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Authors	Elgammal, Ayat;Sheehan, Liz;Shine, Margaret;Mohamed, Reda;Kilcawley, Kieran;Skibinska, Iwona;Bermingham, Margaret;Crean, Abina
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Flucloxacillin formulation odour acceptability: A human sensory assessment

Ayat Elgammal [a,b], Liz Sheehan [c], Margaret Shine [c], Reda Mohamed [d], Kieran Kilcawley [e], Iwona Skibinska [e], Margaret Bermingham [a], Abina Crean [b,*]

[a] Pharmaceutical Care Research Group, School of Pharmacy, University College Cork, Cork, Ireland
[b] SSPC Pharmaceutical Research Centre, School of Pharmacy, University College Cork, Cork, Ireland
[c] SRL Pharma, T12 XF62, Cork, Ireland
[d] Cork University Hospital, Cork, Ireland
[e] Food Quality and Sensory Science, Teagasc Food Research Centre, Fermoy, Ireland

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ABSTRACT

Palatability influences a medicine's acceptability. While medicine's taste and their acceptability have been explored, the relationship between a medicine's odour and its acceptability has received less attention. In this study, the odour acceptability of a range of oral flucloxacillin formulations was assessed by healthy adult volunteers. Flucloxacillin was chosen as it is reported to be malodourous and found to be poorly palatable by children. The odour of a commercial flucloxacillin solution and capsule formulation were rated as acceptable. The commercial solution odour was described as fruity, and aromatic, while the commercial capsule was described as odourless. An unformulated flucloxacillin solution and flucloxacillin minitablets were deemed to have an unacceptable odour described as pungent, musty, plastic, and rotten. The odour of flucloxacillin minitablets including silica was deemed as odourless and acceptable. The ability of silica to suppress flucloxacillin's malodour was attributed to its adsorption of malodourous volatile compounds. Malodourous volatile sulphur compounds, produced during flucloxacillin degradation, were identified by GC-MS in the headspace of an unformulated flucloxacillin solution. The volunteers' smell acuity was assessed and found to be normosmic or microsmic, except for one volunteer who was anosmic (odour blindness). While the odour assessments of normosmic and microsmic volunteers generally aligned, the anosmic volunteer's assessments were contrary to the general findings. This study highlights the ability of formulation to improve the odour acceptability of flucloxacillin, it demonstrates the capability of silica to suppress drug malodour, and determines the importance of volunteer smell acuity screening during medicine odour sensory studies.

1. Introduction

Palatability is a key element influencing paediatric medicine acceptability as highlighted in the European Medicine Agency's guideline on pharmaceutical of medicines for paediatric use [1]. Palatability has been defined as the overall appreciation of the organoleptic properties of an oral medicine such as appearance, smell, taste, aftertaste and mouth feel [2]. Palatability is a key consideration to ensure medication adherence and effective treatment when prescribing oral antibiotics for children [3]. 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 [4].

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 [5]. 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 [3].

Flucloxacillin's poor palatability was related to its taste in a focus

* Corresponding author. School of Pharmacy, University College Cork, College Road, Cork, Ireland.a.crean@ucc.ie

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group study conducted by Venables et al. with nurses, medical practitioners and pharmacists [6]. However, recent studies of pharmacists and primary care doctors found that flucloxacillin's malodour was also a contributing factor to its poor palatability [7,8]. 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 [9]. 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.

The aim of this study was to evaluate influence of formulation approaches on the odour acceptability of commercial and novel flucloxacillin formulations using human adult volunteers. 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 [10,11]. However, use of liquid formulations in paediatric populations can be challenging due to concerns related to palatability, dose volume, and the accurate dose measurement [12]. 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 [13]. It is reported children younger than five years old are not able to swallow solid capsules larger than 10 mm [14]. 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 [15]. The minitablets format has the advantages of both liquid and solid dosage forms with dose flexibility, and better swallowability for paediatric populations [16]. The swallowability of minitablets was reported to be acceptable among children aged 6 months and above [17,18]. The study also investigates the ability of an excipient with high adsorbent capacity, mesoporous silica, to suppress the odour emanating from the flucloxacillin minitablet formulation. The hypothesised mechanism by which silica could suppress flucloxacillin's odour is based on the understanding that smell is triggered by a volatile organic compound (VOCs) emanating from a material which stimulate both orthonasal and retronasal routes of [19,20]. VOCs are low-molecular-weight compounds with a molecular weight of 50–200 Da that evaporate easily at room temperature with boiling points less than 250 °C measured at a standard atmospheric pressure [21]. Mesoporous silica has the capability to adsorb volatile compounds because of large surface area and porosity [22]. It was therefore hypothesised the silica could adsorb the odour active volatile compounds emanating from flucloxacillin and supress the formulation odour. Silica is widely used in pharmaceutical formulations mainly as a flow aid [23]. However, to our knowledge this is the first reported inclusion of silica in pharmaceutical formulations specifically as an odour suppressant.

2. Materials and methods

2.1. Materials

Flucloxacillin sodium drug substance was supplied by Molekula Ltd, UK. Commercial formulations, Athlone Laboratories Flucloxacillin 250mg/5 ml Oral Solution® and 250 mg 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.

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 1–4 year old children. Formulations assessed for odour acceptability were (i) 5 ml of Flucloxacillin 250mg/5 ml Oral Solution®, Athlone Laboratories Ltd, (ii) Flucloxacillin 250 mg 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 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/5 ml 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.

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 min. 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 Material Table S1. Flucloxacillin dose was confirmed by UV spectrometric analysis (Unicam, UK). All minitablets were compacted to a hardness of 85 ± 3 N, which was confirmed by hardness testing using a Erweka TBH 220 Hardness tester, Germany.

Table 1
Composition 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

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)February 06, 2024 and ECM3 (p)March 05, 2024.

2.5. Odour assessment study design

The study was carried out by a panel of adult healthy volunteers. The study protocol is available in Supplementary Material File S1. Medical screening was conducted by a registered medical doctor to ensure that only healthy volunteers were enrolled in the study. All samples were presented in 20 ml amber plastic medicine containers. Photographs are included in Supplementary Material Fig. S1. 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 S2.

The unformulated aqueous flucloxacillin solution and the reconstituted commercial Flucloxacillin 250mg/5 ml 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 [24]. 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 minimize 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.

2.6. 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 odorants that were used in the 2013–2014 U S. National Health and Nutrition Examination Survey (NHANES) [25]. The 8-item Sensonics™ smell test is reported to be an efficient and brief test for evaluating smell function [26]. The test consists of eight odorants’ strips to be scratched and sniffed. The test kit included 4 food-related odorants (chocolate, strawberry, grape and onion), two warning odorants (natural gas and smoke), and two common household odorants (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 [26,27]. 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.

2.7. Sensory study 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). An independent samples *t*-test was performed determine significant differences in odour acceptability rating based on smell acuity score using IBM® SPSS® Statistics Software (Version 28.0.1.1 [15]). Principal component analysis (PCA) was performed on descriptive sensory data using Origin Data Analysis Software (Version 2019b).

2.8. GC-MS analysis

As flucloxacillin does not meet the criteria of a volatile organic compound due to its relatively high molecular weight, 454 Da [21,28], it was hypothesised that the odour was related to trace levels of degradation products related to its sulphur containing thiazolidine ring. To test this hypothesis GC-MS analysis of the headspace above the unformulated flucloxacillin aqueous solution (50 mg/ml) was conducted. A 5 ml of the flucloxacillin solution was added to a 20 ml screw-capped solid phase microextraction (SPME via). The vials was equilibrated to 4 °C for 10 min with pulsed agitation of 5 s at 500 rpm. A single 50/30 μm divinylbenzene/Carboxen/polydimethylsiloxane (DVB/CAR/PDMS) SPME fibre was exposed to the headspace above the samples for 20 min at depth of 1 cm at 40 °C. The fibre 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 × 0.32 mm x 1.8 μm) column using a split/splitless injector with a 1/10 split. 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, 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.

Volatile 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 [29]. MetaMS is an open-source pipeline for GC-MS-based untargeted metabolomics.

3. Results

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 [30]. 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).

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 Fig. 1.

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 analyzed based on the volunteer's smell acuity to probe the relationship between smell acuity and responses obtained, Fig. 2.

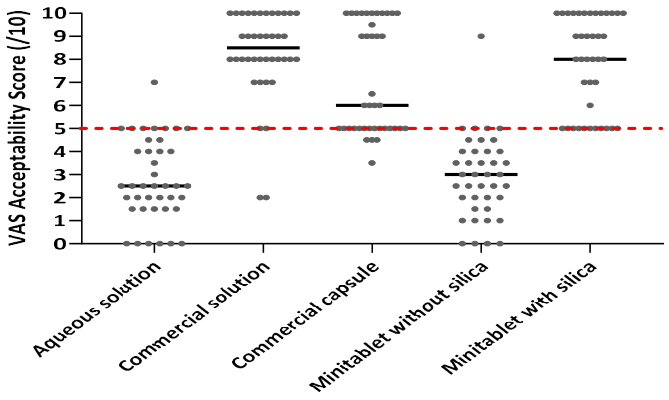


Fig. 1. Individual volunteer's smell acceptability scores for flucloxacillin preparations assessed as shown black circles. The solid black line indicates the average acceptability score for each preparation. The red dashed line indicates score of 5 which represents that the sample was neither acceptable nor unacceptable. Any score above 5 was rated as acceptable and any score below 5 was rated as unacceptable. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

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, Fig. 2.

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. The responses of individual volunteers are detailed in the Supplementary Material Table S3. 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 Fig. 3.

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 bi-plot. 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".

3.4. GC-MS analysis of chemical origin of flucloxacillin malodour

To identify the chemical origin of the malodour described in the human sensory study, GC-MS analysis of the headspace above the unformulated flucloxacillin solution was conducted. As highlighted earlier, flucloxacillin does not meet the criteria for of a volatile organic compound due to its relatively high molecular weight, 454 Da [21,28], it was hypothesised that the odour was related to trace levels of volatile degradation products related to its sulphur containing thiazolidine ring. Volatile compounds containing a sulphur atom in their structure have very low odour thresholds and can be recognized at the parts per billion [31,32]. A number of volatile compounds were identified in headspace of the control aqueous flucloxacillin solution, Supplementary Fig. S2. Only one sulphur containing compound was detected, dimethyl disulfide. Dimethyl disulfide has a specific unpleasant rotten cabbage odour with an approximate odour threshold of 7–12 ppb [33]. Dimethyl disulphide can be produced by flucloxacillin degradation. Dimethyl disulfide is produced by ethynthiol degradation which is a reported flucloxacillin degradation-related volatile compound [34]. Ethanethiol is an extremely smelly thiol substance with a strong unpleasant, rotten

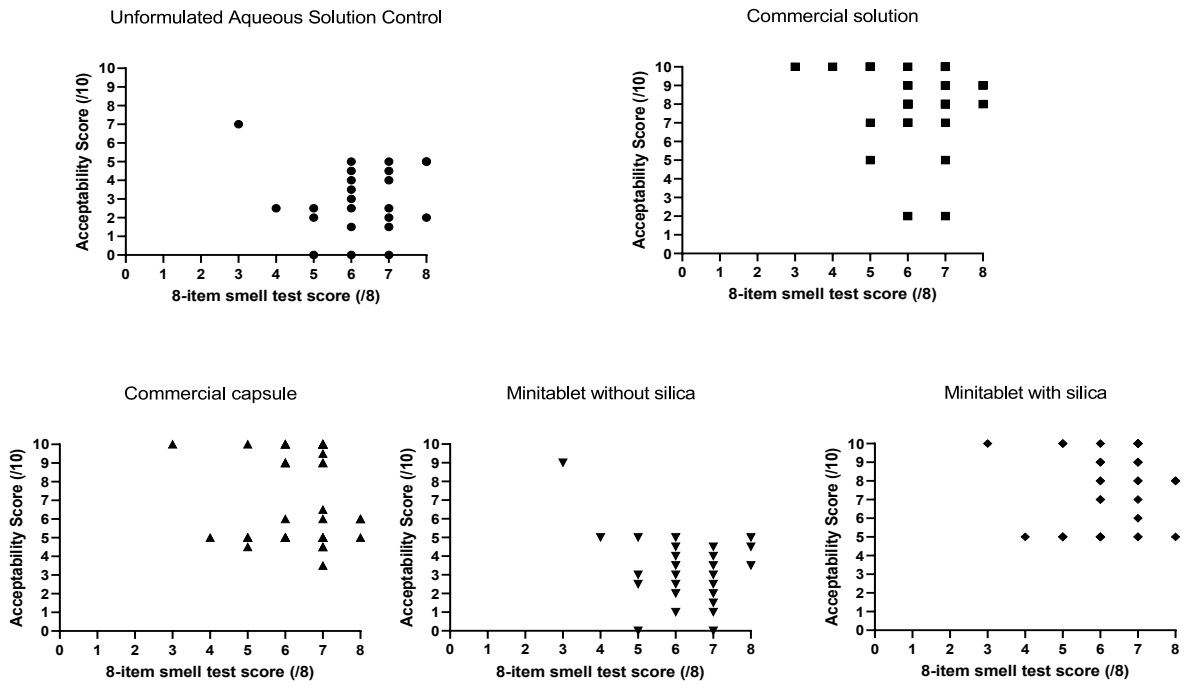


Fig. 2. Individual volunteer's smell acceptability scores for flucloxacillin preparations assessed plotted according to the volunteer's smell acuity score.

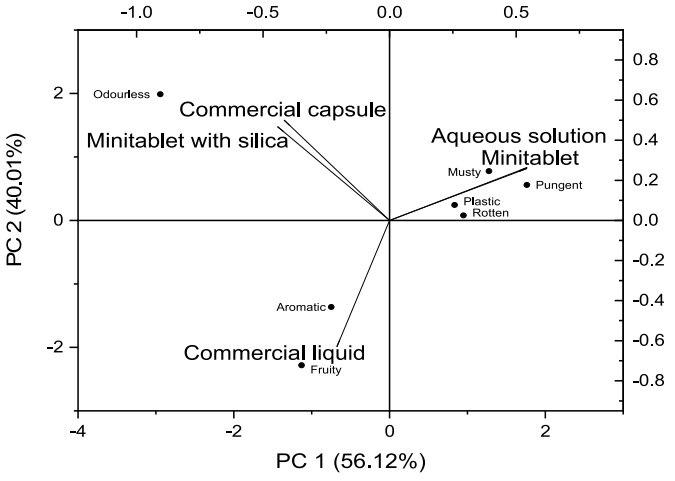


Fig. 3. Principal component analysis (PCA) biplot of the smell sensory attributes study volunteers (n = 40) associated with the flucloxacillin preparations assessed.

cabbage or garlic odour and low odour threshold of ~8.7×10^{-3} ppb/v [35]. The presence of these odour active volatile sulphur compounds in the flucloxacillin headspace provide an explanation for the malodour noted for the unformulated flucloxacillin solution and minitablets without silica by the volunteers. The odourless description of minitablets with silica may be attributed to the adsorption of these odour active volatile compounds and their reduction to level below their odour threshold.

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 [36]. 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 [37]. 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. 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 12 μm [38]. 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 [18]. As mentioned in the introduction, the hypothesised mechanism by which silica suppresses the flucloxacillin odour within the minitablet formulation was related to its high adsorptive capacity and ability to adsorb odour active volatile organic compounds (VOC) emanating from flucloxacillin.

GC-MS analysis of the headspace above the unformulated flucloxacillin solution provided insights into the chemical origin of flucloxacillin's malodour. Based on the findings it was concluded that a major contributor to flucloxacillin's malodour emanates from low levels of odour active VOCs related to flucloxacillin degradation. Malodourous dimethyl disulfide was detected during analysis and traced to a previously reported volatile degradant, ethynethiol [34]. Ethanethiol is reported as the smelliest thiol substance with strong unpleasant, rotten cabbage or garlic with a low odour threshold [35].

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 minitablets is acceptable among children aged 6 months and above [39]. Capsule dimensions can pose an administration barrier for paediatric patients [40]. The available sizes of common paediatric antibiotics capsules range from 8 to 25 mm in length with median 17 mm [41]. A survey conducted with 304 parents of children and youths to assess their medication acceptance revealed that 30 % of children aged 10–14 years were not able to swallow small capsules [42]. To overcome this challenge, parents/carers may opening capsules and mix their content with food or drink to aid administration to children [43]. 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 [5]. 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 [44]. Children can conduct ranking tests through the use of observation-based methods of child's reaction or facial expression by the primary caregiver [45,46]. 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 [47]. However, descriptive tests are challenging for children because of their limited verbal skills, and short span of concentration [44]. 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 [26]. 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) [48]. 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 [49,50]. Similarly, the U.S. NHANES reported that 3 % of people in the U.S. adult population aged $\geq$40 years have anosmia [27]. 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 [51,52]. 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 [53] and therefore also warrants further investigation.

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 adsorption of malodourous volatile sulphur compounds resulting from flucloxacillin degradation identified by GC-MS analysis. 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.

CRediT authorship contribution statement

Ayat Elgammal: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Liz Sheehan:** Methodology, Conceptualization. **Margaret Shine:** Methodology, Conceptualization. **Reda Mohamed:** Investigation, Formal analysis. **Kieran Kilcawley:** Methodology, Investigation, Formal analysis. **Iwona Skibinska:** Methodology, Investigation, Formal analysis, Writing – review & editing, Supervision, Project administration, Conceptualization. **Margaret Bermingham:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Data curation, Conceptualization.

Availability of data

The authors confirm that the data supporting the findings of this study are available within the article supplementary materials.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jddst.2025.106784.

Data availability

The authors confirm that the data supporting the findings of this study are available within the article supplementary materials.

References

[1] EMA, Guideline on pharmaceutical development of medicines for paediatric use [Internet]. https://www.ema.europa.eu/en/pharmaceutical-development-medicines-paediatric-use, 2013.

[2] P. Kozarewicz, Regulatory perspectives on acceptability testing of dosage forms in children, Int J Pharm 469 (2) (2014 Aug) 245–248.

[3] D. Baguley, E. Lim, A. Bevan, A. Pallet, S.N. Faust, Prescribing for children - taste and palatability affect adherence to antibiotics: a review, Arch. Dis. Child. 97 (3) (2012) 293–297.

[4] D.V. Patel, U.K. Acharya, M.K. Shinde, S.M. Nimbalkar, Compliance to antibiotic therapy at paediatric out-patient clinic, J. Fam. Med. Prim. Care 11 (3) (2022 Mar) 1012–1018.

[5] C. Rouse, P. Mistry, O. Rayner, J. Nickless, M. Wan, K.W. Southern, et al., A mixed methods study of the administration of flucloxacillin oral liquid; identifying strategies to overcome administration issues of medicines with poor palatability, Int. J. Pharm. Pract. 25 (5) (2017) 326–334.

[6] R. Venables, H. Stirling, H. Batchelor, J. Marriott, Problems with oral formulations prescribed to children: a focus group study of healthcare professionals, Int. J. Clin. Pharm. 37 (6) (2015) 1057–1067.

[7] A. Elgammal, J. Ryan, C. Bradley, A. Crean, M. 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, Fam. Pract. (2023) 1–8.

[8] A. Elgammal, J. Ryan, C. Bradley, A. Crean, M. Bermingham, Challenges prescribing and dispensing oral antibiotics with poor palatability for paediatric patients: a qualitative interview study with GPs and pharmacists, Explor Res Clin Soc Pharm [Internet] 17 (2025) 100546. https://www.sciencedirect.com/science/article/pii/S2667276624001434.

[9] C. Spence, Just how much of what we taste derives from the sense of smell? Flavour [Internet] 4 (1) (2015) 1–10, https://doi.org/10.1186/s13411-015-0040-2.

[10] A.A. Ali, N.A. Charoo, D.B. Abdallah, Pediatric drug development: formulation considerations, Drug Dev. Ind. Pharm. 40 (10) (2014) 1283–1299.

[11] T. Nunn, J. Williams, Formulation of medicines for children, Br. J. Clin. Pharmacol. 59 (6) (2005) 674–676.

[12] H.K. Batchelor, J.F. Marriott, Formulations for children: Problems and solutions, Br. J. Clin. Pharmacol. 79 (3) (2015) 405–418.

[13] D. Khan, D. Kirby, S. Bryson, M. Shah, Mohammed A. Rahman, Paediatric specific dosage forms: patient and formulation considerations, Int J Pharm [Internet] 616 (January) (2022) 121501, https://doi.org/10.1016/j.ijpharm.2022.121501.

[14] E.S.F. Orubu, C. Tuleu, Medicines for children: Flexible solid oral formulations, Bull. World Health Organ. 95 (3) (2017) 238–240.

[15] D.A. van Riet-Nales, A.F.A.M. Schobben, H. Vromans, T.C.G. Egberts, C.M. A. Rademaker, Safe and effective pharmacotherapy in infants and preschool children: importance of formulation aspects, Arch. Dis. Child. 101 (7) (2016 Jul) 662–669.

[16] F. O'Brien, D. Clapham, K. Krysiak, H. Batchelor, P. Field, G. Caivano, et al., Making medicines Baby size: the challenges in Bridging the formulation Gap in Neonatal medicine, Int. J. Mol. Sci. 20 (11) (2019 May).

[17] J. Münch, I. Sessler, H.M. Bosse, M. Wargenau, J.D. Dreesen, G. Loforese, et al., Evaluating the acceptability, swallowability, and palatability of Film-Coated mini-tablet formulation in Young children: results from an open-Label, single-dose, cross-over study, Pharmaceutics 15 (6) (2023).

[18] N. Mitsui, N. Hida, T. Kamiya, T. Yamazaki, K. Miyazaki, K. Saito, et al., Swallowability of minitablets among children aged 6–23 Months: an Exploratory, randomized Crossover study, Pharmaceutics 14 (1) (2022) 1–11.

[19] Spence Charles, What Is the Relationship between the Presence of Volatile Organic Compounds in Food and Drink Products and Multisensory Flavour Perception?, 2021.

[20] B.C. Sun, B.P. Halpern, Identification of air phase retronasal and orthonasal odorant pairs, Chem. Senses 30 (8) (2005) 693–706.

[21] S.S. Anand, B.K. Philip, H.M. Mehendale, Volatile organic compounds, in: P. Wexler (Ed.), Encyclopedia of Toxicology, third ed., Academic Press, Oxford, 2014, pp. 967–970 [Internet], https://www.sciencedirect.com/science/article/pii/B9780123864543003584.

[22] J. Hou, Q. Ma, X. Du, H. Deng, J. Gao, Inorganic/organic mesoporous silica as a novel fiber coating of solid-phase microextraction, Talanta [Internet] 62 (2) (2004) 241–246. https://www.sciencedirect.com/science/article/pii/S0039914003004429.

[23] Pharmaceutical Excipients, Mesoporous Silica (MPS) [Internet], Medicine Complete, 2024. https://www-medicinescomplete-com.ucc.idm.oclc.org/#/content/excipients/255319?hspl=mesoporous&hspl=silica.

[24] Sensory Analysis - General Guidelines for the Selection, Training and Monitoring of Selected Assessors and Expert Sensory Assessors (ISO 8586:2012) [Internet], German Institute for Standardisation (Deutsches Institut für Normung), 2014.

[25] U.S. Centers for Disease Control and Prevention, NHANES 2013-2014: Taste & Smell Data Documentation, in: Codebook, and Frequencies [Internet], 2016. CSX_H.xpt. https://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/CSX_H.htm.

[26] A. On, S.T. Moein, R. Khan, R.L. Doty, The 8-item NHANES pocket smell test(®): Normative data, Appl Neuropsychol Adult (2023 Jul) 1–6.

[27] H.J. Hoffman, S. Rawal, C.-M. Li, V.B. Duffy, New chemosensory component in the U.S. National Health and Nutrition Examination Survey (NHANES): first-year results for measured olfactory dysfunction, Rev. Endocr. Metab. Disord. 17 (2) (2016 Jun) 221–240.

[28] United States Environmental Protection Agency, Volatile Organic Compounds (VOCs), 2011. Technical Overview.

[29] R. Wehrens, G. Weingart, F. Mattivi, metaMS: an open-source pipeline for GC-MS-based untargeted metabolomics, J. Chromatogr., B: Anal. Technol. Biomed. Life Sci. 966 (2014 Sep) 109–116.

[30] M. Gacula, S. Rutenbeck, Sample size in consumer test and descriptive analysis, J Sens Stud 21 (2) (2006) 129–145.

[31] G. Leonardos, D. Kendall, N. Barnard, Odor threshold determinations of 53 odorant chemicals, J. Air Pollut. Control Assoc. 19 (2) (1969) 91–95.

[32] R.G. B., Flavor chemistry and odor thresholds, Flavor Chem. (1999) 353–365.

[33] F. Mert Sivri, N. Hoda, A. Topuz, L. Budama Akpolat, E. Eroğlu, Adsorption of dimethyl disulfide onto activated carbon cloth, Turkish J Chem 46 (3) (2022) 859–868.

[34] R. Tiwari, C. Bonde, K. Bothara, LC-MS/TOF and MSn studies on forced degradation behavior of flucloxacillin and development of a validated stability indicating LC method, Acta Chromatogr. 26 (1) (2014) 43–55.

[35] J. Wang, T. Zheng, C. Cai, Y. Zhang, H. Liu, Oxidation of ethanethiol in aqueous alkaline solution by ferrate(VI): Kinetics, stoichiometry and mechanism, Chem Eng J [Internet] 361 (2019) 1557–1564. https://www.sciencedirect.com/science/article/pii/S1385894718322058.

[36] I. Gengler, S. Testing, When people are the Instrument : sensory evaluation methods Abstract : when people are the Instrument : sensory, Evaluation Methods 27 (4) (2009) 9–13.

[37] B.E.J. Fridrun Podczeck, Pharmaceutical Capsules, second ed., Pharmaceutical Press, London, 2004.

[38] Q. Shabir, C. Skaria, H.O. Brien, A. Loni, C. Barnett, L. Canham, Taste and mouthfeel assessment of porous and non-porous silicon microparticles, Nanoscale Res. Lett. 7 (1) (2012 Jul) 407.

[39] V. Klingmann, N. Spomer, C. Lerch, I. Stoltenberg, C. Frömke, H.M. Bosse, et al., Favorable acceptance of mini-tablets compared with syrup: a randomized controlled trial in infants and preschool children, J. Pediatr. 163 (6) (2013 Dec) 1728–1732.e1.

[40] C.J. VandenBerg, A. Adams, R. Bockrath, S. Kim, G. Rodriguez, A. Fawcett, et al., Hard to swallow: a review of Interventions to improve swallowing solid medication, Hosp. Pediatr. 13 (5) (2023 May) e123–e132.

[41] L. Jacobsen, K. Riley, B. Lee, K. Bradford, R. Jhaveri, Tablet/capsule size Variation among the most commonly prescribed medications for children in the USA: Retrospective review and Firsthand pharmacy Audit, Pediatr. Drugs 18 (1) (2016) 65–73.

[42] J. Polaha, W.T. Dalton 3rd, B.M. Lancaster, Parental report of medication acceptance among youth: implications for everyday practice, South. Med. J. 101 (11) (2008 Nov) 1106–1112.

[43] J. Martir, T. Flanagan, J. Mann, N. Fotaki, Co-Administration of paediatric medicines with food and drinks in the Context of their Physicochemical properties-a Global Perspective on Practices and Recommendations, AAPS J. 22 (2) (2020 Mar) 54.

[44] J.-X. Guinard, Sensory and consumer testing with children, Trends Food Sci Technol [Internet] 11 (8) (2000) 273–283. https://www.sciencedirect.com/science/article/pii/S0924224401000152.

[45] A. Verrotti, G. Nanni, S. Agostinelli, E.T. Alleva, P. Aloisi, E. Franzoni, et al., Effects of the abrupt switch from solution to modified-release granule formulation of valproate, Acta Neurol. Scand. 125 (3) (2012) 14–18.

[46] N. Moniot-Ville, M. Chelly, M.R. L Consten, The acceptability, efficacy and safety of a new paediatric oral suspension of roxithromycin in respiratory tract infections, J. Int. Med. Res. 26 (3) (1998) 144–151.

[47] P. Mistry, H. Batchelor, Methodology used to assess acceptability of oral Pediatric medicines: a Systematic literature Search and Narrative review, Pediatr. Drugs 19 (3) (2017) 223–233.

[48] R.L. Doty, C. Wylie, M. Potter, R. Beston, B. Cope, K. Majam, Clinical validation of the olfactory detection threshold module of the Snap & Sniff® olfactory test system, Int Forum Allergy Rhinol 9 (9) (2019 Sep) 986–992.

[49] C. Murphy, C.R. Schubert, K.J. Cruickshanks, B.E.K. Klein, R. Klein, D.M. Nondahl, Prevalence of olfactory impairment in older adults, JAMA 288 (18) (2002 Nov) 2307–2312.

[50] A. Brämerson, L. Johansson, L. Ek, S. Nordin, M. Bende, Prevalence of olfactory dysfunction: the skövde population-based study, Laryngoscope 114 (4) (2004 Apr) 733–737.

[51] T. Hummel, D. Podlesek, Clinical assessment of olfactory function, Chem. Senses 128 (4) (2021) 414–418.

[52] K.A. Wilson, Individuating the senses of 'smell': orthonasal versus retronasal olfaction, Synthese [Internet] 199 (1–2) (2021) 4217–4242, https://doi.org/10.1007/s11229-020-02976-7.

[53] M.L. Blankenship, M. Grigorova, D.B. Katz, J.X. Maier, Retronasal odor perception Requires taste Cortex, but orthonasal does not, Curr. Biol. 29 (1) (2019 Jan) 62–69.e3.