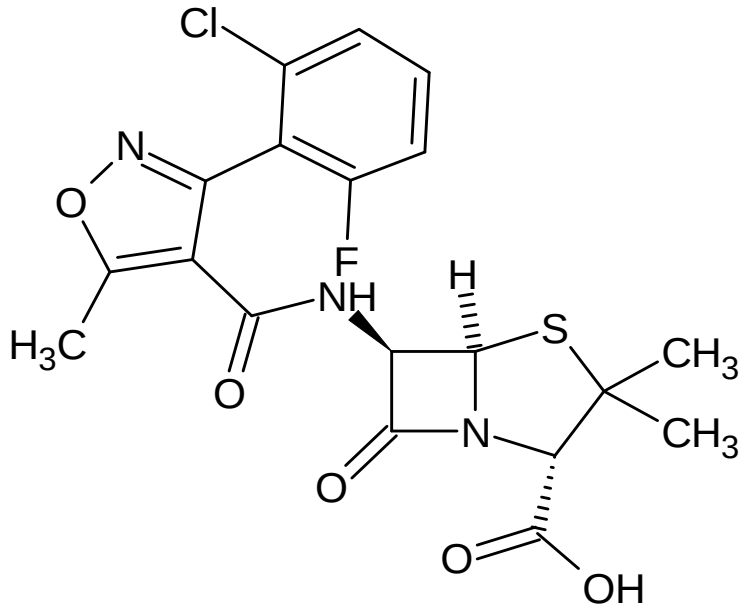

Figure 4.1. Flucloxacillin chemical structure

4.2 Materials and Methods

4.2.1 Materials

Flucloxacillin sodium drug substance was supplied by Molekula Ltd, UK. Commercial formulations, Athlone Laboratories Flucloxacillin 250mg/5ml Oral Solution® and 250mg Capsules® were supplied by a local community pharmacy. PROSOLV® EASYtab SP LM was donated by JRS Pharma GMBH, Germany. Parteck® SLC 500 was donated by Merck Life Science Ltd., Ireland. 8-item Sensonics™ test kit were obtained from Sense Trading B.V. MediSense, Netherlands.

4.2.2 Flucloxacillin Formulations Assessed

The odour acceptability of 4 flucloxacillin formulations and an unformulated aqueous flucloxacillin solution, as a control, were assessed. Each preparation contained 250 mg flucloxacillin, the recommended oral dose for 1- to 4-year-old children. Formulations assessed for odour acceptability were (i) 5 ml of Flucloxacillin 250mg/5ml Oral Solution®, Athlone Laboratories Ltd, (ii) Flucloxacillin 250mg

Capsules®, Athlone Laboratories Ltd, (iii) 250 mg flucloxacillin contained in thirteen 4 mm minitablets, and (iv) 250 mg flucloxacillin contained in thirteen 4 mm minitablets with silica for evaluation as an odour suppressant excipient. **Table 4.1** details the composition of all flucloxacillin preparations assessed.

The commercial flucloxacillin solution was prepared by adding 58 ml of deionised water to reconstitute the dry powder to a final volume of 100 ml and concentration of 250mg/ 5ml as per manufacturers instruction. The aqueous flucloxacillin solution was prepared by dissolving flucloxacillin sodium in 20 ml of deionised water to a final concentration of 250mg/5 ml. Minitablets were manufactured as described below.

4.2.3 Flucloxacillin minitablet manufacture and characterisation

Minitablets were prepared by blending the flucloxacillin sodium with PROSOLV® EASYtab SP LM to produce a total weight of 20 g. Powders were blended in a 100 ml volume plastic container attached to the stainless-steel rods of the Cube Mixer KB attached to an AR 403 Multipurpose drive (Erweka GMBH, Germany) at 40 rpm for 30 minutes. Mintablets were compressed manually using a Fette® E1 Single Punch Tablet Press, Fette Compacting GmbH, Germany using a 4 mm round concave punch and die set supplied by I Holland, UK. The target weight of each minitablet was 40 mg ± 2 containing a theoretical 19 mg ± 1 of flucloxacillin as flucloxacillin sodium. The actual weight, percentage dose and hardness of minitablets produced with and without silica was confirmed and data is available in **Supplementary Table S4.1**. Flucloxacillin dose was confirmed by UV spectrometric analysis (Unicam, UK). All minitablets were compacted to a hardness of 85 ± 1.8 N, which was confirmed by hardness testing using a Erweka TBH 220 Hardness Tester, Germany.

The study initially investigated minitablets containing four different concentrations of 90%, 80%, 70% and 50% of the API, flucloxacillin sodium, mixed with PROSOLV® EASYtab SP LM excipients. Minitablets containing 90%, 80%, and 70% of API were very fragile with cracks on their final shape **Figure 4.2**. However, minitablets with 50% of flucloxacillin sodium were selected for manufacturing because of their ideal shiny appearance that was free of any defects such as chips and cracks with sufficient strength to be used.

Additionally, the percentage of silica was optimized to 5% in minitablets with silica formulation based on a pilot study conducted with two human adult volunteers assessed the smell of three preparation of flucloxacillin powder mixed with 2%, 3%, and 5% of silica. The volunteers in the pilot study reported that the mixture containing 2% and 3% of silica had very faint odour. However, the mixture containing 5% was completely odourless.

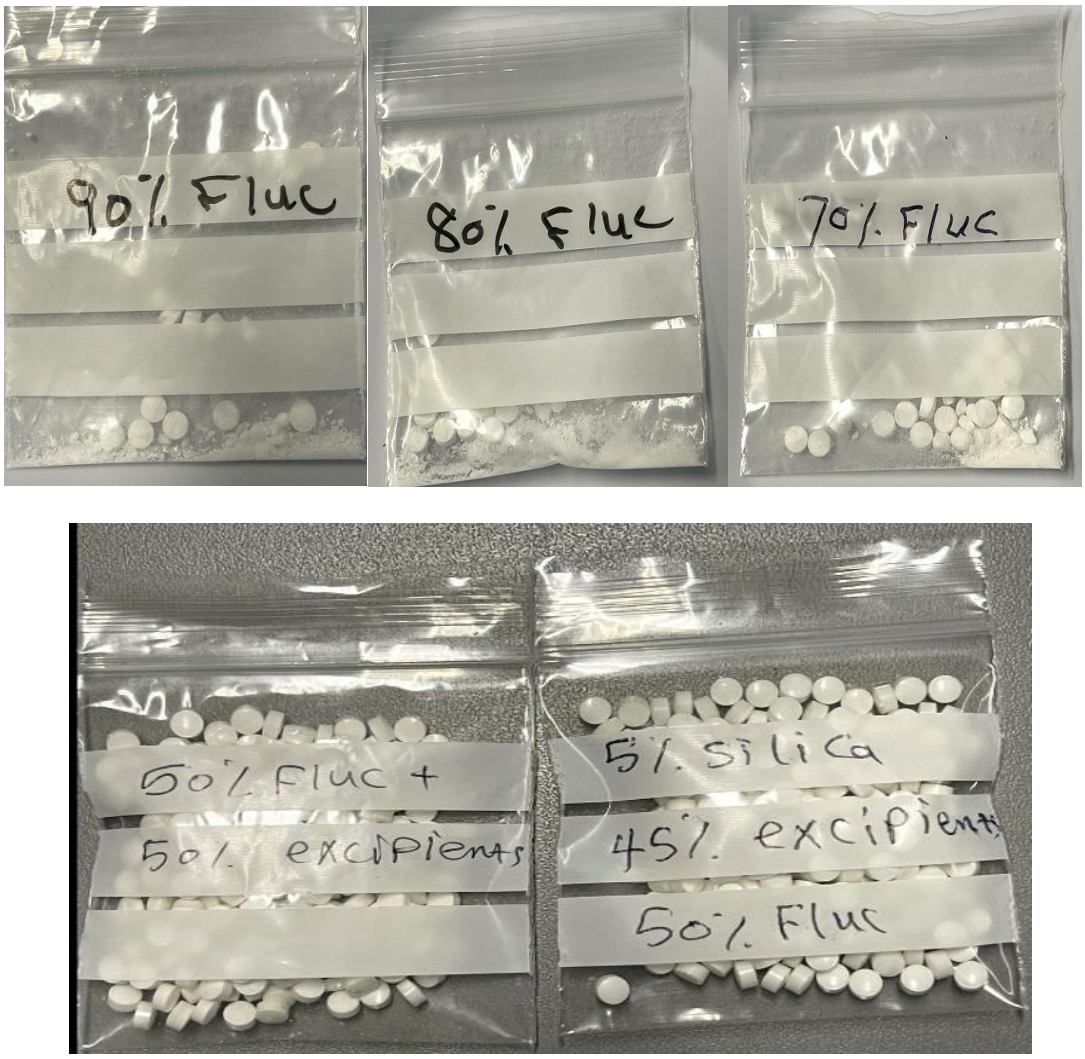

Figure 4.2. Minitablets containing four different concentrations of 90%, 80%, 70% and 50% flucloxacillin

Table 4.1. Composition of flucloxacillin preparations assessed for odour acceptability

Investigational products	Composition	Quantity per dose assessed
Aqueous flucloxacillin solution 250 mg/5 ml	Flucloxacillin sodium Deionised water	272 mg Up to 5 ml
Commercial flucloxacillin solution 250 mg/5 ml	Flucloxacillin sodium Sucrose Sodium benzoate Disodium edetate, saccharin sodium, ammonium glycyrrhizinate, sodium citrate anhydrous, pineapple flavour, menthol flavour, erythrosine	272 mg 2.96 g 5 mg Not disclosed
Commercial flucloxacillin 250 mg capsule	Flucloxacillin sodium Capsule content: Sodium starch glycolate, Magnesium stearate Capsule shell: Gelatin, Black iron oxide, red iron oxide, titanium dioxide, yellow iron oxide	272 mg Not disclosed
Minitablets 250 mg without silica (n=13)	Flucloxacillin sodium PROSOLV® EASYtab SP LM (microcrystalline cellulose, colloidal silicon dioxide, sodium starch glycolate, sodium stearyl fumarate)	272 mg 250 mg
Minitablets 250 mg with silica (n=13)	Flucloxacillin sodium PROSOLV® EASYtab SP LM (microcrystalline cellulose, colloidal silicon dioxide, sodium starch glycolate, sodium stearyl fumarate) Parteck® SLC 500 (non-ordered mesoporous silica)	272 mg 225 mg 25 mg

4.2.4 Ethical Approval

Ethical approval to conduct this odour assessment study was granted by the Clinical Research Ethics Committee of the Cork Teaching Hospitals (CREC), reference number ECM4(n)06/02/2024 and ECM3(p)05/03/2024.

4.2.5 Human sensory study design considerations

To our knowledge, the sensory study conducted to assess flucloxacillin formulation odour acceptability was one of the first reported. Therefore, it is worth discussing some of the study design considerations. One of the key aspects was ensuring that volunteers were well informed regarding the nature of the study and their responsibilities. Volunteers were recruited by direct advertising to the public. The advertisement was also shared by members of the study team via online social networking sites such as WhatsApp. Emails were sent to the UCC staff, and students asking for volunteer panels. The participant information sheet and informed consent document were emailed to each person who responded to the adverts. All potential volunteers were then contacted individually by phone or via the online meeting platform Microsoft Teams prior to being invited to the study site. At the study site, a member of the research team provided potential volunteers with in-depth information about the study, its purpose, expected duration, study steps, and the benefits and risks involved in study participation. Volunteers were given plenty of time at this visit to read the participant information sheet and had the opportunity to ask questions. The volunteer participants were then asked to sign an informed consent form before entering the study procedures.

To avoid any possible disturbances in their own perception or the perception of other participants, volunteers were asked to limit the use of cosmetics (perfumes, creams, deodorants) with intense odours on the day of the assessment session. They were asked not to eat, drink (with the exception of water) or use chewing gum 30 minutes before and during the sensory assessment, and not to attend with a cold or flu that may affect the sense of smell on the day of assessment.

The area where the study was conducted was free from any strong odours to avoid stimulating the smell sense of the participants. The area was set up so that volunteers worked separately to one another and focused on their task as provided by a member of the research team. Noise and distractions were avoided in the assessment area to avoid breaking the focus of the participant. The waiting area of the participants was separated from the assessment area to ensure a relaxing and comfortable waiting time with a low stress environment for the participants.

Medical screening was performed prior to conducting the study to ensure that only healthy volunteers were enrolled in the study and avoid any risk to the health of volunteers. A registered healthcare practitioner conducted a one-by-one medical screening. Commercial urinalysis and pregnancy test kits provided quick screening. Excluding volunteers who had any significant ongoing medical problems can avoid jeopardizing the safety of the volunteer. For this study exclusion criteria included volunteers who had penicillin allergy, and/or those with a previous history of flucloxacillin-associated jaundice/hepatic dysfunction.

4.2.6 Odour Assessment Study Design

The study was carried out by a panel of adult healthy volunteers. The study protocol is available in Supplementary Material **7.3**. All samples were presented in 20 ml amber plastic medicine containers. Photographs are included in Supplementary Material **Figure S4.1**. Samples of individual preparation from the sample set were organized for each volunteer. Each sample was coded with a random three letter code. All preparations were given to the volunteers singularly. The order of sample presentation to volunteers was randomized to prevent biasing effects of the order of sample presentation. A randomized block design was used to minimize bias in the assignment of sample presentation order to volunteers. The 40 volunteers were divided into blocks

of 5 volunteers (8 blocks in total). Each flucloxacillin preparation was assigned and labelled with three-letter random code which remained consistent for that preparation throughout the study. The randomization order of flucloxacillin samples with associated codes are provided in **Supplementary Material Table S4.2**. The unformulated aqueous flucloxacillin solution and the reconstituted commercial Flucloxacillin 250mg/5ml Oral Solution® were prepared fresh each study day. Flucloxacillin minitablets were stored in the fridge at temperature 2-8°C. Volunteers were asked to complete two questions for each sample assessed. The first question was to rate the smell acceptability of each sample using a 10 cm visual analogue scale (VAS) marked with 0 ("extremely unacceptable"; left hand end) to 10 ("extremely acceptable"; right hand end). Any score below 5 was rated as 'unacceptable', a score of 5 was rated as neither acceptable or unacceptable, and any score above 5 was rated as 'acceptable'.

The second question was to describe the smell of the sample by selecting descriptors from a list of possible descriptors with definitions. A pilot odour assessment of the test items was conducted by a panel of 6 volunteers (external to the main study 40 volunteers) to determine the list of descriptors to be used in the study. These odour descriptors were selected from volunteers describing the odour in their own words and then refining the description using a cross-product aroma wheel from the DLG basic vocabulary related to an ISO standard for sensory analysis (*ISO 8586, 2012*). The descriptors list included aromatic (i.e., having a pleasant and distinctive smell), pungent (i.e., having a sharply strong smell), plastic (i.e., having a burning plastic smell), musty (i.e., having a stale, mouldy, or damp smell), rotten (i.e., having an extremely unpleasant smell), fruity (i.e., having fruit smell), with the option for the volunteer to select 'other' and describe. Volunteers had the option to select one or more

answers. Volunteers completed the smell questionnaire privately to avoid biasing of their response by other volunteers' comments. Volunteers were familiarized with the smell questionnaire and were trained on how to carry out the smell test in advance of assessing the preparations. A research team member clarified the questionnaire individually to each participant. A video explaining how to carry out the smell test was showed to each participant. The video showed the participants how to pass the vial under their nose in a standardized and consistent manner to minimise variability between formulation assessment and how to sniff the elbow joint between sample assessments to neutralize the olfactory system. Also break of 5 min between smelling each sample was explained and monitored by a member of the research team during the study.

4.2.7 Volunteer Smell Acuity Assessment

Prior to assessing the acceptability of the flucloxacillin formulations, the volunteer's individual ability to smell was assessed using a validated commercial 8-item Sensonics™ smell test (MediSense). The volunteers were trained on how to use the smell kits before the sensory acuity assessment. Each volunteer was familiarized with scratching methodology and was asked to smell the released odour. Prior to smell acuity assessment, a second video explaining how to scratch the smell kit and smell the released odour was showed to each participant to ensure the reliability of the volunteers' responses. Volunteers were asked to identify the correct odour by selecting from the provided multiple-choice of odour descriptions.

This 8-item Sensonics™ smell test kit employed the validated 8 odourants that were used in the 2013-2014 U.S. National Health and Nutrition Examination Survey (NHANES) (U.S. Centers for Disease Control and Prevention, 2016). The 8-item Sensonics™ smell test is reported to be an efficient and brief test for evaluating smell

function (On et al., 2023). The test consists of eight odourants' strips to be scratched and sniffed. The test kit included 4 food-related odourants (chocolate, strawberry, grape and onion), two warning odourants (natural gas and smoke), and two common household odourants (leather and soap) which volunteers were asked to identify. The classification of volunteers as having normal ability to smell (normosmia), reduced ability to smell (microsmia), and full loss of smell (anosmia) depended on the number of odours correctly identified and their age. Classification was based on literature supplied with the kit and based on studied related to its development (Hoffman et al., 2016; On et al., 2023). Volunteers < 40 years correctly identifying 7 to 8 odours were classified as normosmic. Volunteers ≥ 40 years, correctly identifying 6 odours were also classified as normosmic. Volunteers < 40 years correctly identifying 4-6 odours, and those ≥ 40 years correctly identifying 4 or 5 odours, were classified as microsmic. All volunteers correctly identifying 0-3 odours were classified as anosmic.

4.2.8 Data Analysis

Data were presented as mean values and standard deviations (±SD). Sensory data were analyzed by categorizing the VAS scale continuous data to 3 points (0 - 5 = unacceptable, 5 = neither acceptable nor unacceptable, 5 – 10 = acceptable). Principal component analysis (PCA) was performed on descriptive sensory data using Origin Data Analysis Software (Version 2019b). The data was organised into a 2D matrix (m x n). Each row represented an odour descriptor, and each column represented one flucloxacillin sample. The data values indicated the number of each descriptor selected by the participants for each formulation sample. The biplot graph summarized the outcome of the PCA mapping flucloxacillin formulation characteristics based on descriptors of the samples.

4.3 Results

4.3.1 Volunteer demographics and smell acuity

Forty human volunteers were recruited for the study. The volunteer panel was composed of 28 females (70%) and 12 males (30%) aged from 19 to 67 years with a mean age of 36 years. Across sensory studies the sample number of assessors employed for sensory panels is varied. For this study we aimed to recruit 40 volunteers who met the inclusion criteria based on a recommended sample size of 40–100 to detect significant differences in consumer testing and a minimum of 5 for descriptive analysis (Gacula & Rutenbeck, 2006). The smell acuity assessment was conducted using the 8-item Sensonics™ test kit. The smell acuity testing found 25 volunteers (62%) had normal ability to smell (normosmia), 14 participants (35%) had a reduced ability to smell (microsmia), and 1 participant (3%) aged 67 years old had full loss of smell (anosmia). The odours that were least frequently identified were were grape (n=34), chocolate (n= 12), and leather (n= 8).

4.3.2 Flucloxacillin formulations' odour acceptability

Volunteers were asked to rate the smell acceptability of each formulation using a 10 cm visual analogue scale (VAS), with 0 (extremely unacceptable), 10 (extremely acceptable) and a score of 5 was rated as neither acceptable nor unacceptable. Any score above 5 was rated as acceptable and any below 5 was rated as unacceptable. The individual volunteers' rating for each formulation are shown in ***Figure 4.3***.

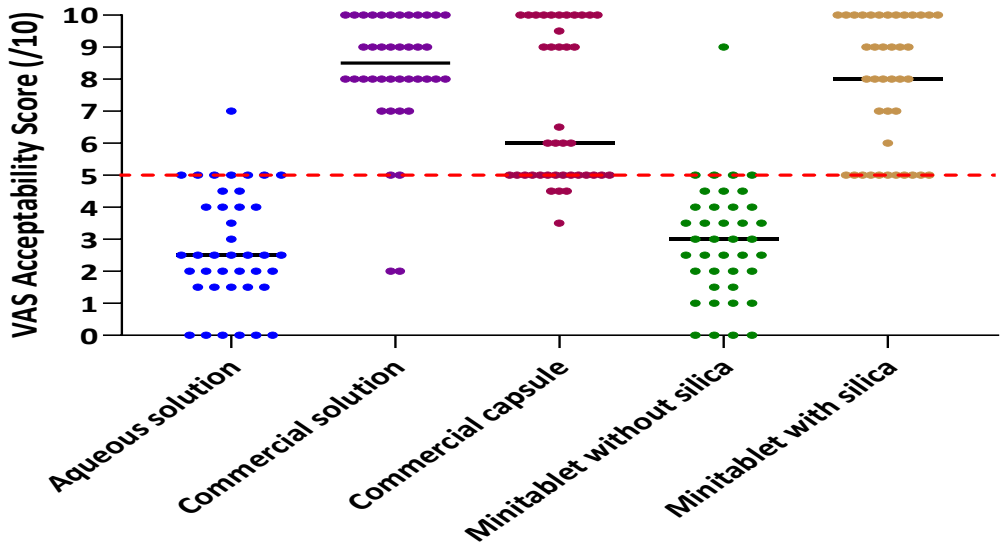

Figure 4.3. Individual volunteer's smell acceptability scores for flucloxacillin preparations assessed as shown in circles. The solid black line indicates the average acceptability score for each preparation. The red dashed line indicates score of 5 which represents that the sample was neither acceptable nor unacceptable. Any score above 5 was rated as acceptable and any score below 5 was rated as unacceptable

The minitablet formulation without silica has a mean acceptability rating of 2.9 (±1.8) which was similar to that of the unformulated flucloxacillin aqueous solution control 2.8 (±1.8). Both samples were deemed unacceptable. The formulated commercial solution, commercial capsule, and minitablets with silica were ranked as more acceptable formulations with a mean score of 8 (±1.9), 7 (±2.3), and 7.9 (±2) respectively. Subsequently, volunteers' acceptability rating responses were analysed based on the volunteer's smell acuity to probe the relationship between smell acuity and responses obtained, ***Figure 4.4***.

No statistical difference was noted in the smell acceptability rating of normosmia and microsmia volunteers for any of the flucloxacillin samples assessed ($p > 0.05$). However, the volunteer classified as anosmic rated the smell of all the samples as acceptable with scores of 7, 10, 10, 9, 10 for the aqueous solution control, commercial

solution, commercial capsule, minitablets, and minitablets with silica respectively. Notably, this participant rated the aqueous solution and minitablet (without silica) as more acceptable than the other participants, ***Figure 4.4***.

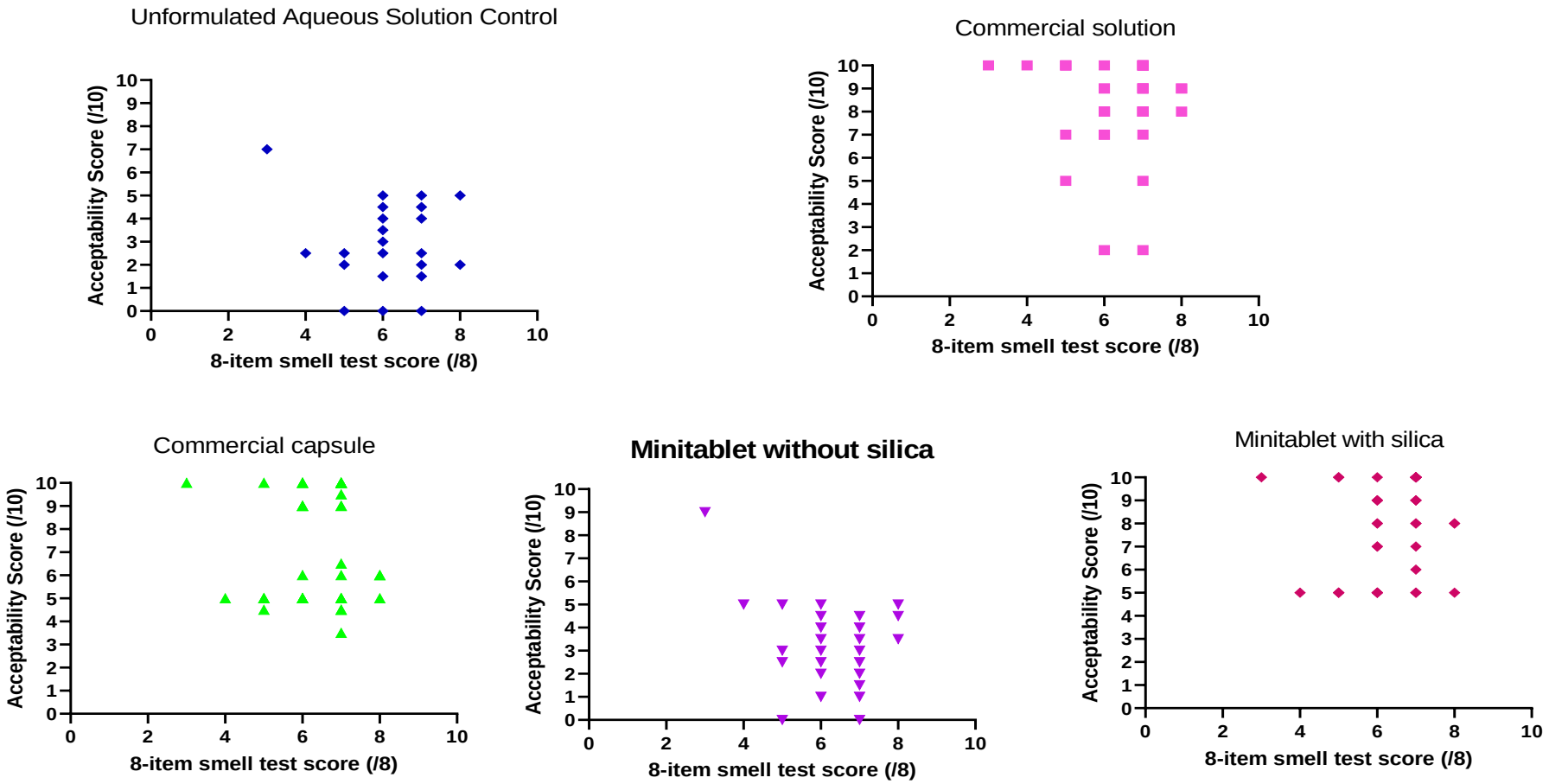

Figure 4.4. Individual volunteer's smell acceptability scores for flucloxacillin preparations assessed and plotted according to the volunteer's smell acuity score.

4.3.3 Flucloxacillin formulations' odour description

To better understand the odour attributes related to the flucloxacillin preparations' odour acceptability or unacceptability, volunteers were asked to select odour descriptors they associated with each preparation from a list of possible descriptors with the option for the volunteer to select 'other' and describe. To aid visualisation and analysis of the responses, principal component analysis (PCA) was performed. PCA has been previously employed in sensory studies to visualize the relationships among products and attributes. The resultant biplot is shown in **Figure 4.5**.

The flucloxacillin aqueous control solution and minitablets without silica grouped together in the right-hand side, while the commercial capsule, minitablets with silica and commercial liquid formulation grouped together in the left-hand side of the biplot. PCA analysis further discriminated, and the commercial liquid formulation from the commercial capsule and minitablets with silica. The total amount of variance explained by PC1 and PC2 is 96.1%, with PC1 and PC2 explaining 56.1 and 40%, respectively. The first principal component, PC1 (56.1%), was separated linked unacceptable smell attributes musty, pungent, plastic, and rotten from attributes more associated with acceptability, odourless, aromatic and fruity. The second principal component, PC2 (40%) further separated the odourless attribute from the aromatic and fruity descriptors. Overall, PCA separated the 5 samples into 3 clear groups with distinct attributes. The attributes "musty", "pungent", "plastic", "rotten" were key in describing both the flucloxacillin aqueous control solution and the minitablets, while "fruity", and "aromatic" descriptors were associated with the commercial liquid formulation. The commercial capsule and minitablets with silica were associated with the descriptor "odourless".

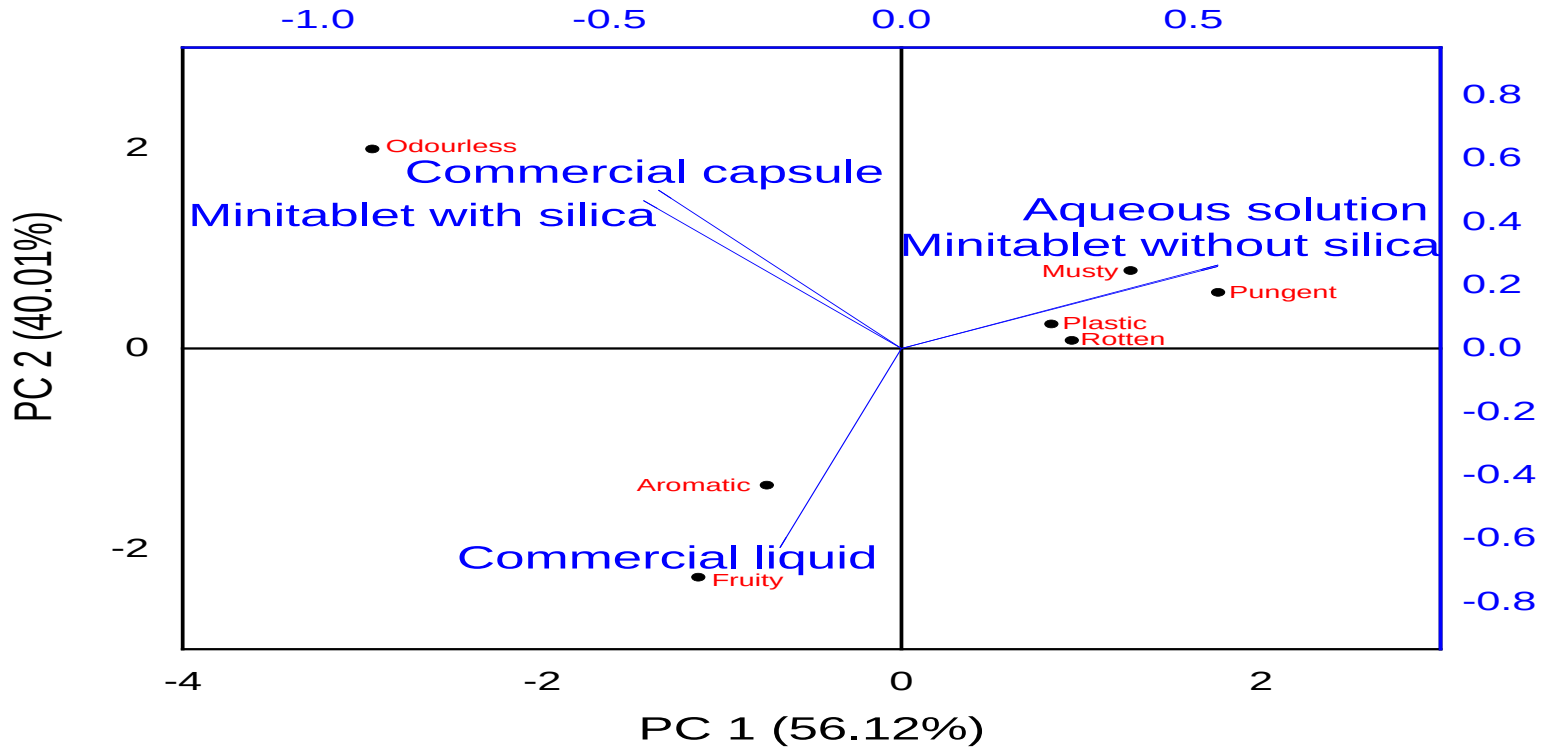

Figure 4.5. Principal component analysis (PCA) biplot of the smell sensory attributes study volunteers (n=40) associated with the flucloxacillin preparations assessed.

4.4 Discussion

The study results detail the odour acceptability and profile of a range of unformulated and formulated pharmaceutical products assessed by the sensory evaluation of human volunteers. Sensory evaluation measures product attributes based on human sensory perception (Gengler & Testing, 2009). The study identified the role formulation plays in mitigating the malodour of flucloxacillin. The flucloxacillin odour noted in the unformulated aqueous control solution was determined to be unacceptable and described as musty, pungent, plastic, and rotten. The odour of the formulated flucloxacillin oral solution and capsule formulation investigated were deemed to be acceptable. The assessed commercial flucloxacillin solution contained pineapple and menthol flavourings, therefore it was unsurprising the volunteers associated fruity and aromatic smell descriptors with this formulation. The odour acceptability of the capsule formulation was associated with the descriptor 'odourless'. Masking unpleasant formulation odours by encapsulation in gelatin capsules has been previously reported (Podczeck & Jones, 2004). Gelatin has also been described as an odourless excipient.

A key finding in this study is the demonstration of the capability of silica within the minitablet formulation assessed to suppress the flucloxacillin malodour. Mesoporous silica was selected based on previous studies reporting the efficiency and sensitivity of silica for adsorbing and extracting volatile organic compounds (Cosseron et al., 2013; Hou et al., 2004; Ncube & Su, 2012). The silica grade selected as an odour suppressant was a non-ordered mesoporous silica with a high surface area 500 m^2/g. Silica itself is reported to have relatively 'bland' taste with pleasant mouthfeel properties at microparticle size less than 12μm (Shabir et al., 2012). Non-ordered mesoporous silica is incorporated into pharmaceutical formulations due to a range of

functionality including moisture protection. Its ability to scavenge moisture within a formulation is due to its high adsorptive capacity. The hypothesised mechanism of action by which silica could suppress flucloxacillin odour within the minitablet formulation was also related to its high adsorptive capacity and ability to adsorb volatile organic compounds (VOC) emanating from flucloxacillin. Odours originate from the presence of a single or combination of odour-active VOCs in a product (Spence, 2021) . These odour-active VOCs perceived in the orthonasal and/or retronasal cavity can interact synergistically or additively to produce the overall odour of a product (Buttery, 1999; Leonardos et al., 1969). The overall odour of a product is a combination of all odour active VOCs (Garvey et al., 2021). Silica can adsorb VOCs because of its porosity and high surface area (Cosseron et al., 2013; Ncube & Su, 2012). Due to the high relatively high molecular weight of flucloxacillin it would not be classified as a VOC (Rowan, 2011) but the odour we propose emanates from low levels of odour active VOCs related to flucloxacillin degradation and impurities.

While both capsule and minitablet formulations were determined to be odourless and acceptable, the minitablet formulation presents a more suitable dosage form for paediatric patients. Compared to capsules the swallowability of 2mm minitablets is acceptable among children aged 6 months and above (Klingmann et al., 2013; Lura et al., 2025). However, the assessed minitablets in the current study were 4 mm diameter minitablets due to the tooling available for the manufacturing process. Thirteen minitablets of 4mm diameter will be needed to administer 250mg of flucloxacillin at 50% drug loading which can be a large volume of minitablets for children. Number and size of tablets needs to be considered for the acceptability attribute according to paediatric Quality Target Product Profile pQTPP tool (Walsh et al., 2022). The pQTPP is a tool that is used to evaluate the paediatric age-appropriateness acceptability of

formulations based on pharmaceutical characteristics such as swallowability, palatability, size of dose, and frequency of dosing. The 4 mm minitablets assessed in the current study might not meet all the target attributes of pQTTP because of the relatively high number and size of minitablets limiting the acceptability for children who can swallow them. Smaller minitablets of 2 mm diameter can be easier to swallow and have higher flexibility of dosing for children from 6 months age. Thus, the odour acceptability of 2 mm minitablets should be assessed to study the potential influence of minitablets' surface on odour release.

Capsule dimensions can pose an administration barrier for paediatric patients (VandenBerg et al., 2023). The available sizes of common paediatric antibiotics capsules range from 8 to 25 mm in length with median 17 mm (Jacobsen et al., 2016). A survey conducted with 304 parents of children and youths to assess their medication acceptance revealed that 30% of children aged 10 to 14 years were not able to swallow small capsules (Polaha et al., 2008). To overcome this challenge, parents/carers may opening capsules and mix their content with food or drink to aid administration to children (Martir et al., 2020). Opening the capsule may increase release of odour and undermine the dosage form acceptability.

A perceived limitation of the methodology used in this sensory evaluation study may be the assessment of odour by healthy adult volunteers rather than children where difficulties associated with administration of oral flucloxacillin medication to children was previously reported (Rouse et al., 2017). For this study adults were selected due to their ability to differentiate accurately between the sensory attributes and adults are preferred when conducting descriptive testing over children (Guinard, 2000). Children can conduct ranking tests through the use of observation-based methods of child's reaction or facial expression by the primary caregiver (Moniot-Ville et al., 1998;

Verrotti et al., 2012). Additionally, children aged from 4 years and above could carry out more complex scaling tests themselves through using 3-, 5- or 7-point hedonic scales anchored with appropriate words for children (Mistry & Batchelor, 2017). However, descriptive tests are challenging for children because of their limited verbal skills, and short span of concentration (Guinard, 2000). The current screening study was conducted using adult volunteers; however, it is envisaged as a formulation is optimised for palatability, sensory studies should be conducted in the target paediatric population due to differences in sensory perception with age.

A secondary finding of this study was the importance of assessing volunteer smell acuity. A level of smell acuity was not included as an inclusion criterion for volunteers in this study. The rationale for this approach was the absence of similar prior investigations upon which we could base the level of smell acuity appropriate for inclusion. By including all volunteers regardless of their smell acuity in this study we evaluated how the responses obtained from anosmic or microsmic volunteers differed from those obtained from volunteers with normosmia. Study findings revealed no difference in the responses from volunteers with normosmia and microsmia. It is important to note that the 8-item smell test that was used in this study could not distinguish between different levels of microsmia (On et al., 2023). In previous studies, microsmia was categorized into mild, moderate, and severe microsmia categories via using tests such as the 40-item University of Pennsylvania Smell Identification Test (UPSITVR) (Doty et al., 2019). However, when designing the study methodology, the 8-item smell test was selected to reduce the duration of the study for volunteers and the need for volunteers to attend multiple days. Only one volunteer (aged 67 years old) assessed was classified as anosmic. The prevalence of anosmia in older age groups was previously reported (Brämerson et al., 2004; Murphy et al.,

2002). Similarly, the United States National Health and Nutrition Examination Survey reported that 3% of people in the U.S. adult population aged ≥ 40 years have anosmia (Hoffman et al., 2016). The single subject with anosmia in the current study deemed all preparation to have acceptable odour and their odour descriptors differed from the other volunteers. Therefore, it was concluded that this volunteer could not distinguish between the odour of the five flucloxacillin preparation. Further studies are needed to confirm the transferability of these findings to anosmic adults in general. However, given the prevalence of anosmia in older age groups, the addition of an exclusion criterion related to volunteer upper age limit would be an important consideration in the design of future odour acceptability studies.

Finally, it should be noted the odour assessment in this study focused on odour via the orthonasal pathway of smell, which can influence medicine acceptability prior to ingestion. However, smell can also reach the main receptors in the nose via the retronasal pathway (Hummel & Podlesek, 2021; Wilson, 2021). Orthonasal odours pass to the nose receptors from the external environment as a result of inhalation, whereas retronasal smells stimulate the nose receptors from inside the mouth during consumption through exhalation via the back of the throat. The influence of formulation on flucloxacillin retronasal odour could also influence a medicine's overall flavour following ingestion (Blankenship et al., 2019) and therefore also warrants further investigation.

4.5 Conclusions

A panel of adult human volunteers assessed the influence of formulation design on the odour acceptability of medications containing a malodourous drug, flucloxacillin. An oral solution formulation described as fruity and aromatic, and a flucloxacillin capsule described as odourless were both deemed to have acceptable odours. The addition of

mesoporous silica, as an odour suppressant agent, to minitablets changed odour from an unacceptable odour described as pungent, musty, plastic, and rotten to odourless and acceptable. The mechanism of odour suppression by silica was attributed to its high adsorptive capacity. The formulation approaches that achieved an acceptable odour in this study were effective for odour via the orthonasal pathway of smell, which can influence medicine acceptability before ingestion. Further studies are warranted to explore the relationship between drug odour via the retronasal pathway post ingestion and a medicine's overall flavour.

Chapter 5

Exploring the capability of GC-MS to identify flucloxacillin malodourous volatile components

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Contribution: As lead author, I was responsible for writing the paper. I developed and conducted the headspace gas chromatography methodology. I contributed to developing the solid phase microextraction gas chromatography methodology that was conducted in collaboration with the co authors. I also analysed the data that was subsequently revised and finalised with the co-authors.

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5 Chapter 5

5.1 Introduction

Flucloxacillin, a widely prescribed oral antibiotic for paediatric indications, is reported as an unpalatable antibiotic for paediatric patients (Baguley et al., 2012). A study by Rouse et al. investigated difficulties associated with administration of different brands of oral liquid flucloxacillin to children because of their poor palatability (Rouse et al., 2017). The studies conducted in chapter 2 and 3 with pharmacists and primary care doctors reported that flucloxacillin's malodour was a contributing factor to its poor palatability. Odour is triggered by the presence of volatile organic compounds (VOCs) in the vapor phase which interact with odourant receptors in the olfactory epithelium of the nasal cavity (Bertuzzi et al., 2018; Pierce & Halpern, 1996; Spence, 2021; Sun & Halpern, 2005).

VOCs are airborne compounds with variable lipophilicity and volatility (Anand et al., 2014; WHO, 1987). Their transfer to the body through the air from the emission source depends on their physical and chemical properties and mean lifetime in the atmosphere, which ranges from a few minutes to several months (Esteve-Turrillas et al., 2012; Montero-Montoya et al., 2018). VOCs can interact synergistically or additively to produce the overall odour of a product (Garvey et al., 2021). Therefore, it is valuable to know which VOCs in a sample are odour active. For pharmaceutical products, VOCs can be related to impurities (Jain & Basniwal, 2013). These impurities could originate during the manufacturing process from raw materials, reaction intermediates, solvents and reagents and/or degradation by-products (Argentine et al., 2007; Baertschi, 2006; Camarasu et al., 2006). VOCs can also arise during storage of

the drug product, from an interaction between a medicinal product and its primary packaging (Saibaba et al., 2016).

VOCs emanating from a material can be determined utilising gas chromatography (GC) (Clarke et al., 2021). GC has been used to analyse the VOCs in food products such as beverages, dairy, fruits/vegetables, honey, meat, seafood, and wine (Starowicz, 2021). GC techniques are sensitive and efficient at detecting trace levels of VOCs which can provide information related to the chemical nature of odour active VOCs (Bertuzzi et al., 2018; Starowicz, 2021). GC techniques, with appropriate detection and sample preparation techniques, provide effective insights into the chemical composition relating to the odour profiles of food products (Bertuzzi et al., 2018; Clarke et al., 2021). Detection method employed in this chapter included mass spectrometry (GC-MS). GC is used to separate the volatile organic compounds based on using a mobile phase of an inert gas like helium or hydrogen to carry the volatile compounds. The carrier gas transports the volatiles through a long, thin glass or metal column coated with a chemical stationary phase. As the column is heated using temperature programming, the separated compounds elute from the column at different retention time based on their affinity for the stationary phase. GC parameters that need to be optimized include column type, flow rate, injector temperature, transfer line temperature, and GC temperature programme for the GC column oven. Volatile compounds are identified when they reach the detector for identification and quantification. An MS detector identifies and measures the separated compounds by their mass-to-charge ratio based on optimizing MS parameters like ionization method and scan mode.

Different sample preparation techniques have been used to isolate and concentrate VOCs from products for analysis utilising GC (Cheng et al., 2022; Clarke et al., 2021;

Hummel et al., 1997). Sample preparation techniques that were used in this chapter include direct headspace (HS), and solid phase microextraction (SPME). The headspace sampling technique involves heating the sample in a sealed vial to allow volatile compounds to evaporate into the headspace until equilibrium is reached. Then, the gas in the vial headspace is injected into a GC-MS. HS parameters that require optimisation include incubation temperature, equilibration time, sample/headspace ratio, and various instrumental variables like sample loop volume and pressure. However, SPME employs a coated fiber to extract, isolate and concentrate volatile organic compounds from different sample matrices. The coated fiber is then inserted directly into the GC injector for thermal desorption and analysis. SPME parameters that require optimisation include the type of fiber coating, temperature, extraction time and the sample matrix.

The aim of this study was to explore the capability of GC-MS to identify flucloxacillin malodourous VOCs. Initially, direct sampling of flucloxacillin powder headspace (HS) was investigated as a sample introduction technique; the sample was heated to generate volatiles in the headspace of the vial (Sithersingh & Snow, 2021). Headspace GC-MS was previously used to determine residual solvents of pharmaceutical formulations of flucloxacillin sodium (Haque, 2014). However, headspace GC-MS in the current study will be used to identify flucloxacillin malodourous VOCs. Subsequently a headspace solid phase micro-extraction (HS-SPME) was explored. For this technique, samples usually require warming only for the analytes to be concentrated on the fiber (Merkle et al., 2015). Furthermore, SPME has the advantage of using small sample volumes, maintaining efficiency and sensitivity, short sample processing time, and automation of the analysis procedure (Agatonovic-Kustrin et al.,

2023). The HS-SPME technique was further explored to detect the VOCs related to flucloxacillin powder, aqueous solutions and flucloxacillin formulations.

5.2 Methodology

5.2.1 Materials

Flucloxacillin sodium was supplied by Molekula Ltd, UK. A commercial formulation, Athlone Laboratories Flucloxacillin 250mg/5ml Oral Solution® was supplied by a local community pharmacy. Parteck® SLC 500 mesoporous silica was donated by Merck Life Science Ltd., Ireland. 20 ml headspace vials were obtained from Agilent Technologies Ltd, Ireland.

5.2.2 Detection of VOCs emanating from flucloxacillin powder

The two sampling techniques, HS and SPME, were investigated to detect VOCs in the headspace above flucloxacillin powder. Samples of flucloxacillin powder with 2% mesoporous silica were also investigated. Mesoporous silica is reported to have high VOC adsorptive capacity (Hou et al., 2004) and potentially can reduce VOCs in sample head space.

5.2.2.1 Head Space GC-MS

Direct HS sampling was the initial VOC sampling method investigated. Analysis was conducted on a GC/MS Agilent 6890N (G1530N) gas chromatograph coupled with a 5973 inert mass spectrometer selective detector (Agilent Technologies) and connected with Agilent 7694E headspace sampler. A capillary column HP-5MS[(5%-phenyl)-methyl polysiloxane] Agilent J & W GC column, with a dimension of 0.25 mm ID x 30 m (length) and a 0.25 μm film coating thickness was used. The temperature programme for the GC equipment comprised an initial temperature 35°C (5 min), followed by temperature ramp of 10°C/min to intermediate temperature 170°C (5

min), and then ramp of 20°C/min to final temperature 260°C (5 min). The carrier gas was helium with flow rate 2 mL/min. Injection was at 200°C in a split ratio 5:1. Transfer line temperature was 230°C; ion source temperature was 200 °C. Compounds were identified using mass spectra comparisons to the DATABASE\NIST02. L mass spectral library.

The sample preparation was conducted by placing flucloxacillin sodium powder or flucloxacillin/silica mixture in a 20 ml sealed vial in the instrument headspace sampler and heated to a predetermined temperature for a specific period of time. A range of temperatures and times were investigated, ***Table 5.1***., to identify conditions which could detect VOCs. The final conditions of headspace were established by placing 2 g of sample powder at equilibration temperature 100°C for 30 minutes with 2 min agitation. The vial pressure was 20 kPa with 3 minutes pressurization time. The valve block temperature and transfer line temperature were 175°C.

Table 5.1. Temperature and times investigated to identify conditions which could detect flucloxacillin volatile organic compounds by direct headspace sampling

Sample composition	Equilibration Temperature	Equilibration Time	Agitation
1 g flucloxacillin sodium powder	80°C	15 minutes	None
2 g flucloxacillin sodium powder	80°C	30 minutes	2 min
2 g flucloxacillin sodium powder	100°C	30 minutes	2 min
1960 mg flucloxacillin sodium powder+ 40 mg silica	100°C	30 minutes	2 min

5.2.2.2 SPME GC-MS

SPME was investigated as a sampling technique. The sample preparation was conducted through adding 0.5 g of flucloxacillin sodium to a 20 ml screw-capped

SPME vial and equilibrated to 40 °C for 10 mins with pulsed agitation of 5 sec at 500 rpm. Sampling was accomplished using a Gerstel MPS Autosampler.

A single 50/30 µm Carboxen/divinylbenzene/polydimethylsiloxane (DVB/ CAR/ PDMS) fiber was used. The SPME fiber was exposed to the headspace above the samples for 20 min at depth of 1 cm at 40°C. The fiber was retracted and injected into the GC inlet and desorbed for 2 min at 250°C. Injections were made on a Shimadzu 2010 Plus GC with an Agilent DB-624 UI (60m x 0.32mm x 1.8µm) column using a split/splitless injector with a 1/10 split. A merlin microseal was used as the septum. The temperature of the column oven was set at 40°C, held for 5 min, increased at 5°C/min to 230°C then increased at 15°C/min to 260°C, and held for 5 min yielding at total GC run time of 65 min. The carrier gas was helium held at a constant flow of 1.2 ml/min. The detector was a Shimadzu TQ8030 mass spectrometer detector, ran in single quad mode. The ion source temperature was 220°C and the interface temperature was set at 260°C. The MS mode was electronic ionization (70v) with the mass range scanned between 35 and 250 amu. An auto-tune of the GC-MS was carried out prior to the analysis to ensure optimal GC-MS performance.

Compounds were identified using mass spectra comparisons to the National Institute of Standards and Technology (NIST 14) mass spectral library, a commercial flavour and fragrance library (FFNSC 2, Shimadzu Corporation, Japan) and an in-house library created using authentic compounds with target and qualifier ions and linear retention indices for each compound using Kovats index. Retention indices were matched against peer-reviewed publications where possible to confirm compound identification. Spectral deconvolution was also performed to confirm the identification of compounds using AMDIS. Batch processing of samples was carried out using

MetaMS (Wehrens et al., 2014). MetaMS is an open-source pipeline for GC-MS-based untargeted metabolomics.

5.2.3 Detection of flucloxacillin solution formulation volatiles

The SPME sampling technique was used to detect the VOCs related to flucloxacillin aqueous solution and a commercial flucloxacillin solution product. Two different batches of the commercial flucloxacillin solution within its expiry date, and one expired flucloxacillin batch were investigated. These flucloxacillin solutions were reconstituted as per the manufacturer's instructions on the day of analysis. Commercial flucloxacillin solutions reconstituted and stored at room temperature for 7 days, and at 4°C for 7 days. Samples were analysed using SPME GC-MS method.

5.2.4 Statistical analysis

Principal component analysis (PCA) was performed using Origin Data Analysis Software (Version 2019b) based on the signal intensity of the detected volatile compounds in each sample. All the samples were tested in triplicate. The PCA data was organised into a 2D matrix (m x n). Each row represented one flucloxacillin sample, and each column represented one volatile compound. The data values indicated the peak intensity of each volatile compound for each formulation sample. The biplot graph summarized the outcome of the PCA mapping flucloxacillin formulations based on the intensity of the volatile compounds.

5.3 Results

5.3.1 Detection of flucloxacillin powder VOCs using HS method

5.3.1.1 Influence of sample mass, temperature and agitation

No VOC peaks were identified under the initial headspace conditions of placing 1 g of flucloxacillin sodium powder and heating to equilibration temperature 80°C for 15 minutes without agitation. Similarly, no peaks were observed after placing 2 g of flucloxacillin sodium powder and modifying the parameters to 80°C for 30 minutes with 2 min agitation time. However, two volatile compounds were identified for samples of 2 g of flucloxacillin powder under the headspace conditions of equilibration temperature 100°C for 30 minutes with 2 min agitation (***Figure 5.1***). These compounds were identified as ethyl acetate and decane. Ethyl acetate is a residual solvent that may have originated during the flucloxacillin manufacturing process. It is a list residual solvent listed on flucloxacillin's certificate of analysis (COA). Decane is a volatile compound that has been detected released from packaging materials (Aznar et al., 2020; Ezquerro et al., 2003).

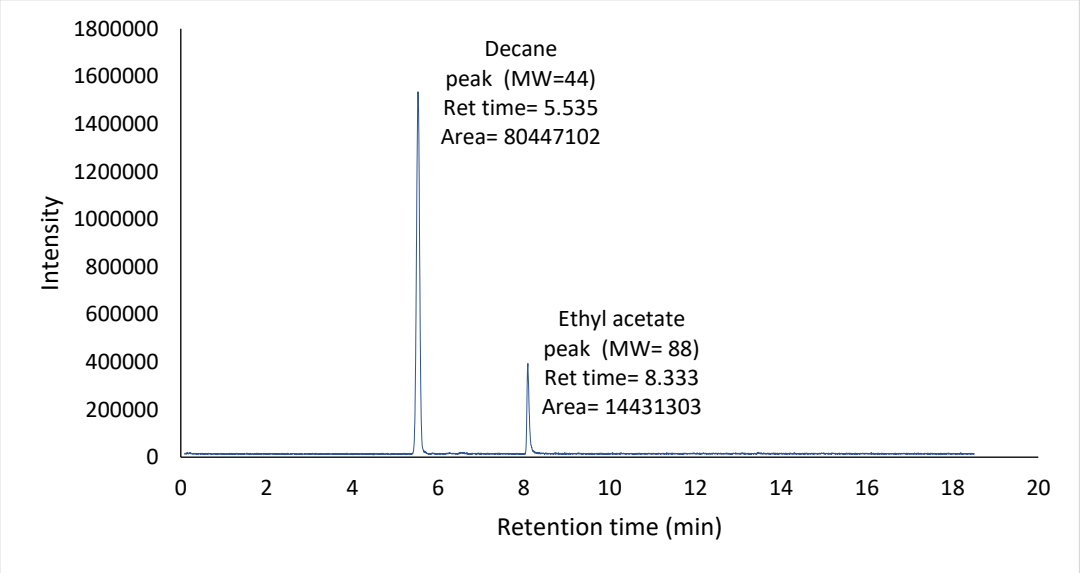

Figure 5.1. Volatile compounds identified by direct headspace sampling of 2g flucloxacillin at temp 100°C for 30 min

5.3.1.2 Effect of silica addition

No VOCs were identified emanating from the flucloxacillin powder after adding 2% silica under the final headspace conditions of equilibration temperature 100°C for 30 minutes with 2 min agitation (**Figure 5.2**).

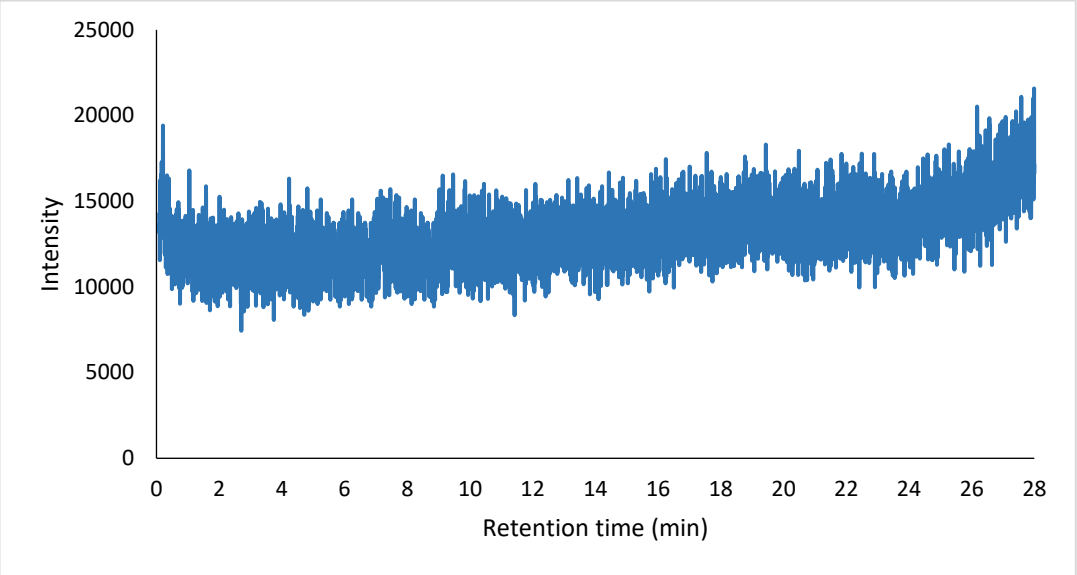

Figure 5.2. No volatile compounds were identified by direct headspace sampling of a 2 g sample consisting of 2% silica and 98% flucloxacillin powder at temp 100°C for 30 min

5.3.2 Detection of flucloxacillin powder VOCs using HS-SPME method

Forty volatile compounds were identified in the headspace above the flucloxacillin powder sample using HS-SPME/GC-MS analyses (**Figure 5.3**). Similar to the first headspace sampling technique, both ethyl acetate and decane were detected. Both compounds were among the most abundant compounds identified in the sample headspace using this technique beside ethyl 2-ethylhexanoate, 2-ethylhexanoic acid, 1,3-di-tert-butylbenzene, 2,4-dimethyl-1-heptene, 3-penten-2-one, 4-methyl-, and acetonitrile. Some of the detected compounds including decane, undecane, toluene, and styrene had a particular malodour that can contribute to the overall malodour of

flucloxacillin. The potential source and the odour of the identified volatile compounds is detailed in **Table 5.2.** The source and the odour of the volatile compounds identified in flucloxacillin powder sample using HS-SPME/GC-MS method**.** The identified VOCs could be released as process volatile impurities originated during manufacturing process from raw materials, reaction intermediates, solvents and reagents, and packaging materials.

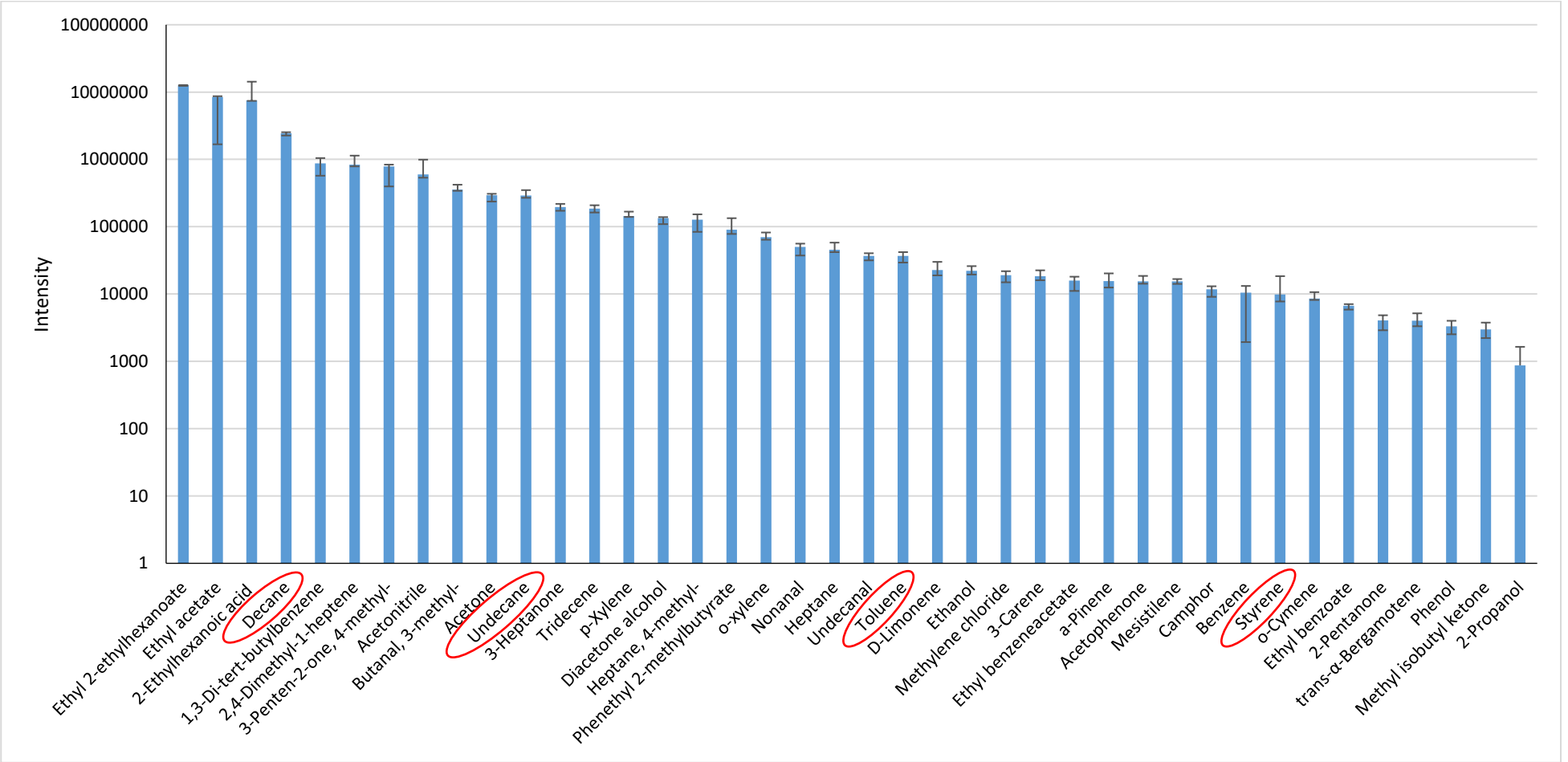

Figure 5.3. The volatile compounds emanating from the flucloxacillin powder using HS-SPME/GC-MS method. Compounds surrounded by red circles are reported to have a particular malodour that can contribute to the overall malodour of flucloxacillin.

Table 5.2. The source and the odour of the volatile compounds identified in flucloxacillin powder sample using HS-SPME/GC-MS method

Volatile compounds	Odour	Manufacturing source	Reference
Benzene	aromatic	Raw materials (N, N dibenzyl ethylenediamine)	(Calkin, 1969)
Mesistilene	aromatic		
1,3-Di-tert-butylbenzene			
Methyl isobutyl ketone	green, herbal, fruity, dairy, spicy		
Acetonitrile	aromatic, ether-like, sweet, faint		
Phenol	sweet, tarry, chemical, phenolic		
3-Penten-2-one, 4-methyl-	Peppermint		
Octane	gasoline-like	Raw materials (flucloxacillin acid)	(Zhenyu et al., 2013)
Methylene chloride	a mild sweet odour		
p-Xylene	grainy, sweet	Reaction intermediates N,N-dibenzyl-ethylenediamin diacetate	(Yongping, 2010)
o-xylene	geranium		
Ethyl benzeneacetate	sweet, floral, honey, rose, balsamic, cocoa		
Acetophenone	must, flower, almond, glue		
Ethanol	sweet, alcoholic, medicinal	Solvents and reagents used in manufacture	(Haque, 2014) & COA
2-Propanol	alcoholic, musty, woody		
Diacetone alcohol	mild, pleasant		
Ethyl acetate	fruity, apple, weedy, green		
Acetone	solvent, ethereal, sour milk, apple		
Toluene	nutty, bitter, almond, plastic		
2-Ethylhexanoic acid	a mild odour	Purification process	(Ming, 2006)
Hexanoic acid	acidic, sweaty, cheesy, sharp, goaty		
Nonanal	green, citrus, fatty, floral	Packaging materials	(Aznar et al., 2020)
Undecanal	waxy, soap, floral, citrus, green, fatty		(Aznar et al., 2020)
Decane	gasoline-like to odourless		(Aznar et al., 2020; Ezquerro et al., 2003)

Undecane	gasoline-like to odourless		(Ezquerro et al., 2003)
Tridecene	mild, pleasant		(Roosen et al., 2023)
3-Heptanone	green, fatty, fruity		(Ezquerro et al., 2003)
Styrene	plastic		(Chiesa et al., 2008; Panseri et al., 2014)

5.3.3 Effect of silica addition on detection of flucloxacillin powder VOCs using HS-SPME method

Several volatile compounds were also identified for flucloxacillin sample with silica by using SPME/GCMS method (**Figure 5.4**). The most abundant compounds in flucloxacillin sample with silica were similar to the compounds detected in flucloxacillin sample without silica. Both powders had a similar volatile profile with the exception of three compounds detected differently in each sample. Phenol, methyl isobutyl ketone and diacetone alcohol were detected in flucloxacillin powder without silica whereas octane, γ-terpinene, and copaene were detected in flucloxacillin powder with silica. The peak areas and the smell of all volatile compound identified in each sample are outlined in **Supplementary Table S5.1**.

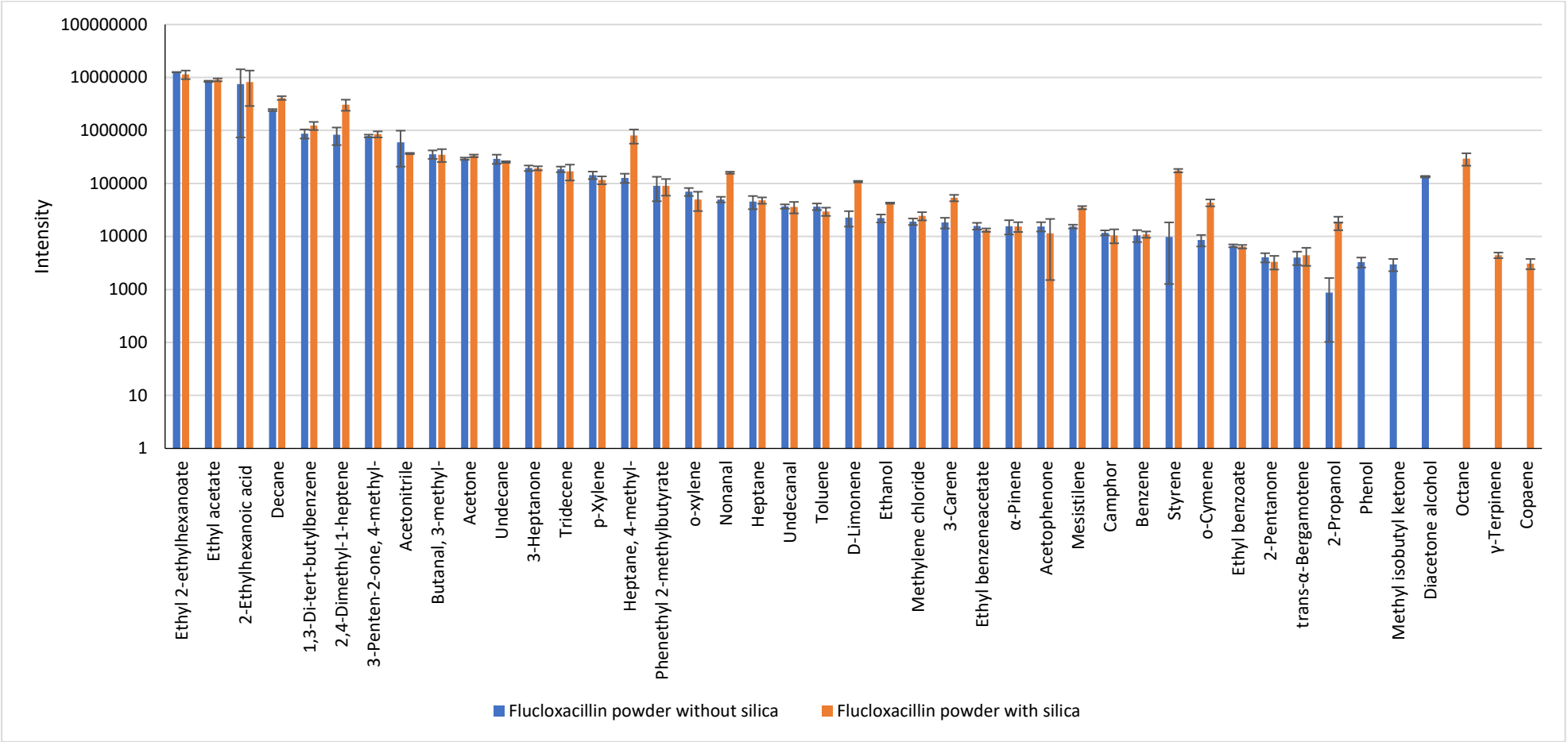

Figure 5.4. The volatile compounds identified emanating from both flucloxacillin powder samples with and without 2% silica using HS-SPME/GC-MS method

5.3.4 Detection of flucloxacillin solution VOCs using HS-SPME method

Forty volatile compounds were identified in control aqueous flucloxacillin solution by using HS-SPME/GCMS method (**Figure 5.5**). Some volatile compounds were detected only in control aqueous flucloxacillin solution compared to flucloxacillin powder. These compounds included dimethyl disulfide, ethyl butanoate, isoamyl acetate, isopropyl pentanoate, butanoic acid, butyl ester, benzaldehyde, hexanoic acid, γ-terpinene, 2-methyl butyl butanoate, and allyl hexanoate. However, some of the volatile compounds that were detected in flucloxacillin powder were not detected in the control aqueous flucloxacillin solution including 2,4-dimethyl-1-heptene, acetonitrile, tridecene, diacetone alcohol, 4-methyl- heptane, o-xylene, undecanal, ethanol, methylene chloride, benzene, and 2-propanol.

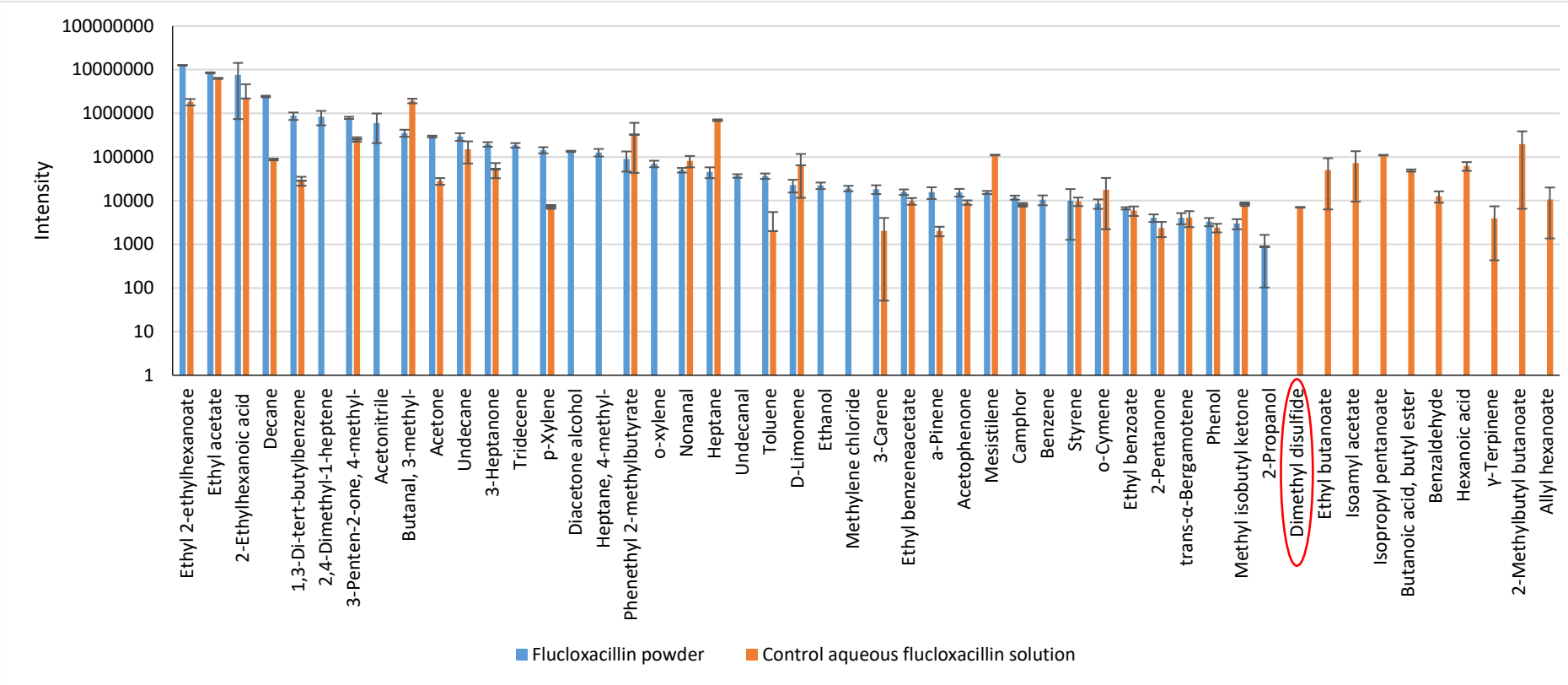

Figure 5.5. The volatile compounds identified emanating from flucloxacillin powder and control aqueous flucloxacillin solution using HS-SPME/GC-MS method. Dimethyl disulfide, surrounded by a red circle, was detected in control aqueous flucloxacillin solution and is reported to have a particular malodour that can contribute to the overall malodour of flucloxacillin.

5.3.5 Analysis of commercial flucloxacillin formulation VOCs

A number of volatile compounds were identified in commercial flucloxacillin solution. The most abundant compounds were different in commercial flucloxacillin solutions compared to the control aqueous solution (**Figure 5.6)**. Ethyl acetate, 2-ethylhexanoic acid, butanal, 3-methyl-, ethyl 2-ethylhexanoate, and heptane were the most abundant compounds in control aqueous flucloxacillin solution. Dimethyl disulfide was a sulfur compound that was detected only in control aqueous flucloxacillin solution. The most abundant compounds in commercial flucloxacillin solution were phenethyl 2-methyl butyrate, isoamyl acetate, d-limonene, allyl hexanoate, ethyl butanoate, myrcene, 2-methylbutyl butanoate, and γ-terpinene. These compounds could originate from the excipients used in the manufacture of commercial formulations, particularly flavouring agents (**Table 5.3**).

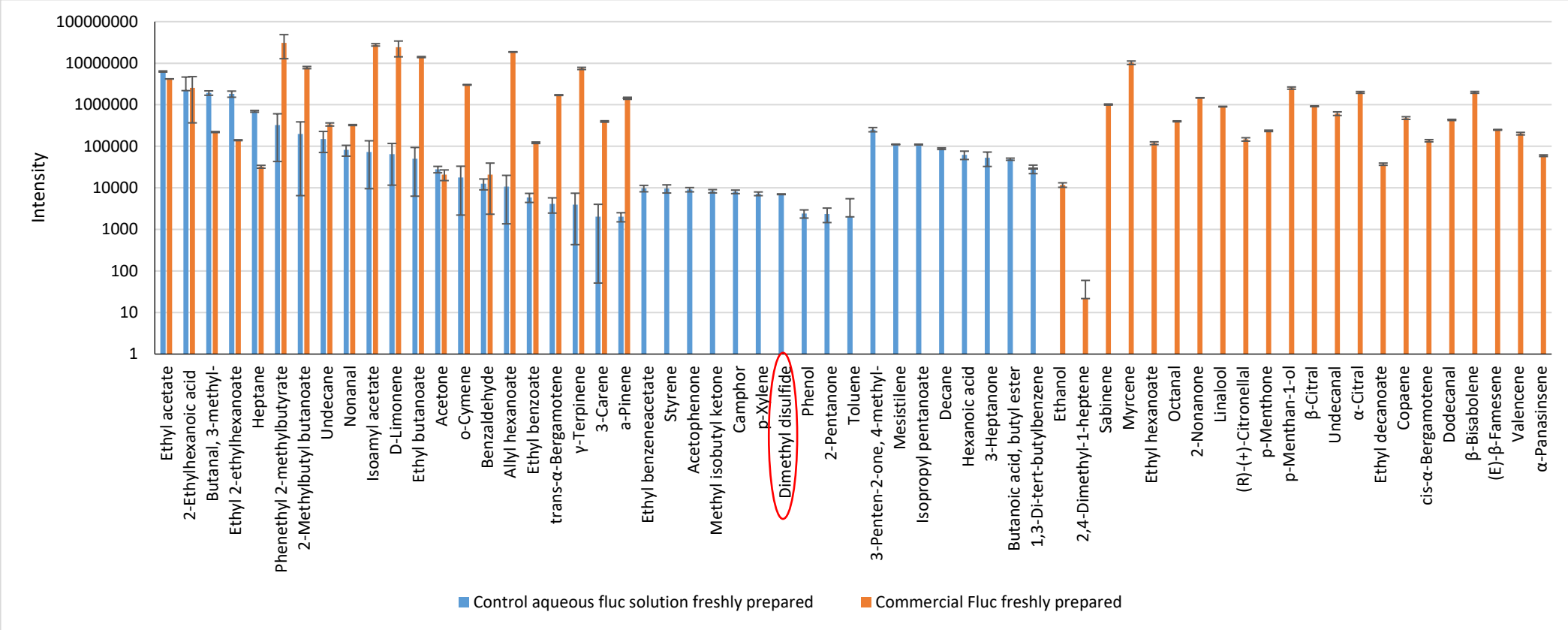

Figure 5.6. The volatile compounds identified emanating from flucloxacillin solution samples using HS-SPME/GC-MS method. Dimethyl disulfide, surrounded by a red circle, was detected in control aqueous flucloxacillin solution and is reported to have a particular malodour that can contribute to the overall malodour of flucloxacillin.

Table 5.3. Flavour VOCs in commercial flucloxacillin solution

Volatile compounds	Odour	Formulation Component	Ref
α-Pinene, Sabinene, Myrcene, 3-Carene, D-Limonene, o-Cymene, γ-Terpinene, Linalool, (R)-(+)-Citronellal, p-Menthone, Camphor, p-Menthan-1-ol, β-Citral, α-Citral, Copaene, cis-α-Bergamotene, trans-α-Bergamotene, β-Bisabolene, (E)-β-Famesene, α-Panasinsene	Pine, camphoreous, earthy, woody, sweet, citrus, fruity, orange, peely, oily, terpenic, lime, herbal, camphoreous, spicy, honey, mild, waxy, minty	Menthol flavour	(Aldogman et al., 2022; Ciotea & Popa, 2020; Kamatou et al., 2013; Tomanić et al., 2022)
Ethyl butanoate, Butanoic acid, butyl ester, Ethyl hexanoate, 2-Methylbutyl butanoate, Allyl hexanoate, Ethyl 2-ethyl hexanoate, Phenethyl 2-methylbutyrate, Hexyl isobutyrate, Valencene	Fruity, apple, pear, floral, green, tropical, waxy, rose, fruity, pineapple, banana, sweet, fresh, orris, fruity	Pineapple flavour	(Wei et al., 2011; Zheng et al., 2012)

5.3.6 Impact of storage on commercial flucloxacillin formulation VOCs

Forty volatile compounds were identified in each flucloxacillin solution (**Figure 5.7**). The most abundant compounds were very similar in all formulations including phenethyl 2-methyl butyrate, isoamyl acetate, d-limonene, allyl hexanoate, ethyl butanoate, myrcene, 2-methylbutyl butanoate, and γ-terpinene. However, the flucloxacillin solution analysed after 7 days of storage at 21°C had lower total peak areas for most of the flavour volatile compounds. Two additional volatile compounds were detected in the expired flucloxacillin commercial solution compared to the other commercial solution. These compounds were allyl heptanoate and hexyl isobutyrate. The peak areas and the smell of each volatile compound identified in each sample are outlined in **Supplementary Table S5.2**.

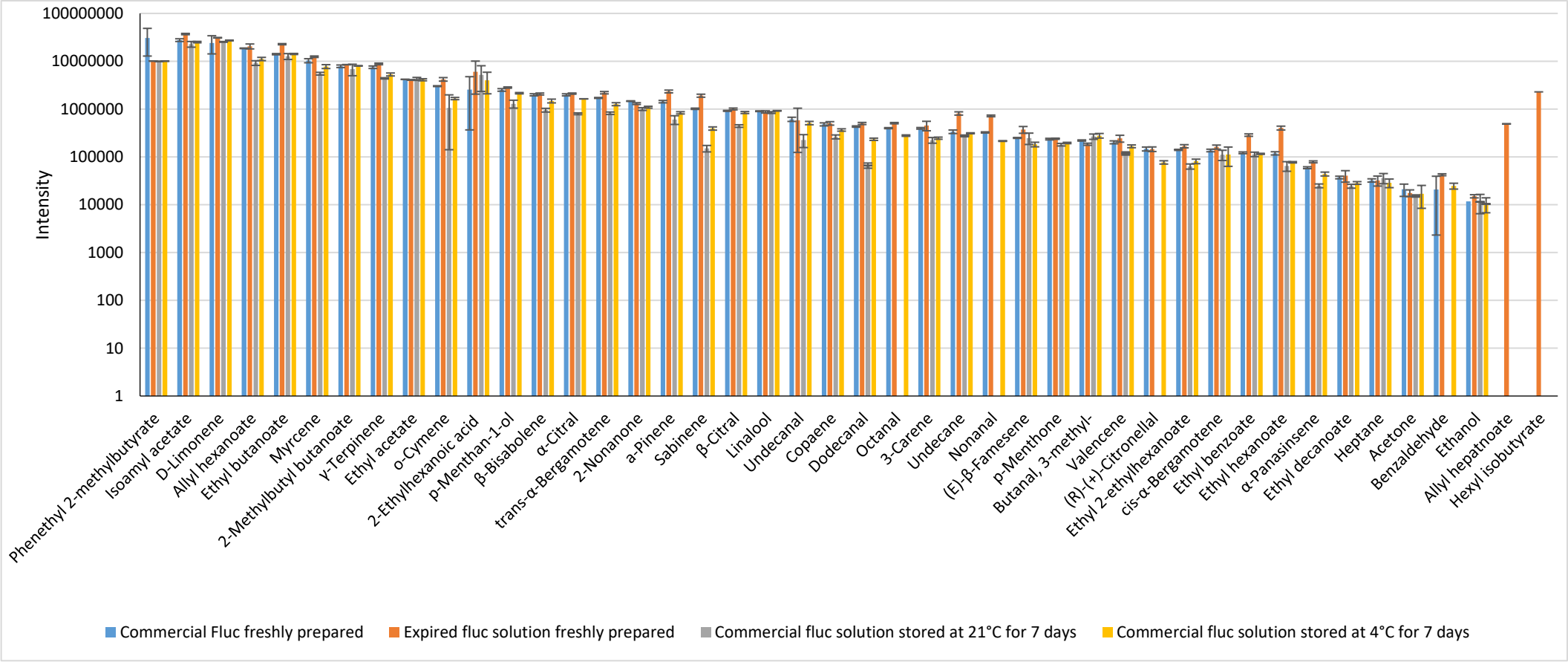

Figure 5.7. The volatile compounds identified emanating in flucloxacillin solution formulations under different storage conditions using HS-SPME/GC-MS method

Principal component analysis (PCA) was performed to aid visualization of the relationship between flucloxacillin solution formulation and storage samples and identified VOCs. The total amount of variance explained by PC1 and PC2 is 93.53% with PC1 and PC2 explaining 80.91 and 12.62% respectively (**Figure 5.8**). PC1 discriminated the control aqueous flucloxacillin solution and commercial flucloxacillin solution stored at 21°C for 7 days from the other commercial flucloxacillin solutions. PC2 further separated the expired commercial flucloxacillin solution from the commercial flucloxacillin solutions within their expiry date. Similarly, PC2 further separated the control aqueous flucloxacillin solution from commercial flucloxacillin solution stored at 21°C for 7 days. PCA also separated the freshly prepared commercial flucloxacillin solution (both batches), from commercial flucloxacillin solutions stored at 4°C for 7 days and 21°C for 7 days. The different batches of freshly prepared commercial flucloxacillin solutions and commercial solution stored at 4°C for 7 days were associated with VOCs of flavourings such as phenethyl 2-methyl butyrate, 2-methyl butyrate, 2-methylbutyl butanoate, menthone, D-Limonene, and linalool.

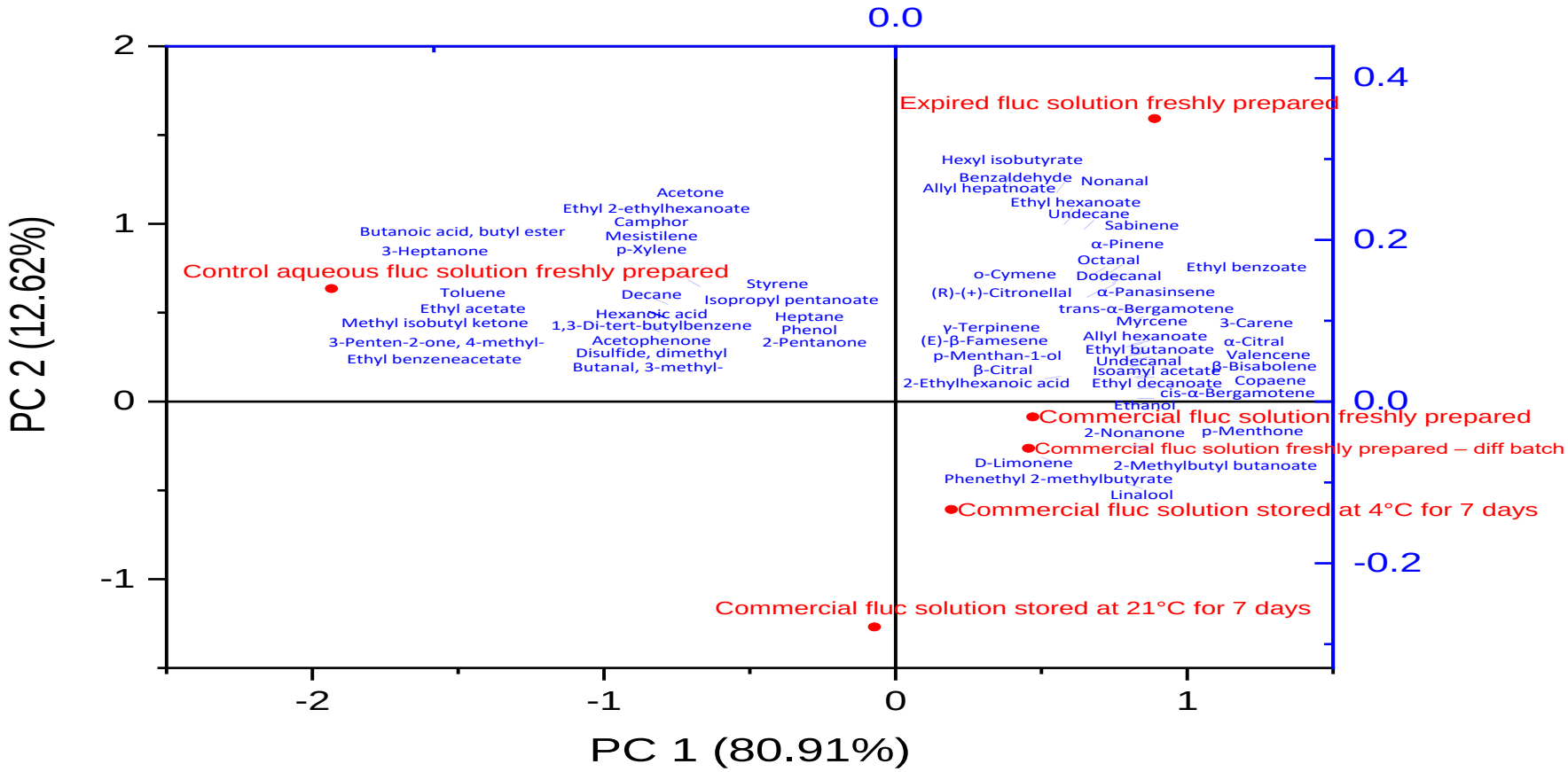

Figure 5.8. Principal component analysis (PCA) biplot of volatile compounds associated with flucloxacillin liquid samples using HS-SPME/GC-MS method

5.4 Discussion

Direct HS sampling detected two volatile compounds of which decane has a particular malodour that can contribute to the overall malodour of flucloxacillin. However, SPME analysis detected forty volatile compounds of which octane, decane, undecane, toluene, and styrene have a particular malodour that can contribute to the overall malodour of flucloxacillin. Both volatile compounds, detected using direct HS sampling technique, were not detected under the same conditions after adding silica to the flucloxacillin powder. Silica has the capability to adsorb VOCs because of large surface area and pores (Hou et al., 2004). This adsorption is based on the amount of VOC entering the pores of silica particle (Cosseron et al., 2013; Ncube & Su, 2012). In the current study, silica adsorbed the two volatile compounds and were not released in the headspace even after heating the sample at 100°C.

In comparison to direct HS sampling, SPME analysis detected a similar VOC profile for both flucloxacillin powder samples with and without silica. This similar VOC profile could be related to the high extraction efficiency of the SPME coated fiber and the potential competitive adsorption of VOCs with the added silica. The coat of fused-silica fiber used in this study was DVB-CAR-PDMS that provides high extraction efficiencies. Cho et al. evaluated the extraction efficiency of six different fibers by comparing the peak areas obtained from using each coating fiber (Cho et al., 2003). The study revealed that DVB-CAR-PDMS had the second highest responses.

In the current study, no sulfur compounds were detected amongst the flucloxacillin powder VOCs. However, dimethyl disulfide ($C_2H_6S_2$) was detected in the control aqueous flucloxacillin solution. The addition of water can enhance the release of the volatiles into the gas phase from a matrix (Llompart et al., 1999) which could explain the detection of disulfide compound in the flucloxacillin solution rather than the

powder. Dimethyl disulfide compound can be emitted from degradation impurities of flucloxacillin. The degradation pathway of flucloxacillin and potential losses of VOCs have previously been reported as shown in **Supplementary Figure S5.1** (Tiwari et al., 2014)**.** The molecular formulas of these VOCs are C_2H_2S, $C_2H_7NO_2$, C_4O, HF, and HCl and the odour of each compound are provided in **Table 5.4**. One of the flucloxacillin degradation-related VOC impurities is a sulfur compound, ethynethiol, with the molecular formula C_2H_2S. Ethanethiol was previously reported as the smelliest thiol substance that has a strong unpleasant, rotten cabbage or garlic with a quite low odour threshold of $\sim 8.7 \times 10^{-3}$ ppb/v (Wang et al., 2019). The mild oxidation of thiols gives disulfides (Elzinga et al., 2022). Therefore, dimethyl disulfide can be produced by the degradation of ethanethiol.

Table 5.4. Flucloxacillin volatile compounds result from flucloxacillin degradation

Molecular formula	Potential names	Odour
C_2H_2S	Ethynethiol	Strong unpleasant, rotten cabbage or garlic at 0.36 parts per billion
$C_2H_7NO_2$	Ammonium Acetate	Slight vinegar-like odour
C_4O	Diacetylene ether	Strong chlorine-like odour
HF	Hydrogen fluoride	Pungent odour at 0.04 ppm
HCL	Hydrochloric acid	Characteristic pungent odour

PCA analysis revealed relationships between flucloxacillin solution samples and associated VOCs. The aqueous flucloxacillin solution had a different profile to commercial flucloxacillin solutions. This is expected due to the VOCs released from the excipients used in the manufacture of commercial formulations (Argentine et al., 2007; Camarasu et al., 2006). The assessed commercial flucloxacillin solutions contained pineapple and menthol flavour that explains the presence of VOCs associated with these flavourings. Similar VOCs were previously reported to be

released from pineapple (Wei et al., 2011; Zheng et al., 2012) and menthol (Aldogman et al., 2022; Ciotea & Popa, 2020; Kamatou et al., 2013; Tomanić et al., 2022) flavours. Batches of freshly prepared commercial flucloxacillin solutions and commercial solutions stored at 4°C for 7 days (recommended storage conditions) had similar VOC profiles which associated with VOCs of flavourings. However, PCA revealed that commercial flucloxacillin solution stored at room temperature for 7 days was separated from the other commercial solutions. A previous study revealed that flucloxacillin formulations kept at room temperature were the least stable and had the largest degradation of flucloxacillin sodium (Klu et al., 2018). Interestingly, flavouring volatiles intensity decreased in the commercial flucloxacillin solution stored at 21°C for 7 compared to the commercial freshly prepared and commercial solution stored at 4°C for 7 days. PCA analysis also separated the expired commercial flucloxacillin solution from the other commercial solutions. This could be due to the rise of VOCs from the expired compounds. Two volatile compounds, allyl heptanoate and hexyl isobutyrate, were only detected in the expired solution. However, both compounds are unlikely to contribute to flucloxacillin malodour because they have a pleasant smell.

Unlike control aqueous flucloxacillin solution, the disulfide compound was not detected in commercial formulations. This could be related to the presence of sodium in the commercial formulations. Each 5 ml spoonful of commercial flucloxacillin solution contains 18 mg of sodium according to the Summary of Product Characteristics (SmPC). Sodium was previously reported to have a chemical neutralization effect on sulfur compounds forming a non-volatile sodium sulfide (Na_2S) (Gupta et al., 2007). However, a limitation of the GC-MS approach explored

is its lack of sensitivity to detect volatile sulfur compounds (VSCs) associated with flucloxacillin powder.

Volatile sulfur compounds (VSCs) detection is challenging because of their very low concentration in samples with a very low odour threshold values of parts per billion (Dziekońska-Kubczak et al., 2020; Leonardos et al., 1969). HS–SPME/GC–MS was previously investigated to detect VSCs using DVB/CAR/PDMS fibers (Dziekońska-Kubczak et al., 2020). However, it was challenging to identify ethanethiol using this extraction technique because of the low affinity of these compounds for fiber coatings or their degradation under the analytical conditions (Dziekońska-Kubczak et al., 2020). Ethanethiol was previously detected through using gas chromatography (GC) with a sulfur chemiluminescence detector (SCD) and mass spectrometry coupled with olfactory detection port (MS-O) (Barczak et al., 2022; Li et al., 2012). A wide range of sulfur-selective detectors can be used for the analysis of a variety of VSCs at trace levels (Lu et al., 2012). These detectors include flame photometric detector (FPD), pulsed flame photometric detector (PFPD), sulfur chemoluminescence detector (SCD), and atomic emission detector (AED), together with a universal mass spectrometry mass selective detector (MSD).

5.5 Conclusions

GC-MS method using SPME technique as the sample introduction technique identified a large number of VOCs in the headspace above flucloxacillin powder and flucloxacillin formulations. The technique identified VOCs released from flavour excipients in commercial solutions. Dimethyl disulfide ($C_2H_6S_2$) was detected in the control aqueous flucloxacillin solution which has an unpleasant, garlic-like odour and can be related to flucloxacillin degradation. Future development of analytical methodology is needed to identify and quantify volatile sulfur compounds which

emanate from flucloxacillin formulation causing their malodour and inform odour suppression formulation strategy.

Chapter 6

General discussion

6 Chapter 6

The overall aim of this PhD thesis was to define the organoleptic properties associated with the poor palatability of oral liquid antibiotics that impact their acceptability amongst paediatric patients. The first aim was to investigate the impact of poor palatability on the clinical prescribing and dispensing of oral liquid antibiotics for paediatric patients. This aim was achieved by conducting a cross-sectional survey of general practitioners and pharmacists in chapter 2, and a qualitative interview study with both professions in chapter 3. The challenges faced by GPs and pharmacists when prescribing and dispensing poorly palatable paediatric oral liquid antibiotics were identified. Flucloxacillin's odour was noted to influence its palatability in chapters 2 and 3, which led to the second thesis aim, exploring the impact of formulation on the odour profile and odour acceptability of flucloxacillin. The odour of flucloxacillin formulations was assessed using a human sensory panel in chapter 4 and in chapter 5 GC-MS methodology was explored to identify the volatile organic compounds (VOCs) related to the malodour of flucloxacillin.

Based the results of the research chapters 2-5, the following key findings were identified,

1. Definition of issues associated with the poor palatability of paediatric oral liquid antibiotics that impact clinical practice by conducting mixed method studies using a survey and interviews of general practitioners and pharmacists.
2. Description of the odour profile of commercial and novel flucloxacillin formulations via a human sensory study.
3. Assessment of a formulation approach that suppresses the malodour of flucloxacillin via the inclusion of mesoporous silica.

4. Identification of a GC-MS approach for monitoring the key VOCs associated with flucloxacillin's malodour.

6.1 Poor palatability impact on clinical practice

The impact of oral antibiotics' poor palatability on paediatric clinical practice was determined using a survey study in chapter 2 and an interview study in chapter 3. Chapter 2 identified palatability issues reported by GPs and pharmacists in primary care via survey responses. In chapter 3 a deeper and richer understanding of the experience, attitudes, and challenges faced by both professions was obtained via interview study. In chapter 2, the majority of both GPs and pharmacists reported that they had switched oral liquid antibiotics because of palatability issues. GPs had at times deviated from clinical prescribing guidelines, and the majority pharmacists had changed antibiotic dispensing choice because of palatability issues to ensure treatment adherence. This highlights challenges faced, as GPs and pharmacists prefer to follow the guidelines and select a first-choice antibiotics (Bergene et al., 2019). However, study findings highlight that poor palatability can lead to the prescribing of second-choice antibiotic agents.

This concern was further discussed in chapter 3 with both professions reporting that in some circumstances they had to select an unpalatable antibiotic despite knowing that it has poor palatability. These circumstances included the type of infection, lack of alternatives, and allergies. The type of infection and allergy status of the child confined healthcare professionals' selection of antibiotics. Similarly, it was reported in previous studies that patients, both adults and children, with a medical history of antimicrobial allergy had limited choices of antibiotics compared to non-allergic patients (Lee et al., 2000).

In chapter 2, almost half of respondents of each profession indicated that they rarely or never discussed palatability with a child's parents or caregivers. Such lack of discussion with parents was similarly highlighted in previous studies (Barden et al., 1998; Biezen et al., 2019). The reasons for not starting the palatability discussion with parents were clearly determined in chapter 3. These reasons included avoiding negotiation because of the lack of alternatives, avoiding raising the potential issue until the child tries to take the antibiotic, and avoiding raising palatability issues with parents in case parents pass this fact to the child who will then be primed to refuse the antibiotic. However, the communication gap between healthcare professionals and parents can lead to inappropriate use of antibiotics (Barden et al., 1998; Mangione-Smith et al., 2006). Proactive dialogue discussing antibiotic palatability with parents and carers during the prescribing process and prior to dispensing can reinforce parents and carers' understanding of the importance of following the prescribed treatment, despite potential palatability issues. Improving the relationship between healthcare professionals and parents could decrease non-disclosure of manipulation/non-adherence practices by parents and support them, providing advice about the importance of following the prescribed first-choice antibiotic treatment, despite potential palatability issues.

Based on the interviewee responses in chapter 3, to be able to support parents it is considered important to increase flavour and palatability awareness through training programs for both GPs and pharmacists. A particular focus of this training should be increasing understanding of the challenges around oral liquid antibiotic palatability for paediatric patients. Additionally, providing parents with information regarding the colour and flavour of the selected antibiotic before reconstitution was suggested to

decrease wastage by avoiding switching antibiotic brands after the initial formulation is reconstituted.

The differences between GPs, pharmacists, and parents' knowledge regarding oral liquid antibiotics were discussed in chapter 3. Parents often associate antibiotics with the colour of the formulation rather than the formulation name. However, GPs reported that they are unfamiliar with antibiotic product colour or are only aware through parent comments, while pharmacists are familiar with the colour of different antibiotic products. However, both professions rarely taste the antibiotic formulations and are unfamiliar with their palatability. A previous interventional study reported that physicians may not think primarily about taste when prescribing and they altered their prescribing preferences after taste testing different medications (Bradshaw et al., 2016). Bergene and colleagues recommend that pharmacists could integrate shared decision-making into their practice and that they could discuss the availability of different formulations with a parent/caregiver in order to dispense the best choice oral liquid antibiotic for every child (Bergene et al., 2019).

Chapter 2 results also highlighted that when parents find difficulties in administering an unpalatable oral liquid antibiotic to a child, they may manipulate the required doses by mixing with food or diluting in a flavoured liquid. Similarly, a previous study reported that parents might manipulate the oral dosage form to achieve better palatability (van der Vossen et al., 2019). Chapter 3 identified that parents may perform unlicensed manipulation to disguise either the consistency or the flavour of the original product. Pharmacists reported that parents thought it is better to try and give the child part of the dose rather than taking nothing at all. However, unlicensed manipulation can lead to administration of an underdose and can affect stability, efficacy and bioavailability of medicines and should be avoided (Venables, Batchelor,

et al., 2015). There is a need for pharmacists to discuss and give suitable administration advice to parents based on the specific characteristics of each dispensed antibiotic formulation, its palatability and its associated challenges prior to dispensing. The development of manipulation guidelines for paediatric medicines by authorities such as medicines and healthcare regulators are needed (Richey et al., 2013).

Availability of supply was ranked as one of the most important factors that influence the antibiotic prescribing and dispensing practices in chapter 2. This factor was further discussed in chapter 3 which highlighted that the shortage of paediatric antibiotic formulations caused pharmacists to manipulate solid dosage form into liquid dosage form for children. This manipulation because of shortage can result in dispensing an unpalatable antibiotic to children despite knowing that it has poor palatability. Children need medicines that are suitable to their unique requirements of acceptability and palatability with adequate guarantee of quality, safety and efficacy (Ranmal et al., 2016).

6.2 Palatability of antibiotics

The factors that affect oral liquid antibiotic acceptability were clearly identified in chapter 3. These factors were frequency, volume, and palatability which were similarly reported in a previous review conducted by Liu et al. (Liu et al., 2014). Palatability factors included taste, smell, and texture. It was reported in chapter 3 that it is a challenge for parents to give antibiotics to children, particularly if it requires a high number of doses per day, a large volume, or poor palatability. The parent's task is so much more difficult when the antibiotic is unpalatable. Parents sometimes administer their child poorly palatable antibiotics by forcing a child to take it, which was previously reported as one of the strategies of drug administration (Bergene et al.,

2017). Forcing a child to take a poorly palatable oral liquid antibiotic can cause stress at home for both child and parent.

Flucloxacillin and clarithromycin were reported to be the least palatable oral liquid antibiotics for children in chapters 2 and 3. Clarithromycin was identified as an antibiotic with texture issues. Similarly, Steele *et al*. reported that the texture and acceptability of clarithromycin can be improved by decreasing the grittiness of the product during pharmaceutical processing (Steele et al., 1997). Flucloxacillin was highlighted as the least palatable oral liquid antibiotic for children with a malodour. However, previous studies reported that the unpalatability of flucloxacillin relates to its taste (Baguley et al., 2012; Rouse et al., 2017; Venables, Stirling, et al., 2015).

As flucloxacillin was highlighted as the least palatable oral liquid antibiotic for children with notable malodour in chapters 2 and 3, the acceptability of different flucloxacillin formulations was assessed in a human sensory study in chapter 4. Human volunteers assessed the odour of a control unformulated aqueous flucloxacillin solution, as well as commercial and novel flucloxacillin formulations. The novel formulation approach investigated was the flucloxacillin dose presented as minitablets. Both flucloxacillin aqueous control solution and minitablets were deemed to have an unacceptable odour which was described as musty, pungent, plastic, and rotten by human volunteers. However, the odour of commercial solution was deemed to be fruity and aromatic. The assessed commercial flucloxacillin solution contained pineapple and menthol flavour that would contribute to the overall fruity and aromatic smell of the formulation.

The odour of commercial capsules and minitablet formulations with mesoporous silica was deemed to be acceptable with the descriptor ‘odourless’. The perceived absence

of odour for flucloxacillin capsules was attributed to gelatin which is an odourless excipient widely used to create the shell for capsules and plays a role in masking the unpleasant odour of formulations (Podczeck & Jones, 2004). The perceived absence of odour for minitablets with silica was related to the inclusion of mesoporous silica which has high adsorptive capacity (*Pharmaceutical Excipients, Mesoporous Silica (MPS)*, 2024). Silica can adsorb volatile organic compounds (VOCs) because of its large surface area (Hou et al., 2004) which may explain the mechanism by which it suppresses the malodour in flucloxacillin minitablets. Odours originate from the presence of a single or combination of odour-active VOCs in a product (Spence, 2021) . These odour-active VOCs perceived in the orthonasal and/or retronasal cavity can interact synergistically or additively to produce the overall odour of a product (Buttery, 1999; Leonardos et al., 1969). The overall odour of a product is a combination of all odour active VOCs (Garvey et al., 2021).

GC-MS was used in chapter 5 to identify the VOCs associated with flucloxacillin's malodour. Two sampling techniques, HS and SPME, were investigated to detect VOCs in the headspace above flucloxacillin samples in combination with GC-MS. The direct HS sampling detected two volatile compounds in flucloxacillin powder of which decane has a particular malodour that could contribute to the overall malodour of flucloxacillin. Both volatile compounds, detected using direct HS sampling technique, were not detected under the same conditions after adding silica to the flucloxacillin powder. This result provides supporting evidence regarding the capability of silica to adsorb volatile compounds. This capability can in part explain how the odour of flucloxacillin minitablets with silica was described as odourless by human volunteers in chapter 4, despite the odour of flucloxacillin minitablets without silica being described as musty, pungent, plastic, and rotten.

SPME analysis detected a greater number of VOCs (over 40 compounds) of which octane, decane, undecane, toluene, and styrene are associated with a malodour that can contribute to the overall malodour of flucloxacillin. In comparison to direct HS sampling, SPME analysis detected a similar VOC profile for both flucloxacillin powder samples with and without silica. This similar VOC profile could be related to the high extraction efficiency of the SPME coated fiber and the potential competitive adsorption of VOCs with the added silica (Cho et al., 2003). SPME analysis also detected VOCs associated with the pineapple and menthol flavourings of flucloxacillin commercial formulations (Aldogman et al., 2022; Ciotea & Popa, 2020; Kamatou et al., 2013; Tomanić et al., 2022; Wei et al., 2011; Zheng et al., 2012)

Interestingly, dimethyl disulfide ($C_2H_6S_2$) was detected in headspace over the control aqueous flucloxacillin solution but not in any other preparations assessed. The addition of water can enhance the release of the volatiles into the gas phase from a matrix (Llompart et al., 1999) which could explain the detection of disulfide compound in the flucloxacillin solution rather than the solid samples. The non detection of disulfide compound in commercial formulations may be related to the presence of sodium in the commercial formulations. Sodium was previously reported to have a chemical neutralization effect on sulfur compounds forming a non-volatile sodium sulfide (Na_2S) (Gupta et al., 2007). Dimethyl disulfide has a specific unpleasant rotten cabbage odour with an approximate odour threshold of 7–12 ppb (Mert Sivri et al., 2022). Dimethyl disulfide can result from degradation of ethynthiol which is one of the flucloxacillin degradation-related VOC impurities. It was challenging to identify ethanethiol using the investigated GC-MS methods may be because of the low affinity of this compound for fiber coatings used in SPME method or their degradation under the analytical conditions (Dziekońska-Kubczak et al., 2020).

6.2.1 Advantages and limitations of GC-MS and future directions

In this thesis, GC-MS was employed to identify the volatile compounds that can contribute to the overall malodour of flucloxacillin. However, as observed from the results obtained in chapter 5 the identification of a volatile profile of medicines may not always be effective in the characterization of VOCs that are associated particularly to their malodour. The volatile profile of medicines can include both process-related volatile impurities and degradation-related volatile impurities which may or may not be malodourous.

While some of the GC-MS identified volatile compounds can contribute to the overall malodour of flucloxacillin, a key concern is the limited number of volatile sulfur compounds identified using the GC-MS methodology employed. Flucloxacillin has a sulfur atom in its thiazolidine ring that is thought to contribute to its overall malodour. The degradation pathway of flucloxacillin reveals a volatile sulfur compound ethythiol (Tiwari et al., 2014). Volatile sulfur compounds are organic compounds containing sulfur and mostly are responsible for unpleasant odours. Interestingly, dimethyl disulfide was the only volatile sulfur compound detected and only detected in the aqueous flucloxacillin solution headspace. Dimethyl disulfide can result from degradation of ethynthiol. Therefore, it is worth considering a methodology to specifically identify and quantify the volatile sulfur compounds in flucloxacillin headspace and measure their intensity across formulations. A wide range of sulfur-selective detectors can be used for monitoring the key sulfur VOCs associated with flucloxacillin's malodour to measure such volatiles (Barczak et al., 2022; Li et al., 2012; Lu et al., 2012).

GC-O-MS is a combination of the olfactometric detector with mass spectrometry that merges the characteristics of both devices into an integrated instrument. It is efficient

for the identification of odour-active compounds from numerous volatile constituents and may be worth exploration. The identification of odour-active compounds is conducted by comparison of the mass spectrum, retention index and odour descriptions with reference compounds. GC-O is useful for the identification of aroma-active compounds. However, it is not efficient for the qualitative analysis of volatile compounds. Thus, GC–MS is still needed to obtain the structural information of these odour-active compounds. GC-O-MS could be used to determine the contribution of individual volatile compounds to flucloxacillin's overall odour profile and inform an odour suppression formulation strategy based on component chemistry.

6.3 Future work

Based on the findings from this thesis, the following areas would warrant further exploration:

I. A follow-on study developing and testing educational intervention with health care professionals, parents, and children. There is a need to increase awareness of palatability and the importance of receiving the first-choice antibiotic among parents to avoid non-disclosure manipulation practices by the parents. There is also a need to increase palatability awareness of oral liquid antibiotics among healthcare professionals.

II. Future studies using a human sensory assessment are suggested to assess the retronasal odour and the taste of flucloxacillin minitablets after combining taste masking excipients and an odour suppressant such as silica. Investigating the relationship between odour, taste and flavour can inform formulation approaches to enhance the palatability and acceptability of paediatric formulations.

III. Future studies using GC-O-MS analysis can be used to screen the volatile compounds associated with flucloxacillin malodour. GC-O-MS will determine the contribution of individual volatile compounds to flucloxacillin's overall odour profile and inform an odour suppression formulation strategy based on component chemistry.

6.4 Conclusions

Antibiotic palatability issues caused GPs and pharmacists to switch oral liquid antibiotics to ensure treatment adherence despite their preference to follow the guidelines and select a first-choice antibiotics. In some circumstances, both professions had to select an unpalatable antibiotic despite knowing that it has poor palatability. Flucloxacillin was identified as a poorly palatable antibiotic with a malodour. Human volunteers associated the odour of unformulated aqueous flucloxacillin solution and minitablets with the descriptors musty, pungent, plastic, and rotten and unacceptable. The odour of a commercial solution was described as acceptable, fruity and aromatic whereas, commercial capsules and minitablets with silica were deemed acceptable and odourless. GC-MS using SPME analysis detected a number of volatile compounds which could contribute to overall flucloxacillin malodour, and the odours of flavourings added to commercial oral liquid formulations. This thesis presented evidence that the organoleptic properties associated with the poor palatability of oral liquid antibiotics can impact paediatric acceptability. Additionally, the thesis established a new medicine insight on using both human and GC methods to screen the odour profile of the poorly palatable antibiotic, flucloxacillin. These insights would support the pharmaceutical industry in screening the odour of medications with poor palatability.

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7 Appendix

7.1 Supplementary Information Chapter 2

7.1.1 Survey Questionnaire

Title page: Attitudes and experiences of healthcare providers to prescribing and dispensing of oral liquid antibiotics for paediatric patients.

If you agree to take part in this study, please complete the consent form overleaf.

Consent Form

Do you consent to participate in this study? *

Yes ☐

No ☐

Survey questions

*Required

Section 1: General Section

1. What is your gender?

Please tick one box.

☐ Male

☐ Female

☐ Prefer not to say

☐ Other:

2. What is your clinical discipline? *

Please tick one box.

☐ GP Skip to section 2

☐ Pharmacist Skip to section 7

Section 2: GP profile section

3. What is your current GP status?

Please tick one box.

☐ GP principal

☐ GP non-principal

☐ Sessional GP

☐ Locum GP

☐ GP trainee

☐ Other:

4. How long have you worked in general practice?
Please tick one box.

☐ 0–4 years

☐ 5–10 years

☐ more than 10 years

Section 3: GP practice section

5. How many GPs are in your practice?
Please tick one box.

☐ Single handed

☐ 2-3

☐ 4–5

☐ more than 6

6. How would you characterise your practice location?
Please tick one box.

☐ Urban

☐ Rural

☐ Mixed urban and rural

7. What approximate percentage of your patients have a GMS full medical card? (your best estimate)

8. What approximate percentage of your patients are children (age of birth to 12 years)? (your best estimate)

Section 4: factors that influence the prescribing of oral liquid antibiotics.

9. Please rank the following factors you consider when prescribing an oral liquid antibiotic product for children (age of birth to 12 years): Rank 1 for the factor considered most important, 2 for next most important etc.*

☐ Dosage regime (e.g., once daily, twice daily, three times daily)

☐ Clinical guidelines

☐ Palatability (e.g., smell, taste, aftertaste, and texture)

10. If you have other factors you consider when prescribing an oral liquid antibiotic product for children, please list them.

11. How often in the past have you changed your oral liquid antibiotic prescription choice because of dosage regimen? (your best estimate)
Please tick one box.

☐ Frequently (approximately weekly)

☐ Occasionally (approximately monthly)

☐ Rarely (approximately yearly)

☐ Never

12. How often in the past have you deviated from clinical guidelines related to oral liquid antibiotic prescribing because of poor palatability? (your best estimate) *
Please tick one box.

☐ Frequently (approximately weekly) skip to section 5

☐ Occasionally (approximately monthly) skip to section 5

☐ Rarely (approximately yearly) skip to section 5

☐ Never skip to section 6

Section 5: Palatability of oral liquid antibiotics

13. Please rank the reasons which cause you to deviate from clinical guidelines because of medicine's poor palatability (e.g., smell, taste, aftertaste, and texture) (where 1 is the most common reason and 3 is the least common reason): *

☐ Ensure compliance and adherence to treatment

☐ Maintain a good physician-patient relationship

☐ Parental/ caregiver pressure

14. If you have other reasons which cause you to deviate from clinical guidelines because of medicine's poor palatability, please list them.

15. How often in the past have you written ‘’*Do Not Substitute’’* when prescribing an oral liquid antibiotic for children (age of birth to 12 years) because of palatability issues (e.g., smell, taste, aftertaste, and texture)? (Your best estimate)
Please tick one box.

☐ Frequently (approximately weekly)

☐ Occasionally (approximately monthly)

☐ Rarely (approximately yearly)

☐ Never

16. How often in the past have you discussed the palatability (e.g., smell, taste, aftertaste, and texture) of oral liquid antibiotics with parents/caregivers when prescribing? (Your best estimate)
Please tick one box.

☐ Frequently (approximately weekly)

☐ Occasionally (approximately monthly)

☐ Rarely (approximately yearly)

☐ Never

17. From the following list of oral liquid antibiotics, please select the medicines you are aware patients can experience palatability (e.g. smell, taste, aftertaste and texture) issues with: *
Tick all that apply.

☐ Amoxicillin

☐ Azithromycin

☐ Cefalexin

☐ Ciprofloxacin

☐ Clarithromycin

☐ Co-amoxiclav

☐ Co-trimoxazole

☐ Erythromycin

☐ Flucloxacillin

☐ Metronidazole

☐ Nitrofurantoin

☐ Phenoxymethylpenicillin

☐ Trimethoprim

☐ Other:

18. Which oral liquid antibiotic do you think is the most palatable to children (age of birth to 12 years)? Indicate specific brand if possible. *

19. Which oral liquid antibiotic do you think is the least palatable to children (age of birth to 12 years)? Indicate specific brand if possible. *

20. We would like to further explore the issues around the palatability of oral liquid antibiotics for children. If you are interested in taking part in a telephone/online interview (approximately 15 minutes) on this research topic, please provide your contact details:

Name:

Phone number:

Email address:

Section 6: Palatability of oral liquid antibiotics

Similar to Section 5 (Questions 15-20) with question 13,14 excluded

Section 7: Pharmacist profile section

3. Which title would describe your current practice of pharmacy?
Please tick one box.

☐ Supervising community pharmacist

☐ Non supervising community pharmacist

☐ Locum community pharmacist

☐ Other:

4. How long have you been working as a community pharmacist?
Please tick one box

☐ 0–4 years

☐ 5–10 years

☐ more than 10 years

☐ Other:

Section 8: Pharmacist practice section

5. How many full-time equivalent pharmacists work in your community pharmacy?
Please tick one box.

- ☐ 1-2 pharmacists
- ☐ 3-5 pharmacists
- ☐ More than 5

6. What type of pharmacy business do you work in?
Please tick one box.

- ☐ Large multiple of eleven or more pharmacies
- ☐ Medium chain of 6 to 10 pharmacies
- ☐ Small chain of 5 to 2 pharmacies
- ☐ Single independent pharmacy

7. How would you characterise the community pharmacy you work in?
Please tick one box.

- ☐ Urban
- ☐ Rural
- ☐ Mixed urban and rural

8. What approximate percentage of your prescription patients have a GMS full medical card? (Your best estimate)

9. What approximate percentage of your prescription patients are children (age birth to 12 years)? (Your best estimate)

Section 9: Factors that influence the dispensing of oral liquid antibiotics.

10. Please rank the following factors you consider when dispensing an oral liquid antibiotic product for children (where 1 is the most important factor and 3 is the least important factor) *

- ☐ Availability of supply
- ☐ Product cost
- ☐ Palatability (e.g. smell, taste, aftertaste and texture)

11. If you have other factors you consider when dispensing an oral liquid antibiotic product for children, please list them.

12. How often in the past have you switched an oral liquid antibiotic product because of dosage regimen? (your best estimate)
Please tick one box.

- ☐ Frequently (approximately weekly)
- ☐ Occasionally (approximately monthly)
- ☐ Rarely (approximately yearly)
- ☐ Never

13. How often in the past have you switched an oral liquid antibiotic product because of palatability issues (e.g., smell, taste, aftertaste and texture)? (your best estimate) *
Please tick one box.

- ☐ Frequently (approximately weekly) skip to section 10
- ☐ Occasionally (approximately monthly) skip to section 10
- ☐ Rarely (approximately yearly) skip to section 10
- ☐ Never skip to section 11

Section 10: Palatability of oral liquid antibiotics (1)

13.a. If you have switched an oral liquid antibiotic product/s because of palatability issues (e.g. smell, taste, aftertaste and texture), please indicate which products you have switched from and which products you have switched to?

14. If you have switched an oral liquid antibiotic product/s because of dosage regimen, please indicate which products you have switched from and which products you have switched to?

15. From the following list of oral liquid antibiotics, please select the medicines you are aware patients can experience palatable issues with: *
Tick all that apply.

- ☐ Amoxicillin
- ☐ Azithromycin
- ☐ Cefalexin
- ☐ Ciprofloxacin

☐ Clarithromycin

☐ Co-amoxiclav

☐ Co-trimoxazole

☐ Erythromycin

☐ Flucloxacillin

☐ Metronidazole

☐ Nitrofurantoin

☐ Phenoxymethylpenicillin

☐ Trimethoprim

☐ Other:

16. Which oral liquid antibiotic do you think is the most palatable to children (age from birth to 12 years)? Indicate specific brand if possible. *

17. Which oral liquid antibiotic do you think is the least palatable to children (age from birth to 12 years)? Indicate specific brand if possible. *

18. How would you identify an oral liquid antibiotic product that may have poor palatability?

Tick all that apply.

☐ Parent/caregiver feedback

☐ Parent/caregiver unwilling to administer the drug to the children

☐ Drug smell during preparation

☐ Drug texture during preparation

☐ Other:

Section 11: Palatability of oral liquid antibiotics (1)

Similar to Section 10 (Questions 14-18) with question 13.a excluded.

Section 12: Palatability of oral liquid antibiotics (2)

19. What oral liquid antibiotic product/s with smell issues have you encountered during their preparation? State the brand name of such product(s) if applicable.

20. What oral liquid antibiotic product/s with texture issues have you encountered during their preparation? State the brand name of such product(s) if applicable.

21. How often do you discuss with parents/caregivers about oral liquid antibiotic palatability when dispensing? (your best estimate)
Please tick one box.

☐ Frequently (approximately weekly)

☐ Occasionally (approximately monthly)

☐ Rarely (approximately yearly)

☐ Never

22. What advice would you give to a parent/ caregiver who is unable to administer an unpalatable oral liquid antibiotic to children?

☐ Dividing the required dose into smaller portions

☐ Manipulate the required doses (e.g., mixing with food or diluting in a flavoured liquid)

☐ Promising a reward to the child after taking dose

☐ Other:

23. We would like to further explore the issues around the palatability of oral liquid antibiotics for children. If you are interested in taking part in a telephone/online interview (approximately 15 minutes) on this research topic, please provide your contact details:

Name:

Phone number:

Email address:

7.1.2 Demographic data

Supplementary Table S2.1. *Healthcare professional demographics. Total responses n = 244.*

Parameters	**GPs % (n)**	**Pharmacists % (n)**
Clinical discipline	24.2 (59)	75.8 (185)
Gender Male Female Prefer not to say	 32.2 (19) 66.1 (39) 1.7 (1)	 26.5 (49) 72.4 (134) 1.1 (2)
Role	GP principals 7.5 (28) GP trainees 35.6 (21) GP non-principals 8.5 (5) Sessional GPs 6.8 (4) Other 1.7 (1)	Supervising community pharmacist* 51.1 (94) Non supervising community pharmacist 33.2 (61) Locum community pharmacist** 13.6 (25) Other 2.2 (4) & **Missing (n= 1)**
Period of working 0–4 years 5–10 years more than 10 years	 37.3 (22) 13.6 (8) 49.2 (29)	 14.1 (26) 13.5 (25) 72.4 (n=134)
Full-time staff working in the practice	Single handed 8.5 (5) 2-3 GPs 39 (23) 4–5 GPs 37.3 (22) More than 6 GPs 15.3 (9)	1-2 pharmacists 76.1 (140) 3-5 pharmacists 21.7 (40) More than 5 pharmacists 2.2 (4) **Missing (n= 1)**
Practice location Urban Rural Mixed urban and rural	 44.8 (26) 27.1 (16) 27.1 (16) & **Missing (n= 1)**	 43.8 (81) 19.5 (36) 36.8 (68)
Type of pharmacy business Large multiple of 11 or more Medium chain of 6 to 10 Small chain of 5 to 2 Single independent pharmacy		 24.5 (45) 8.7 (16) 23.4 (43) 43.5 (80) & **Missing (n= 1)**

* Supervising community pharmacist is the person responsible for the day-to-day management and operation to the pharmacy.

** Locum community pharmacist is a pharmacist employed on a contractual basis through an agency, rather than having a permanent salaried position.

Percentage of prescription patients with a GMS full medical card		
0-50%	36.8 (21)	36.8 (68)
51-100%	63.2 (36) & **Missing (n=2)**	63.2 (117)
Percentage of prescription patients are children		
0-20%	64.9 (37)	77.5 (141)
20-50%	35.1 (20)	20.9 (38)
51-100%	0 (0) & **Missing (n=2)**	1.6 (3) & **Missing (n=3)**

7.1.3 Other factors that influence prescribing and dispensing of oral liquid antibiotics

Supplementary Table S2.2. *Other factors that influence prescribing and dispensing of oral liquid antibiotics reported by GP and pharmacist respondents. Responses were received from 76 pharmacists with 122 responses and from 20 GPs with 20 responses.*

Other factors	List of the factors	GPs % (n)	Pharmacists % (n)
Patient factors	Allergy	20 (4)	6.6 (8)
	Customer preference, patient feedback	10(2)	3.3 (4)
	Antimicrobial history	10 (2)	0.8 (1)
	Age appropriate	5 (1)	4.1 (5)
	Ability to swallow or whether the child can take tablet medication	5 (1)	0.8 (1)
	Parental attitude and education	15 (3)	-
	Child's weight	10 (2)	-
	Compliance	5 (1)	-
	Illness	5 (1)	-
	Co-morbidities	-	3.3 (4)
	Ease of dosing delivery	-	2.5 (3)
Product factors	Duration of therapy	5 (1)	4.1 (5)
	Route of administration	5 (1)	1.6 (2)
	Cost	5 (1)	-
	Dose volume	-	21.3 (26)
	Frequency	-	2.5 (3)
	Shelf life	-	7.4 (9)
	Stability	-	2.5 (3)
	Storage	-	6.6 (8)
	Strength	-	4.9 (6)
	What is prescribed	-	4.9 (6)
	Indication	-	4.1 (5)
	Preferred generic	-	3.3 (4)
	Immediate use or dry, easy to disperse when given dry	-	3.3 (4)
	Expiry date	-	2.5 (3)
	Ease of measuring dose	-	2.5 (3)
	Choice of manufacturer	-	2.5 (3)
	Pack size	-	1.6 (2)
	Discount	-	0.8 (1)
	Dosage form	-	0.8 (1)
	appropriate labelling	-	0.8 (1)
	Viscosity	-	0.8 (1)

7.1.4 Switching antibiotic products by pharmacists because of palatability issues

Supplementary Table S2.3. Switching antibiotic products by pharmacists because of palatability issues. 113 pharmacists answered this question with 143 responds of which 9 were could not remember.

Antibiotics	**Examples revealed of switching between products of the same antibiotic (n=44)**	**Examples revealed of switching to a different antibiotic (n=64)**	**Examples revealed of products switched from without specifying which product switched to (n=26)**
Phenoxymethylpenicillin (33.6%, n=38)	Kopen® to Calvepen® (n=17) and from Calvepen® to Kopen® (n=7)	Calvepen® to Amoxicillin® (n=4), penicillin v to Cefaclor® (n=1), penicillin v to Oramox® (n=1). Calvepen® to another antibiotic (n=6)	Calvepen® (n=2)
Clarithromycin (25.7%, n=29)	-	Klacid® to Distaclor® (n=10), Klacid® to another antibiotic (n=7)	Klacid® (n=12)
Flucloxacillin (22.1%, n=25)	Switching to Floxapen® (n=3), from liquid to tablet (n=1), between flucloxacillin brands (n=3)	Flucloxacillin® to Amoxicillin® (n=7), Flucloxacillin® to another antibiotic (n=6)	Flucloxacillin® (n=5)
Amoxicillin (11.5%, n=13)	Oramox® to Amoxicillin® (n=1) and Clonamox® to Amoxicillin® (n=1), between amoxicillin brands (n=4)	Pinamox® to Augmentin duo® (n=2), Amoxicillin® to Distaclor® (n=2), Amoxicillin® to another antibiotic (n=3)	-
Co-amoxiclav (10.6%, n=12)	Germentin® to Augmentin® (n=1)	Augmentin® to Distaclor® (n=2), Augmentin® to Amoxicillin® (n=3), Augmentin® to another antibiotic (n=3)	Augmentin duo® (n=2), Augmentin® (n=1)
Other (15%, n=17)	From a flavour to another flavour (n=5), from Primacine® to Erythroped® (n=1)	Zinnat® to Distaclor® (n=2), Erythroped® to Distaclor® (n=1), Kefflex® to Amoxicillin® (n=1) or to Augmentin duo® (n=1), Zithromax® to Erythrocin® (n=1), from macrolide to penicillin (n=1)	Zithromax®, Erythromycin®, Suprax®, and Furantoin®

7.1.5 Switching antibiotics because of dosage regimen

All respondents were asked how often in the past had they switched an oral liquid antibiotic product for children because of dosage regimen. Almost half of the pharmacists (47%) and GPs (51%) indicated that they rarely (approximately yearly) changed dispensing or prescription choice because of dosage regimen. Similarly, occasionally (approximately monthly) was reported by 37.3% and 39%. of pharmacists and GPs respectively. It was apparent that the same proportion of both professions (10%) reported that they never switched for this reason.

Pharmacists who reported that they had switched an oral liquid antibiotic product because of dosage regimen (89.7%, n=166) were asked to indicate which products they had switched from and which products they had switched to. Eighty participants (48.2%) responded to this question of whom 14 were unsure or cannot recall.

28.8% of the participants switched from low strength (125mg/5ml) to high strength (250mg/5ml) either of the same product or between products of the same antibiotic (n=23). Changing to a more concentrated products was reported by the participants that it reduces the volume for poor palatability, avoid needing to dispense a second bottle by halving the dosage volume, easier to disguise in food, and decrease the compliance issue. In contrast, 6.3% switched from high strength (250mg/5ml) to low strength (125mg/5ml) of the same product (n=5). However, 15% of the participants reported switching between co-amoxiclav products (n=12). Examples of the products reported are shown in ***Supplementary Table S2.***.

Supplementary Table S2.4. Switching antibiotic products by pharmacists because of dosage regimen. 80 pharmacists responded to this question of whom 14 were unsure or cannot recall.

Switching antibiotic products by pharmacists because of dosage regimen	**Examples of switching strengths of the same product**	**Examples of switching between products of the same antibiotic**	**Examples of switching to a different antibiotic**
Switching from low strength (125mg/5ml) to high strength (250mg/5ml) of the same product (28.8%, n=23)	Pinamox® (n=4), Amoxicillin® (n=3), Oramox® (n=1), Kopen® (n=1)	From Kopen® to Calvapen® (n=3), and from Amoxicillin® generic to Amoxil® (n=1)	-
Switching from high strength (250mg/5ml) to low strength (125mg/5ml) of the same product (6.3%, n=5)	Amoxicillin® (n=2), Oramox® (n=1)	-	-
Switching between co-amoxiclav products (15%, n=12)	-	From Augmentin junior® and Augmentin paediatric® to Augmentin duo® (n=5), from Augmentin duo® to Augmentin® (n=2), and Germentin® to Augmentin® (n=1)	-
Other (16.3%, n=13)	Switching between various strengths such as Amoxicillin® (n=4), Flucloxacillin® (n=1)	Switching from solid to liquid dosage forms (n=5)	From Flucloxacillin® to Co-amoxiclav® (n=1), to Augmentin® (n=1), or to Augmentin duo® (n=1)

7.1.6 Advice pharmacists give to a parent/caregiver who is unable to administer an unpalatable oral liquid antibiotic to a child

Supplementary Table S2.5 *Other Advice would pharmacists give to a parent/caregiver who is unable to administer an unpalatable oral liquid antibiotic to a child with a total of 37 responses from pharmacists for this question.*

Advice would a pharmacist give to a parent/ caregiver	% (n)
Using a syringe aimed to back of the mouth to avoid tastebuds and administer small amounts into side of the mouth	32.4 (12)
Taking water or a flavoured drink afterwards to wash the medicine down	13.5 (5)
Switching to an alternative antibiotic if unable to take	8.1 (3)
Distraction techniques	8.1 (3)
Treat the child like a grown up and highlight the importance of the medicine	8.1 (3)
Mix with soft food such as chocolate syrup, yoghurt or squash	5.4 (2)
Suck an ice pop or ice cube beforehand to numb the tastebuds	5.4 (2)
If possible, use higher dose & less volume to administer	2.7 (1)
Ask how manageable the palatability issues are	2.7 (1)
Praising the child for taking the antibiotic	2.7 (1)
Offering the child, a reward	2.7 (1)
Ensure the full dose is consumed	2.7 (1)
If pain relief is due give the immediately after to mask taste	2.7 (1)
Changing to tablets for children 8+	2.7 (1)

7.2 Supplementary Information Chapter 3

7.2.1 Interview Topic Guides

GPs and trainee GPs

1. Which factors do you consider when prescribing oral liquid antibiotics for children?

2. How do you decide which drug / brand to prescribe?

3. To what extent could poor palatability affect your prescription?

4. How are you made aware that an oral liquid antibiotic is poorly palatable for a child?

5. In what manner could discussions with parents/ caregivers about antibiotic palatability and their willingness to give it to their children change your antibiotic prescribing?

6. What advice would you give to a parent/ caregiver who is unable to administer an unpalatable oral liquid antibiotic to children?

7. Which oral liquid antibiotics do you think are more palatable/ unpalatable to children? Why do you think they are palatable/unpalatable?

8. Under what circumstances would you prescribe oral liquid antibiotic with poor palatability?

9. Having completed this interview, to what extent has it raised your awareness of palatability issues when prescribing?

10. Having completed this interview, to what extent will you change your practice with regards to prescribing antibiotics for children?

11. Is there anything else you would like to add?

Pharmacists

1. Which factors do you consider when selecting a prescribed oral liquid antibiotic product for children?

2. How do you decide which drug formulation/ brand to dispense?

3. To what extent could poor palatability affect your choice of product to dispense?

4. How are you made aware that an oral liquid antibiotic is poorly palatable for a child?

5. In what manner could discussions with parents/ caregivers about antibiotic palatability and their willingness to give it to their children change your antibiotic dispensing practice?

6. What advice would you give to a parent/ caregiver who is unable to administer an unpalatable oral liquid antibiotic to children?

7. Which oral liquid antibiotics do you think are more palatable/ unpalatable to children? Why do you think they are palatable/ unpalatable?

8. Under what circumstances would you dispense an oral liquid antibiotic with poor palatability?

9. Having completed this interview, to what extent has it raised your awareness of palatability issues when dispensing?

10. Having completed this interview, to what extent will you change your practice with regards to dispensing antibiotics for children?

11. Is there anything else you would like to add?

Supplementary Table S3.1. *Healthcare professional demographics. Total responses n = 20.*

Parameters	**% (n)**
Clinical discipline	
GPs	35 (7)
Pharmacists	65 (13)
Gender	
Female	80 (16)
Male	20 (4)
Period of working	
2–9 years	55 (11)
≥ 10 years	45 (9)
Status	
Parent	30 (6)
No children	70 (14)

7.3 Supplementary Information Chapter 4

7.3.1 Study protocol

7.3.1.1 Study Synopsis

Full Study Title	Assess the aroma of flucloxacillin formulations using a human panel
Abstract (Brief)	A single-blind observational study will be used to evaluate the smell of five flucloxacillin samples using a panel of 20 to 50 healthy adult volunteers. Prior to testing the samples, volunteer's sensory acuity will be tested using commercially available smell kits.
Study Design	Observational study
Study Population	20 to 50 healthy volunteer adults aged over 18 years.
Entry Criteria	**Inclusion Criteria:** Healthy volunteers aged over 18 years will be recruited. **Exclusion Criteria:** Volunteers who have any significant ongoing medical problems that would jeopardize the safety of the volunteer or impact the validity of the study results.
Estimated Study start and End Dates	**Start date:** January 2024 **End date:** June 2025
Data collection and Statistical Analysis.	The smell of the five flucloxacillin samples will be assessed using a data collection form designed for the purpose. Data pertaining to all evaluated samples will be summarized using descriptive statistics. All documentation and correspondence pertaining to the study (source workbooks, raw data, emails etc.) will be kept in accordance with University College Cork data protection procedures and guidelines.

7.3.2 Background and Significance of the question

7.3.2.1 Introduction

Flucloxacillin is an antibiotic indicated for the treatment of skin, wound, bone, and ear infections in children, adolescents, and adults including throughout pregnancy and while breastfeeding. However, flucloxacillin has a malodour that causes it to be an unpalatable antibiotic, in particular for paediatric patients. Palatability is the overall appreciation of a drug related to its smell, taste, aftertaste, and texture (i.e., feeling in the mouth). Smell is the main sense that contributes to the overall flavour of products. The palatability of antibiotic products is a key consideration to ensure compliance, adherence and effective treatment. However, poor palatability, leading to incomplete antibiotic treatment, can result in disease recurrence and can lead to the use of broad-spectrum antibiotics which is discouraged because it may then cause antimicrobial resistance and rising rates of resistance in the general population. The motivation for this study is to evaluate formulation approach which can minimise the malodour of flucloxacillin at paediatric doses and hence improve its overall palatability.

7.3.2.2 Aims of the study

The aim of this study is to assess the odour of a range of flucloxacillin formulations, suitable for paediatric administration, using a cohort of adult human volunteers. This aim will be achieved by comparing the smell of an unformulated flucloxacillin solution with a commercial flucloxacillin liquid formulation and flucloxacillin tablet and capsule formulations.

7.3.2.3 Hypothesis

Formulation approaches, such as addition of flavourings and silica, can alter and suppress flucloxacillin's malodour.

7.3.2.4 Investigational products

Five flucloxacillin samples will be smelled:

- 5 ml of a commercial flucloxacillin solution that contains 250 mg flucloxacillin sodium.
- 5 ml of aqueous flucloxacillin solution that contains 250 mg flucloxacillin sodium.
- Commercial capsule formulation containing 250 mg flucloxacillin sodium.
- Tablet formulation containing 250 mg flucloxacillin sodium and approved pharmaceutical ingredients (without silica).
- Tablet formulation containing 250 mg flucloxacillin sodium and approved pharmaceutical ingredients (including silica).

7.3.3 Trial Objectives and Purpose

7.3.3.1 Primary objective

The primary objective of the study is to generate palatability smell responses from a small cohort of human volunteers for the five flucloxacillin formulations. Patient acceptability of the smell is likely to have a significant impact on patient adherence,

and consequently on the effectiveness of the medicinal product as well as patient wellbeing.

7.3.3.2 Secondary objective(s) (if applicable)

The secondary objective of the study is to test volunteers' sensory acuity and their ability to smell.

7.3.3.3 Safety Objectives (if applicable)

Safety and tolerability will be evaluated throughout the study (e.g., by adverse events, AEs, etc.). However, as all samples will be smelled and NOT ingested, adverse effects are unlikely to occur. No active ingredient will be tasted or swallowed. This will ensure that there will be minimal or no risk.

7.3.4 4.0 Description of methodology

7.3.4.1 Type of Study- study design

This is a single-blind observational study to evaluate the sensory smell of five flucloxacillin samples using a panel of 20 to 50 healthy adult volunteers. Prior to testing the samples, volunteer's sensory acuity will be tested using commercially available smell kits. The study steps will be as follow:

1. Recruitment – Provision of volunteers for medical assessment

- It is planned to recruit sufficient volunteers to ensure there are 20 to 50 evaluable data sets.
- Eligible volunteers will attend the study facility for a period of between 1-3 hours.

2. Medical screening for eligibility for inclusion in the study

- A registered health practitioner external to the School of Pharmacy (i.e. a registered nurse, pharmacist, or medical doctor) will conduct medical screening to ensure that only healthy volunteers are enrolled on the study.

3. Sensory acuity assessment

- Following medical assessment and prior to smelling flucloxacillin samples the smell acuity of volunteers will be assessed using commercially available smell test kits.
- The commercial Sensonics™ smell test kit employed will be used to conduct the validated 8-item National Health and Nutrition Survey (NHANES) smell test which is reported to be an efficient and brief test for evaluating smell function. The test includes micro encapsulated (scratch & sniff) odours. Each scratch and sniff strip is embedded with an odourant. By scratching / rubbing the strip, odours are released. Each volunteer will be asked to identify the correct odour using a multiple-choice form provided. The test includes four food-related odourants (chocolate, strawberry, grape and onion), two warning odourants (natural gas and smoke), and two common household odourants (leather and soap).

4. Smell questionnaire familiarization

- Following on from the acuity assessment, volunteers will be familiarized with the smell questionnaire that they will fill out in the study and will be trained on how they will carry out the smell test.
- There will be a break of at least 5 min before starting the test solutions.

5. Preparation of samples

- All formulations will be prepared and stored in line with a standard operating procedure.
- All formulations will be given to the volunteers singularly.
- To prevent biasing effects of the order of sample presentation and sample carry-over, the order of sample presentation to volunteers will be randomized.

6. Volunteers smell the five samples

- When each volunteer receives each sample, they will smell it and will complete a smell questionnaire individually and privately thereafter.
- There will be a break of at least 5 min between smelling each of the samples.
- In total, volunteers will smell 5 samples containing flucloxacillin.
- Accountability and volunteer compliance with study procedures will be assessed by maintaining dispensing and returning records.
- All samples will be disposed of in line with a standard operating procedure.
- It is expected that the study will be executed over approximately 8-12 weeks.

7. Criteria for individual volunteer data evaluation

- A volunteer is considered evaluable if he has completed the smell questionnaires for all smell tests during that visit and their sensory acuity has been measured.

8. Data collection, evaluation, reporting & output

- A description of Data Management is provided in section 7.0 and 8.0. Data Protection and Confidentiality is provided in section 8.0 below. The results of this study will be presented in the PhD thesis of Ms. Ayat Elgammal and at national and international conferences, published in relevant peer-review journals and outreach and public engagement opportunities.

7.3.4.2 4.2 Recruitment of study participants

Volunteers will be recruited by direct advertising to the public. The aim is to recruit 20 to 50 human panels to smell five samples of flucloxacillin. Volunteers who are withdrawn will be replaced as required, to ensure 20 to 50 evaluable volunteers at the end of the study.

7.3.4.3 Subjects Eligibility Criteria

Inclusion criteria:

a. Volunteers aged over 18 years.
b. Negative pregnancy test (female volunteers only).
c. Female volunteers of child-bearing potential must be using an effective form of contraception such as abstinence, condoms, combined oral contraceptive pill, progestogen only pill, hormonal implants, intrauterine contraceptive device (IUCD) etc. A history of tubal ligation, hysterectomy, or vasectomy (male partner) is also acceptable.
d. Volunteers must be non-smokers.
e. Volunteers must be able and willing to give written informed consent and to comply with the requirements of this study protocol.
f. Clinically acceptable urinalysis results.

Exclusion criteria

Volunteers who meet any of the following criteria will be excluded from the study:

a. Volunteers with penicillin allergy.
b. Volunteers with a previous history of flucloxacillin-associated jaundice/hepatic dysfunction.
c. Volunteers who have any significant ongoing medical problems that, in the opinion of the Investigator, would jeopardize the safety of the volunteer or impact the validity of the study results.
d. Volunteers with medically diagnosed or self-perceived smell disorder (anosmia 'complete lack of smell'; hyposmia 'decreased ability to smell'; dysosmia 'altered perception of odour')
e. Volunteers who are pregnant or lactating.
f. Volunteers of childbearing potential who refuse a pregnancy test.

7.3.5 4.3 Sampling and Randomisation (if applicable)

No formal sample size calculation has been made. The aim is to achieve 20 to 50 enrolled and evaluable volunteers.

This is a single-blind study in which the smell procedure assignment for each sample will not be known to the volunteers only.

Sample randomisation will be used to minimize bias in the assignment of volunteers to different sequence groups, to increase the likelihood that known and unknown attributes (e.g., demographic and baseline characteristics) are evenly balanced across sequence group.

7.3.6 Study Procedures and Schedule of Events

Table 1: Schedule of Events

Procedure	Description
Recruitment	Volunteers will be advised regarding protocol restrictions during the recruitment.
Volunteer information	Demographic information will be taken (date of birth and gender will be recorded).
Informed consent	An explanation of the study (its nature, purpose, expected duration and the benefits and risks involved in study participation) will be given. Data subject rights under Data Protection regulations will be explained.
Inclusion/Exclusion Criteria	Determination if volunteers pass inclusion/exclusion criteria will be made by the Clinical Investigator.
Urinalysis	Urine will be checked before the sensory acuity assessment using a commercially available urinalysis kit. If an abnormality is identified during urine analysis, volunteers will be advised to visit a general practitioner (GP) for further evaluation.
Pregnancy Test (females only)	A pregnancy test will be performed for females only before the sensory acuity assessment using a commercially available pregnancy test kit. If a positive pregnancy result is identified, the volunteer will be advised to visit her GP to confirm the pregnancy and sign-up for antenatal care. UCC-based volunteers will also be provided be contact information for UCC confidential staff and student counselling services.
Sensory acuity assessment	The sensory acuity of volunteers will be assessed using commercially available smell kits.
Smelling of Products	The volunteers will smell each sample and will complete a smell questionnaire individually and privately
Smell Questionnaire	
Throughout the study	A certified first aider will be available at all times during the study in case of an adverse event is experienced. Before leaving the study centre, each volunteer will be provided with a copy of the signed consent form stating the email address of the investigator.

7.3.7 6.0 Outcome measures

7.3.7.1 6.1 Primary Outcome

The primary outcome is to generate palatability smell responses from a small cohort of human volunteers for the five flucloxacillin formulations.

7.3.7.2 6.2 Secondary Outcome

Test volunteers' sensory acuity and their ability to smell.

7.3.7.3 6.3 Safety outcomes (if relevant)

Adverse events

7.3.8 Data Management

- Sensory smell of the five flucloxacillin formulations will be assessed using a data collection form designed for the purpose. Data collected for all evaluated products will be summarized using descriptive statistics.
- All documentation and correspondence pertaining to the study (source workbooks, raw data, emails etc.) will be kept in accordance with University College Cork data protection procedures and guidelines.
- All study related documents will be retained for a minimum period of 5 years. After this time, the sponsor will be contacted to ascertain whether continued storage or destruction is required in accordance with current regulations.
- Quality control of all data collected from this study will be performed in accordance with internal quality assurance procedures within the School of Pharmacy.
- Direct access will be granted to authorised representatives from the host institution to permit trial-related monitoring, audits and inspections.

7.3.9 Data Protection and Confidentiality:

All relevant national and local requirements regarding data protection, including GDPR and Health Research Regulations, will be adhered to. The data will be pseudonymised. The trial staff will ensure that the volunteers' anonymity is maintained. The volunteers will be identified only by initials and a volunteer's identification number on the case report form (CRF) and any database. All documents will be stored securely. The study will comply with the Data Protection Act (General Data Protection Regulation 2016/679).
Pseudonymity of volunteer data is assured by means of the unique study ID number allocated on enrolment. Throughout the study, volunteers will be identified by this study ID number. At each site, the Principal Investigator will hold a hard copy list linking the study ID to patient details. This list will be kept in a locked filing cabinet. If the patient's name, initials, or year of birth appears on a document (e.g. laboratory report), that must be transferred patient identifiers will be redacted before a copy of the document is transferred.

Participants will receive a copy of the Sponsor Data protection Notice (DPN). The DPN will inform them of their rights about their data and provide contacts for Sponsor Data controller and Data protection commissioner.

Participants will also be informed that study monitors and the Ethics Committee may inspect their urinalysis, and pregnancy results to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with legal data protection requirements.

7.3.10 CREC approvals and Governance:

This trial has been reviewed by and received approval from the Clinical Research Ethics Committee of the Cork Teaching Hospitals.

7.3.11 Insurance:

This trial is covered by University College Cork clinical trials insurance policy.

7.3.12 Potential Risks of the intervention and the study procedures: (if applicable)

As the products under investigation will be smelled and not ingested the risks associated with participation can be considered negligible and the burden can be considered minimal.

7.3.12.1 Adverse Event reporting (if applicable)

The adverse events will be evaluated throughout the study in accordance with a standard operating procedure designed for this purpose. However, it is unlikely to occur as all samples will be smelled and not be tasted or ingested. However, in the case of occurrence of an adverse event a Certified First Aider will be available throughout the study period. Immediate reporting should be done as follows:
Immediate phone call to PI and the Clinical Research Reporting Officer, UCC.
Non-serious adverse events will be fully documented in the CRF and will not be reported to the sponsor on a non-expedited basis.
When reporting an adverse event, the following information should be provided at a minimum:
- Patient's information (e.g., initials, date of birth, age, sex, etc.)
- Reporter's information (including profession)
- Details about the event/reaction
- Name of drug

7.3.12.2 Deviations from the Protocol

Any Deviations from the protocol will be noted by the PI or research team members. Any deviations which have the potential to affect participant safety, or the integrity of the study data will be reported to the sponsor.

7.3.13 Withdrawal of Participants from the study - (If relevant)

Volunteers have the right to voluntarily discontinue study treatment or withdraw from the study at any time for any reason without any consequences. The investigator has the right to discontinue a volunteer from study treatment or withdraw a volunteer from the study at any time if it is in the best interest of the volunteer.
Volunteers must be withdrawn from the study for any of the following reasons:

- Withdrawal of consent by the volunteer.
- Any medical condition that the investigator or sponsor determines may jeopardize the volunteer's safety if she or he continues receiving the study treatment.
- Ineligibility (either arising during the study or retrospectively having been overlooked at screening).
- An adverse event which requires discontinuation of participation in the study.

If a volunteer is withdrawn before completing the study, the reason for withdrawal must be entered on the appropriate CRF page. If a volunteer is withdrawn due to an adverse event, the investigator will arrange for follow-up visits until the adverse event has resolved or stabilized.

7.3.14 End of study

7.3.14.1 Definition of end-of-trial

The definition of the end of the trial/study is defined as the last visit of the last volunteer.

7.3.14.2 Premature termination of the study

If the study is abandoned prior to commencement of any protocol activities, the PI must notify the independent ethics committee IEC by letter outlining the reasons for abandonment of the trial.

After the start of protocol activities (recruitment) but prior to the commencement of testing (medical assessment & smelling the samples), the study may be terminated by the PI without consultation with the Independent Ethics Committee (IEC). The IEC must be notified if the study is terminated, immediately and at the latest within 15 days after the study is halted, clearly explaining the reasons.

Once testing (medical assessment & smelling the samples) has begun, the study will be completed as planned unless the following criteria are satisfied that require temporary solution or early termination of the study.

- New information regarding the safety of the flucloxacillin that indicates a change in the risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for volunteers participating in the study.
- Significant violation of the protocol that compromises the ability to achieve the primary study objectives or compromises volunteer safety.
- The study may be terminated or suspended at the request of the IEC.

7.3.15 Approval and Agreement to the Protocol

The Principal Investigator agrees to perform the clinical study as written and to abide by this protocol except in case where deviation is necessary for urgent safety reasons.

Supplementary Table S4.1. *Weight and hardness specification of individually 20 minitablets taken at random*

Tablet	Weight mg	Hardness N	% Tablet label claim dose
1	39	88	99.2
2	40	87	101.5
3	40	84	96.6
4	42	88	102.3
5	40	83	97.4
6	41	84	102.4
7	38	82	98.7
8	40	86	101.6
9	38	85	97.1
10	40	84	98.3
11	38	85	-
12	40	88	-
13	40	84	-
14	42	83	-
15	42	85	-
16	38	85	-
17	40	88	-
18	39	83	-
19	42	85	-
20	41	83	-
Mean	**40**	**85**	**99.5**
Standard Deviation	**1.3**	**1.8**	**2.1**

Supplementary Table S4.2. *Randomization order of flucloxacillin samples*

Sample order	Volunteer 1	Volunteer 2	Volunteer 3	Volunteer 4	Volunteer 5
1	WAA	DAB	AOA	HAS	RRA
2	DAB	RRA	DAB	WAA	HAS
3	AOA	WAA	RRA	RRA	AOA
4	RRA	HSA	WAA	AOA	DAB
5	HSA	AOA	HSA	DAB	WAA

DAB: Flucloxacillin control aqueous solution

RRA: Flucloxacillin commercial solution

WAA: Flucloxacillin commercial capsule

AOA: Flucloxacillin minitablet without silica

HAS: Flucloxacillin minitablet with silica

Supplementary Figure S4.1. Medicine containers of flucloxacillin samples

7.4 Supplementary Information Chapter 5

Supplementary Table S5.1. Compounds identified by HS-SPME/GC-MS in flucloxacillin powders.

Class	Name	CAS	RI	Ref	Compound	Flucloxacillin powder peak area	Flucloxacillin powder + 2% silica peak area
Acid	2-Ethylhexanoic acid*	149-57-5	1183	NA		7504359	8203101
Alcohol	Ethanol	64-17-5	501	506	sweet, alcoholic, medicinal	22178	42573
Alcohol	2-Propanol	67-63-0	536	539	alcoholic, musty, woody	873	18354
Alcohol	Diacetone alcohol	123-42-2	910	913	mild, pleasant	134295	0
Aldehyde	Butanal, 3-methyl-	590-86-3	691	692	malty, cheese, green, cocoa	355494	349317
Aldehyde	Nonanal	124-19-6	1148	1150	green, citrus, fatty, floral	49992	159709
Aldehyde	Undecanal	112-44-7	1340	1354	waxy, soap, floral, citrus, green, fatty	36871	36050
Alkane	Heptane	142-82-5	700	700	sweet, ethereal	45364	48048
Alkane	Heptane, 4-methyl-*	589-53-7	768	NA		127665	804609
Alkane	Octane	111-65-9	823	800	gasoline-like	0	294002
Alkane	2,4-Dimethyl-1-heptene	19549-87-2	847	848		834390	3082904
Alkane	Decane	124-18-5	999	1000	gasoline-like to odourless	2430988	4103838
Alkane	Undecane	1120-21-4	1099	1100	gasoline-like to odourless	291843	253741
Alkane	Tridecene	41446-57-5	1316	1300	mild, pleasant	185711	170269
Benzene	Benzene	71-43-2	686	682	aromatic	10509	10936
Benzene	Toluene	108-88-3	792	794	nutty, bitter, almond, plastic	36686	29703
Benzene	p-Xylene	106-42-3	897	898	grainy, sweet	144276	116326
Benzene	o-xylene	95-47-6	926	929	geranium	70092	49985
Benzene	Styrene	100-42-5	927	929	plastic	9843	174758
Benzene	Mesistilene*	108-67-8	997	NA		15417	35042
Benzene	1,3-Di-tert-butylbenzene	1014-60-4	1284	1286		875044	1235208
Ester	Ethyl acetate	141-78-6	640	642	fruity, apple, weedy, green	8442629	9038343
Ester	Ethyl 2-ethylhexanoate*	2983-37-1	1133	NA	fresh, orris, fruity	12599737	11397449
Ester	Ethyl benzoate	93-89-0	1229	1232	fruity, medicinal, cherry	6665	6430
Ester	Ethyl benzeneacetate	101-97-3	1303	1305	sweet, floral, honey, rose, balsamic, cocoa	15786	13201
Ester	Phenethyl 2-methylbutyrate*	24817-51-4	1570	NA	floral, green, tropical, waxy, rose	90032	90098
Ketone	Acetone	67-64-1	535	533	solvent, ethereal, sour milk, apple	293905	332033
Ketone	2-Pentanone	107-87-9	740	730	sweet, fruity, ethereal, fermented	4038	3339
Ketone	Methyl isobutyl ketone	108-10-1	781	784	green, herbal, fruity, dairy, spicy	2986	0

Ketone	3-Penten-2-one, 4-methyl-*	141-79-7	839	NA	peppermint	788120	850349
Ketone	3-Heptanone	106-35-4	925	927	green, fatty, fruity	195103	194058
Ketone	Acetophenone	98-86-2	1142	1030	must, flower, almond, glue	15490	11457
Other	Acetonitrile**	75-05-8	552	NA	aromatic, ether-like, sweet, faint	599603	367304
Other	Methylene chloride*	75-09-2	564	NA		19122	24423
Phenol	Phenol	108-95-2	1095	1112	sweet, tarry, chemical, phenolic	3300	0
Terpene	α-Pinene	80-56-8	947	950	pine, camphoreous, earthy, woody	15575	15365
Terpene	3-Carene	13466-78-9	1036	1027	sweet, citrus	18323	53561
Terpene	D-Limonene	5989-27-5	1055	1055	fruity, citrus, orange, sweet, peely	22694	108275
Terpene	o-Cymene*	527-84-4	1055	NA		8573	43488
Terpene	γ-Terpinene	99-85-4	1080	NA	oily, woody, terpenic, lime, herbal	0	4436
Terpene	Camphor	464-49-3	1228	1217	camphoreous	11753	10534
Terpene	Copaene*	3856-25-5	1423	NA	woody, spicy, honey	0	3088
Terpene	trans-α-Bergamotene*	13474-59-4	1473	NA	mild, waxy, oily, woody, citrus	4025	4449

Compounds identification, chemical class, and average abundance values measured (n=3)

CAS: Chemical CAS (Chemical Abstract Service) (Blanks relate to isomers where not be 100% sure of identification and therefore could not provide full identification.

LRI: Linear Retention Indices as determined using the method by Van Den Dool & Kratz, (1963)

REF LRI: These values were obtained from published papers or NIST 2014; NA: No published reference available to date (not many published yet on a DB624 column); *tentative identification, might be isomer of this chemical compound; **isomer of methyl isocyaninde, tentative identification.

Supplementary Table S5.2. Compounds identified by HS-SPME/GC-MS in flucloxacillin solutions.

Name	CAS	RI	Ref	Compound	Control aqueous fluc solution freshly prepared peak area	Commercial fluc solution freshly prepared peak area	Commercial fluc solution freshly prepared – diff batch peak area	Expired fluc solution freshly prepared peak area	Commercial fluc solution stored at 21°C for 7 days peak area	Commercial fluc solution stored at 4°C for 7 days peak area
Acid										
Hexanoic acid	142-62-1	1050	1049	acidic, sweaty, cheesy, sharp, goaty	62268	0	0	0	0	0
2-Ethylhexanoic acid	149-57-5	1183			2187992	2561359	4374141	6063169	5196662	3989133
Alcohol										
Ethanol	64-17-5	501	506	sweet, alcoholic, medicinal	0	11778	8985	15045	11465	10361
Aldehyde										
Butanal, 3-methyl-	590-86-3	691	692	malty, cheese, green, cocoa	1926101	220423	209526	184220	266736	278042
Benzaldehyde	100-52-7	1028	1031	bitter almond, sweet cherry	12643	20870	10612	42366	0	24667
Octanal	124-13-0	1045	1047	waxy, citrus, orange, soapy, green	0	399127	386261	507710	0	278944
Nonanal	124-19-6	1148	1150	green, citrus, fatty, floral	81713	324849	312207	720198	0	214770
Undecanal	112-44-7	1340	1354	waxy, soap, floral, citrus, green, fatty	0	613444	593672	583583	224416	511538
Dodecanal	112-54-9	1457		soapy, waxy, citrus, green, floral	0	431533	410357	499915	66243	234042
Alkane										
Heptane	142-82-5	700	700	sweet, ethereal	695062	32253	28497	32152	36170	28603
Decane	124-18-5	999		gasoline-like to odourless	87694	0	0	0	0	0
Undecane	1120-21-4	1099		gasoline-like to odourless	149452	336599	321577	811800	275151	311771
Benzene										
Toluene	108-88-3	792	794	nutty, bitter, almond, plastic	2006	0	0	0	0	0
p-Xylene	106-42-3	897	898	grainy, sweet	7226	0	0	0	0	0
Styrene	100-42-5	927	929	plastic	9658	0	0	0	0	0
Mesistilene	108-67-8	997			110880	0	0	0	0	0
1,3-Di-tert-butylbenzene	1014-60-4	1284	1286		28602	0	0	0	0	0
Ester										
Ethyl acetate	141-78-6	640	642	fruity, apple, weedy, green	6319402	4183907	3898512	4072357	4284553	4108892
Ethyl butanoate	105-54-4	824	826	fruity, pineapple	50030	14051483	14735314	22734015	12673796	14196429
Isoamyl acetate	123-92-2	901	902	banana, sweet, pear, apple peel	72612	27701238	26933046	37061528	22794981	25163100
Isopropyl pentanoate	18362-97-5	960			110195	0	0	0	0	0
Butanoic acid, butyl ester	109-21-7	1019	1019	pineapple, banana, sweet	49018	0	0	0	0	0
Ethyl hexanoate	123-66-0	1022	1024	fruity, pineapple, waxy, fatty, banana	0	119002	116341	402624	64755	77235

2-Methylbutyl butanoate	51115-64-1	1084		fruity, spicy, rummy	196725	7867595	7540944	8486843	6818093	8016052
Allyl hexanoate	123-68-2	1120		pineapple	10677	18627155	18165115	20531047	9219664	11180248
Ethyl 2-ethylhexanoate	2983-37-1	1133		fresh, orris, fruity	1823074	140195	132200	167527	63297	80923
Allyl hepatnoate	142-19-8	1205		fruity, pineapple, banana	0	0	0	490855	0	0
Ethyl benzoate	93-89-0	1229	1232	fruity, medicinal, cherry	5908	121884	136808	286066	113538	115742
Ethyl benzeneacetate	101-97-3	1303	1305	sweet, floral, honey, rose, balsamic, cocoa	9754	0	0	0	0	0
Ethyl decanoate	110-38-3	1420	1422	fruity, grape, cognac, waxy	0	37157	36076	40587	24436	28524
Phenethyl 2-methylbutyrate	24817-51-4	1570		floral, green, tropical, waxy, rose	324515	30774715	29490116	10079210	9931993	10050389
Hexyl isobutyrate	2349-07-7	1172		fruity, apple, pear	0	0	0	2262847	0	0
Ketone										
Acetone	67-64-1	535	533	solvent, ethereal, sour milk, apple	27949	20952	14959	17599	15259	16871
2-Pentanone	107-87-9	740	730	sweet, fruity, ethereal, fermented	2360	0	0	0	0	0
Methyl isobutyl ketone	108-10-1	781	784	sharp, green, herbal, fruity, dairy, spicy	8316	0	0	0	0	0
3-Penten-2-one, 4-methyl-	141-79-7	839		peppermint	253144	0	0	0	0	0
3-Heptanone	106-35-4	925	927	green, fatty, fruity	52679	0	0	0	0	0
2-Nonanone	821-55-6	1138	1140	fresh, green, earthy, woody, herbal	0	1466582	1403888	1303293	1002806	1093971
Acetophenone	98-86-2	1142	1030	must, flower, almond, glue	9082	0	0	0	0	0
Phenol										
Phenol	108-95-2	1095	1112	sweet, tarry, chemical, phenolic	2409	0	0	0	0	0
Sulfur										
Dimethyl disulfide	624-92-0	777	771	sulfurous, vegetable, cabbage, onion	7025	0	0	0	0	0
Terpene										
α-Pinene	80-56-8	947	950	pine, camphoreous, earthy, woody	2020	1432930	1500847	2337146	601219	835689
Sabinene	3387-41-5	1003		pepper, turpentine, wood	0	1014482	1051768	1908680	150298	393113
Myrcene	123-35-3	1003	1004	herbaceous, metallic	0	10299683	9747747	12445269	5505358	7766187
3-Carene	13466-78-9	1036	1027	sweet, citrus	2033	396152	375252	453308	223815	246377
D-Limonene	5989-27-5	1055	1055	fruity, citrus, orange, sweet, peely	64394	24196385	29991413	31012532	25413143	27161247
o-Cymene	527-84-4	1055			17677	3016739	2928660	4195103	1061876	1662564
γ-Terpinene	99-85-4	1080		oily, woody, terpenic, lime, herbal	3929	7508006	7019528	8789823	4388589	5303256
Linalool	78-70-6	1144	1148	citrus, floral, woody, green	0	902380	841309	872658	847118	918114
(R)-(+)-Citronellal	2385-77-5	1201		lemon	0	146938	138825	145631	0	76897

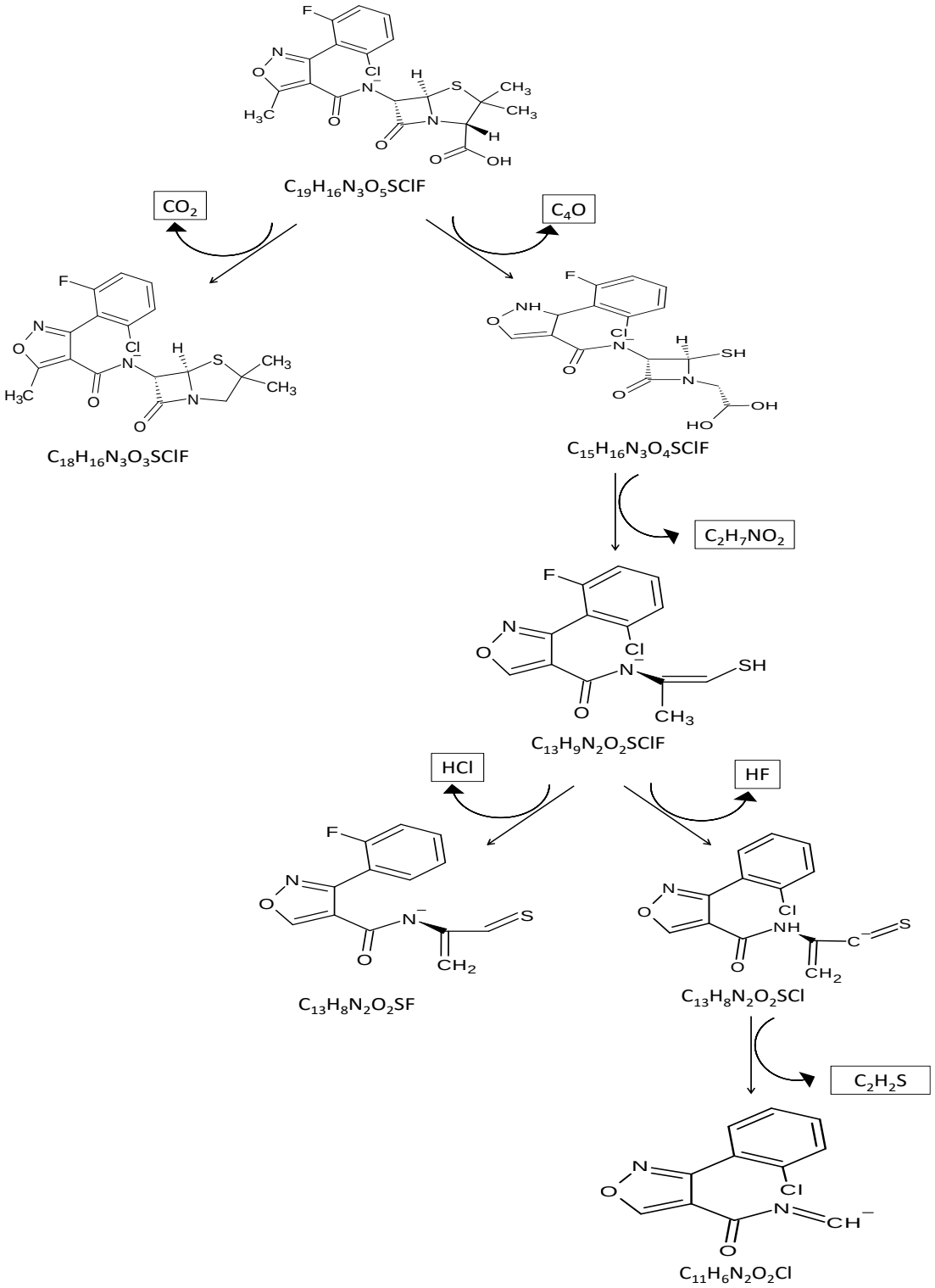
p-Menthone	89-80-5	1224		minty	0	235479	235797	239658	180265	195547
Camphor	464-49-3	1228	1217	camphoreous	8052	0	0	0	0	0
p-Menthan-1-ol	21129-27-1	1240			0	2518803	2452328	2818831	1290130	2147018
β-Citral	106-26-3	1314		sweet, citrus, lemon peel	0	918196	911039	1006140	442437	847555
α-Citral	141-27-5	1342		citrus, lemon	0	1987851	1862059	2107632	796928	1634084
Copaene	3856-25-5	1423		woody, spicy, honey	0	479726	442749	503405	263005	365724
cis-α-Bergamotene	18252-46-5	1451		wood, warm, tea	0	136485	122928	160973	110854	112077
trans-α-Bergamotene	13474-59-4	1473		mild, waxy, oily, woody, citrus	4108	1709486	1598395	2202480	819862	1268171
β-Bisabolene	495-61-4	1549		balsamic, woody	0	1992307	1861871	2068861	950728	1479625
(E)-β-Famesene	18794-84-8	1476		woody, citrus, herbal, sweet	0	249123	210892	371797	248068	182499
Valencene	4630-07-3	1557		citrus, woody, dry	0	202122	194847	243312	118210	166781
α-Panasinsene	56633-28-4	1607			0	59465	58889	78833	24894	44018

Compounds identification, chemical class, and average abundance values measured (n=3)

CAS: Chemical CAS (Chemical Abstract Service) (Blanks relate to isomers where are not 100% sure of identification and therefore could not provide full identification.

LRI: Linear Retention Indices as determined using the method by Van Den Dool & Kratz, (1963)

REF LRI: These values were obtained from published papers or NIST 2014; NA: No published reference available to date (not many published as yet on a DB624 column); *tentative identification, might be isomer of this chemical compound



Supplementary Figure S5.1. Degradation products of flucloxacillin and potential losses of volatile compounds corresponding to difference