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A Retrospective Biopharmaceutical Analysis of >800 Approved Oral Drug Products: Are Drug Properties of Solid Dispersions and Lipid-Based Formulations Distinctive?

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Abstract

Increasing numbers of poorly water soluble drugs in development has intensified need for bio-enabling formulations including Lipid-Based Formulations (LBF) and Solid Dispersions (SD). Resultantly, a data-driven approach is required to increase formulation development efficiency. This review provides a retrospective analysis of molecular and biopharmaceutical properties of drugs commercialised as LBFs or SDs. A comprehensive stepwise statistical analysis of LBF and SD drug properties was conducted and compared to drugs not commercialised via either technology (Others), aiming to identify key predictors of successful formulation development. This review demonstrates LBF and SD drugs differ significantly in molecular weight, polar surface area, rotatable bonds and hydrogen bond acceptor count. Meanwhile, LBF and SD drugs display significantly different aqueous solubility, lipophilicity, size, molecular flexibility, hydrogen bonding capacity and rule-of-5 violations versus Others. LBF and SDs were 3 and 5 times more likely to display >1 rule-of-5 violation versus Others, over 55% of LBF drugs exceeded the reported melting point guide of <150°C, while 24% of SD drugs contained >10 Hydrogen Bond Acceptors. Overall, by focusing on successfully commercialised drugs, this review provides improved understanding of links between drug properties and successful SD/LBF approaches, providing a framework for guiding pharmaceutical development on formulation approaches.

Keywords:

Solid dispersion(s), Lipid-based formulation(s), Poorly water-soluble drug(s), Formulation, Drug-like property(s), Amorphous Solid Dispersion(s) (ASD), Bioavailability, Drug delivery systems.

Abbreviations:

LBF, Lipid-Based Formulations; SD, Solid Dispersions; Ro5, Rule-of-5; BCS, Biopharmaceutics Classification System; DCS, Developability Classification System; BDDCS, Biopharmaceutics Drug Disposition Classification System; SLAD, Solubility Limited Absorbable Dose; GIT, Gastrointestinal Tract; PWSD, Poorly Water-Soluble Drug, LFCS, Lipid Formulation Classification System; SEDDS, Self-Emulsifying Drug Delivery Systems; MW, Molecular Weight; MDS, Maximum Dosage Strength; HBA, Hydrogen Bond Acceptors; HBD, Hydrogen Bond Donors; PSA, Polar Surface Area; logP, Measured Partition Coefficient; clogP, Calculated Partition Coefficient (clogP); U%, Percentage Excreted Unchanged in Urine; logS, Logarithm of Aqueous Solubility; $logD_{7.4}$, Partition Coefficient at pH 7.4; T_m, Melting Point; RB, Rotatable Bonds; FDA, Food and Drug Administration; EMA, European Medicines Agency; HPRA, Health Products Regulatory Authority; GFA, Glass Forming Ability; eRo5, Extended Rule-of-5; bRo5, Beyond Rule-of-5.

1. Introduction

Increasing utility of and investment into bio-enabling formulations such as Lipid-Based Formulations (LBF) and Solid Dispersions (SD) has been fuelled through increasing prevalence of poorly water soluble drugs (PWSD) in development pipelines and the ensuing necessity for more non-traditional systems to successfully deliver them. Approximately 75-90% of all compounds in modern drug discovery programmes display solubility-limited absorption, consequentially presenting the pharmaceutical industry with a "poor solubility challenge" [1-4]. Such modern drug candidates display high lipophilicity, poor aqueous solubility and resultant reduced oral bioavailability [5, 6]. Such properties are common negative penalties traded for high potency and selectivity for contemporary lipophilic binding pockets or drug targets [7, 8]. Recent drug discovery trends indicate a greater number of drugs emerging in the beyond "rule-of-5" (Ro5) chemical space [9, 10]. This increasingly molecularly diverse pipeline portfolio creates need for bio-enabling approaches to achieve sufficient oral absorption *in vivo* [10]. Undoubtedly, an emerging burden in the pharmaceutical industry involves adjusting long standing traditions of drug delivery to develop new strategies and tools able to translate such non-optimal drugs into viable commercial products.

PWSD encompass Class II/IV of the "Biopharmaceutics Classification System" (BCS) (Figure 1). The BCS aims to identify the rate limiting step to oral bioavailability as being either solubility or permeability. While the BCS is widely used to guide drug candidate and formulation development, it primarily serves a regulatory purpose and is rightly conservative in its estimates of *in vivo* solubility while also providing limited mechanistic assessment of *in vivo* permeability limitations. As a result, the BCS has been refined on several occasions to provide increased utility in guiding formulation development. The "Biopharmaceutics Drug Disposition Classification System" (BDDCS) aims to predict the drug disposition characteristics of novel drugs earlier in drug development by assessing drug metabolism rather than human intestinal permeability as a predictor of absorption, while also incorporating effects of metabolising enzymes and transporters *in vivo* and drug disposition in development [11, 12]. It has been demonstrated to be applicable to both the Ro5 and beyond-Ro5 chemical space [9]. The "Developability Classification System" (DCS) aims to address the use of the sub-optimal aqueous solubility measurement implemented by the BCS/BDDCS [13] by providing an estimate of *in vivo* solubility using biorelevant media (i.e. Fasted Stated Simulated Intestinal Fluid). The DCS also considers the concept of a solubility limited absorbable dose (SLAD), which is the maximal dose that could potentially be absorbed, factoring in both biorelevant solubility in physiologically relevant fluid volumes in the gastrointestinal tract (GIT) and the compensatory effects of permeability on dissolution *in vivo*. The numerous classification systems developed have focused on identifying difficult-to-formulate compounds, and those likely to be amenable to formulation as bio-enabled preparations, however the choice of a specific formulation approach remains challenging.

Bio-enabling formulations are drug delivery technologies specifically intended to improve the release, dissolution and absorption of PWSD [14]. Through enhanced drug dissolution and absorption, bio-enabling formulations possess ability to provide necessary *in vivo* drug exposure not possible through more conventional dosage forms [15]. Examples include lipid-based formulations (LBF), solid dispersions (SD),

mesoporous silica formulations, salt formation, nanosized or micronized formulations and surfactant or cyclodextrin enabled formulations [7]. At present cumbersome, iterative formulation screening assays are often used to determine which bio-enabling formulation is most appropriate, and significant efforts are being made to refine this process by improving the efficiency of current bio-predictive screening tools and by moving towards data-driven drug and formulation development [16, 17]. Contributory factors in guiding formulation choice can include in-house company expertise, equipment availability and cost. For these reasons the physiochemical properties of such drugs, and their biopharmaceutical implications, may be overlooked. However, a renewed emphasis is being placed on understanding the molecular properties of these drugs and their impact on biopharmaceutical properties, moving from simple classification systems to truly computationally informed pharmaceutics.

Efforts have been made to advance computational pharmaceutics from predictions of intrinsic solubility, solubility in simulated intestinal fluids and permeability, to models predicting aspects of formulation developability related to either solubility or stability in LBFs and SDs from molecular structure [18-22]. In addition to modelling efforts, decision trees allowing for differentiation between "conventional" and "enabled" technologies [23] as well as structured development approaches for LBFs and SDs have been suggested [24, 25]. Despite such advances in the tailoring of formulation choice based on drug properties, analysis of the current landscape of commercial drugs utilising bio-enabling technologies in order to establish trends in physiochemical characteristics and molecular properties is lacking. The current review aims to provide a retrospective, top-down, analysis of the current landscape of commercial products, to identify which drug properties are likely to identify successful delivery technologies at an earlier stage in development. This review focuses on the commercial utility of the two most commonly encountered bio-enabling formulation approaches; Lipid-Based Formulations (LBF) and Solid Dispersions (SD), due to the extensive reports in the literature on their capacity to enhance oral delivery, and numerous examples of commercial successes as licensed drug products in clinical use.

The current review aims to provide an up-to-date and comprehensive list of commercially available LBF and SD formulations, discuss trends in the type of drugs and formulations currently reaching the marketplace and identify key physicochemical and biopharmaceutical predictors of successful formulation development. In order to achieve these aims, the commercial examples to date of drug products formulated as either SDs or LBFs is examined and classified according to BDDCS class of the formulated active substance, while selected physiochemical characteristics and molecular properties of these commercial drugs are statistically analysed and compared to a list of compounds not produced via either technology. The aim of this analysis is to explore which drug properties signal suitability of a drug for LBFs or SDs, or moreover, properties which potentially distinguish between them. This analysis attempts to bridge a gap in current drug development, involving widespread use of drug likeness filters and ADME optimisation to guide drug discovery and refine drug candidate selection. While many merits exist for their use, there also exists a risk that current filters may be overly conservative and conceptually simplistic. As increasing numbers of drugs emerge beyond the preferred chemical space it could be argued that complementary use of "formulation likeness filters" in such instances

could inform developers of bio-enabling technologies which may be appropriate, based on properties of their drug candidate, simultaneously analysing potential for success in terms of both drug likeness and bio-enabling potential. As the numbers of drug compounds using both LBF and SD in licensed commercial products continues to grow, so too does the database of information regarding suitable drugs compatible for such systems. This data bank could guide future commercial success of LBF and SD products, reflecting backwards in order to move forwards in the “bio-enabling” field with confidence.

2. Lipid-Based Formulations and Solid Dispersions as Bio-Enabling Formulations

In response to this need to deliver challenging drug candidates orally, methods overcoming poor solubility are vital in drug development (26). Two such approaches methods involve the utilisation of LBF and SD.

2.1 Lipid-Based Formulations

The term "lipid-based formulation" spans a wide range of formulations composed of pure oils or mixtures of oils, surfactants and/or co solvents in various proportions as classified in the lipid formulation classification system (LFCS) [27, 28]. Previous research has suggested that many of the marketed LBF products consist of Type II or III formulations, often referred to as self-emulsifying drug delivery systems (SEDDS) [29]. These can spontaneously emulsify upon dispersion due to the presence of surfactants and hydrophilic excipients, decreasing reliance on endogenous lipid digestion to facilitate emulsification [7]. LBFs have been traditionally employed for drug which display poor aqueous solubility and high lipophilicity (logP). The administration of lipid excipients enhances the drug solubilisation capacity of the GI environment, stimulating endogenous bile acid secretion, leading to production of a mixture of solubilising colloidal structures composed of endogenous and exogenous lipids [30]. These can effectively solubilise the PWSD [26, 31, 32] and the drug is retained either solubilised or in a transiently supersaturated state allowing for increased absorption [26]. The "spring and parachute" analogy applies here to the generation and prolongation of supersaturation where the "spring" involves the self-emulsifying properties of the LBF, incorporating the solubilised active substance [33], while "parachute" refers to formulation additives which increase stability, reducing drug precipitation *in vivo* [34] (Figure 2).

LBFs are also biopharmaceutically advantageous regarding impact on intestinal permeability [35], metabolism [36] and lymphatic transport [37, 38]. Additionally, from a pharmaceutical manufacture standpoint, once acceptable manufacturing equipment is in place, large scale manufacture of LBFs is relatively low risk and less technologically demanding which can usually be completed on a smaller scale than other delivery technologies [15, 39].

2.2 Solid Dispersions

The merits of SD to improve oral absorption has been demonstrated as far back as the 1960s. SDs are generally two-component systems, containing one or more active substances dispersed in an inert matrix. Depending on the physical state of the carrier, SDs are classified as either crystalline or amorphous, while the API can be also be presented as amorphous or crystalline particles or as a molecular dispersion [40]. SDs can facilitate increased solubility and dissolution through a reduction in API particle size, potentially to a molecular level, enhanced wettability and porosity, and altered drug crystalline state, preferably to an amorphous state [41]. In its most commonly used form, a SD involves dispersion of drug in an amorphous polymer matrix with drug present in the molecularly dispersed state (a glass solution) [42]. This composition exploits the fact that the solubility of the dispersed or amorphous state can be much higher than comparative solubility of the most stable crystalline polymorph, thus, a supersaturated solution is more easily attained [7]. Upon amorphisation, the impact of

crystalline long range order on drug solubility and dissolution is largely reduced as intermolecular interactions are weaker and Gibbs free energy is increased [43, 44]. Thus, SDs are considered useful for drugs which exhibit solid state limited solubility (i.e. 'brick dust' molecules), but can also be of merit for "grease ball" type molecules due to reduced particle size and increased hydrophilicity due to excipients [45, 46]. SD systems contain stored potential energy similar to a "spring" which when dispersed can release and forms a supersaturated state when exposed to the GIT (Figure 2). The innate thermodynamic instability of the supersaturated state may lead to precipitation or in the case of amorphous SD premature recrystallization. A variety of excipients such as polymers can be utilised to act as a "parachute" in the prevention of precipitation or recrystallization and maintain the solubility advantage. Successive generations of SDs have been produced each providing updated and altered excipients such as polymers to maintain this amorphous solubility advantage or more recently facilitating sustained drug release [40, 47, 48].

3. Methods

3.1 Dataset Selection

An original databank of approximately 1000 drug compounds was collated from previous literature sources [9, 49] using the BDDCS classification and an in house database of oral drug compounds commercially approved by the EMA and FDA between 2010 and 2017 [50]. Where information regarding BDDCS classification was not available, a drug's BCS classification was used as a surrogate due to the same parameter of solubility being used in both classifications. This master databank was split into three, namely, drugs commercially developed as LBF, SD and Others i.e. not commercially developed via either technology. LBF and SD drugs were identified from previous literature referencing commercial products [7, 43, 51-58], along with analysis of the online databases of the US and EU respective drug licensing authorities (Food and Drug Administration, European Medicines Agency, Health Products Regulatory Authority of Ireland) where dosage, licencing and excipient information regarding all products was also then obtained. Where a product was identified in peer reviewed literature but was not authorised in these three areas another national authority was investigated to establish if the product had been commercialised. A LBF was defined as Class I-IV of the Lipid Formulation Classification System [59]. All types of solid dispersions were considered based on description in product or published literature that the product is a SD (i.e. both amorphous versus crystalline API dispersed in amorphous carriers.) Omega-3-acid ethyl esters, Florfenicol and Silibinin were removed from the database due to the lack of drug property data available. Exclusion criteria for the Others list included any drugs used in LBF or SD commercial products, active metabolites and non-orally delivered drugs. The final datasets contained 49 drugs grouped as LBF, 37 as SD and 763 as Others drugs. When including only poorly soluble BDDCS Class II/IV drugs there remained 38 drugs grouped as LBF, 30 as SD and 307 as Others drugs.

3.2 Compilation of Physicochemical Descriptors

Physiochemical properties to be assessed were identified and compiled from the literature publication BDDCS Applied to Over 900 Drugs [49]. Physiochemical and molecular properties for the drugs not listed in Benet *et al.* were obtained from PubChem, DrugBank or ADMET Predictor 9.5 (Simulations Plus, USA). The final properties of the drugs analysed included: Molecular Weight (MW), Maximum Dosage Strength (MDS), Hydrogen Bond Acceptors (HBA), Hydrogen Bond Donors (HBD), Polar Surface Area (PSA), Measured Partition Coefficient (logP), Calculated Partition Coefficient (clogP), Percentage Excreted Unchanged in Urine (U%), pDose, Logarithm of Aqueous Solubility (logS), Partition Coefficient at pH 7.4 ($logD_{7.4}$) , Rule-of-5 Violations (Ro5), pKa (Strongest Acidic), Melting Point (T_m) and Rotatable Bonds (RB). These are defined in Table 1.

3.3 Statistical Analysis

A stepwise statistical analysis approach was adopted using SPSS (IBM Corporation, US). Frequency distributions of the variables were graphed for each of the three groups and normality was checked visually with Q-Q and P-P plots. Ratios of samples sizes between the 3 groups were obtained. Variances of the datasets were analysed and compared to Levene's Test for Equality of Variances. A p-value <0.05 indicated a violation

of equal variance. The null hypotheses were that no differences were seen in a drug property between drug groups. Three separate comparison were made i.e. LBF vs SD; LBF vs Others; SD vs Others rather than a three-group comparison, using for example ANOVA. This enabled use of the most appropriate comparison method based on assessment of data normality and equality of variance in each group and is in line with the null hypotheses identified. Comparison between groups were made using the t-test, Welch's test, Bootstrap independent samples test (5000 samples) or Chi-Square test, all 2-sided, where appropriate. Rule-of-5 violations was recoded to a category variable or ≤1 or >1 violation and Chi-Square tests were used to test independence of this categorical variable. If 1 or more cells had an expected count below 5, Fisher's exact test was employed. A p-value of 0.05 was used as the significance level for all tests. Finally, in order to analyse only PWSD, subsets of the three datasets were created containing only BDDCS Class II/IV drugs and the statistical analysis described above was repeated.

4 Results

4.1 Commercial Success to Date

While previous studies have evaluated trends by comparing drugs formulations reported in scientific literature, this does not provide a true measure of clinical development success. Therefore, we envisage a gap in the literature in terms of a comprehensive list of drugs which have been commercially developed as either LBF or SD. Information involving product names, drug compounds and excipients used, dosage forms, strengths and the geographical areas in which the products were licensed was collated (Supplementary Materials). Some products have been subsequently withdrawn from the commercial market however, all products were licensed at one point in time.

4.1.1 Commercial Lipid-Based Formulations

LBF products have been successfully authorised internationally since the 1940s. Early examples of commercial products consisted of Type I formulations of the LFCS e.g. Drisdol® [60]. As years progressed interest in self-emulsifying systems intensified [26] and resulted in a large surge in increasingly complex Type III and IV LBF products in the 1980s-1990s [53]. Review of the published literature and online databases of drug product regulatory authorities in the US and EU identified 67 commercial LBF products. As illustrated in Figure 3, a higher number of the LBF products have been authorised in the US (47/67) compared to the EU (26/67). Differences in the number of marketed products could represent strategic commercial decisions based on factors such as level of clinical demand or regulatory burden.

In a small number of cases more than one dosage form e.g. capsule and oral solution, have been produced for the same drug product (6/67 products). In comparison, multiple dosage strengths have been licensed almost half of the products (28/67 products). It was observed that soft gelatin capsules dominantly account for the most popular LBF product dosage form (40/67), followed by oral solutions (10/67), hard capsules (10/67) and oral suspensions (1/67) (Figure 4). There are also 6 products which are controlled release, demonstrating a further drug delivery advantages of LBFs. These are extended release capsules (3/67), extended release suspension (1/67) prolonged release capsule (1/67) and sustained release granules (1/67). Clearly, soft gelatin capsules represent the more prevalent dosage form as they can safely encapsulate liquid dosage forms in comparison to hard capsules. While there has been successful suspensions produced [61], solutions remain the most popular approach for commercial products according to our analysis.

In terms of year of authorisation, it can be seen (Figure 5) that the period of 2000-2009 contained the highest number of commercial LBF approvals (37%). As such, combining the 1990s and 2000s accounts for 63% of all commercial LBF products. However, this spike in approvals did not continue into the period since 2010 where only 9% of all LBF products have been commercialised. Overall, the findings here are comparable to analysis examining growth in the number of LBF/SEDDS publications in PubMed from 1966 to 2016 where they saw a large surge of publication numbers from the mid-1990s [26]. Finally, a number of the listed products have been either discontinued or withdrawn from the market (12/67). No trends were evident where the reasons for

withdrawal were linked to reasons of efficacy, safety nor stability. In the majority of cases a lack of clinical demand or switch to another dosage form was cited by the manufacturer.

4.1.2 Commercial Solid Dispersions

The earliest example of a commercial SD product is Cesamet® (Nabilone) from 1982 [62]. Overall 39 commercial SD products were identified. Four of these have been marketed under a different brand name in a different region (Certican® = Zortress®, Incivek® = Incivo®, Cokiera® = Viekira XR®, Galvumet® = Eucreas®). Compared to LBFs, commercial SDs form a smaller number of licensed products, which may reflect that LBF products were a more established commercial pathway in the 1980's and 1990's, relative to SDs [26, 63]. As an example, the first LBF was approved over 40 years before the first SD commercial products (Drisdol®, 1941 and Cesamet®, 1982). When commercial SD products manufacturing methods were analysed we found the majority of products were produced via either spray drying or melt extrusion methods in line with previous research analysis [45].

The widespread global market for SD products is apparent. From Figure 3 close to 50% of SD commercial products are authorised in both the United States and EU markets. Multiple dosage strengths were seen for a majority of products (23/39), similar to LBFs, potentially due to scalability and manufacture of dose proportional preparations of SDs. In terms of dosage forms immediate release tablets are most popular (27/39) (Figure 4). While capsules (4/39) and granules for oral suspension (1/39) are also seen, as well as controlled release tablets and capsules, in the form of extended, delayed or prolonged release. 5/39 identified SD products have been either discontinued or withdrawn from the market. Upon review no evidence could be found to suggest the majority of removals were due to efficacy or safety issues and were voluntary due to declining clinical demand or alternative dosage forms. Conversely, in the case of Rezulin® (Trogslitazone), its removal was linked to the development severe idiosyncratic hepatocellular injury [64]. However, this is due to the drugs intrinsic toxicity rather than lack of effective formulation delivery.

In contrast to only 9% of LBF products, 54% of SD commercial products have been authorised since 2010 (Figure 5), demonstrating a sharp growing development trend toward SDs in recent years. It has previously been suggested that SD formulation technologies have been embraced to a much greater extent since 2012 [45], with comparative spikes in terms of related research articles seen from 2010-2015 [54]. As evidence of the commercial success of SD technology, Harvoni® (Gilead Sciences, Inc.), containing Ledipasvir and Sofosbuvir, used to treat chronic Hepatitis C was second in the blockbuster list of drugs ranked by sales revenue in 2015 [65].

4.1.3 Commercial Products via Both Formulation Technologies

Four drugs have been commercially produced via both LBF and SD technologies. These are Fenofibrate, Lopinavir, Ritonavir and Nimodipine. In the case of Lopinavir, it was originally produced in combination with Ritonavir in Kaletra® as an LBF capsule and subsequently replaced by AbbVie Inc.© with the SD tablet form exhibiting a higher dose loading capacity. This resulted in a reduced pill burden and aided compliance while also providing the added advantage of absence of food effect [66]. Similarly, Ritonavir has also been commercialised as both a SD and LBF in Norvir® [67]. In this case, original liquid filled capsules containing

Ritonavir in an ethanol, surfactant and water based solution were withdrawn from the market due to discovery of a previously unknown polymorph, leading to a significant decline in drug solubility and potential for poor bioavailability [68, 69]. When this original form was removed from the market, patients were encouraged to switch to the oral liquid form. In 1999, AbbVie Inc. (previously Abbott), applied for approval of an LBF soft gelatine capsule form overcoming this stability problem which required refrigeration. Ultimately in 2010, this LBF form was replaced by an SD 100 mg tablet which overcame the requirement for refrigeration, which improves convenience. Therefore, in two cases, choices of both LBF and SDs were largely based on commercial strategies (Fenofibrate and Nimodipine), whereas for Lopinavir and Ritonavir, initially the more established formulation strategy of LBFs were launched, however, due to problems with dose loading and stability were ultimately replaced with SDs. Overall, this relatively small overlap of drugs produced by both technologies observed, could suggest existence of distinctive drug properties which render a drug candidate more suitable for SD delivery over LBF delivery or vice versa.

4.2 BDDCS Classifications

The three drug sets were grouped according to BDDCS classification. These visual representations are found in Figure 6. As expected, the highest numbers of LBF (76%) and SD (60%) drugs in commercial products belong to BDDCS Class II. Also as anticipated, the second highest proportion of SD commercially used drugs come from BDDCS Class IV. In contrast, the second highest proportion of LBF drugs were found to be BDDCS Class I which indicates that, not only solubility limited compounds are successfully commercialised via LBFs. This most likely reflects a strategic commercial decision, as opposed to a strategy to address a solubility or permeability limitation, and may reflect that the large scale manufacture of LBFs are generally well established, and require relatively lower technologically input compared to other more expensive bio-enabling platforms such as SDs [15].

4.3 Retrospective Statistical Analysis of Properties of Commercialised LBF and SD Drug Compounds.

Molecular properties of drugs previously commercialised using LBF and SD formulation technologies were statistically compared with properties of drug substances not commercialised via either technology. Tabular results of the statistical analysis are shown in Supplementary Materials. A visual representation of significant differences obtained is illustrated in Figure 7.

Upon analysis of all BDDCS classes, 8/15 properties were significantly different between the LBF and Others datasets, namely MW, logP, %U, logS, $logD_{7.4}$, Ro5, T_m and clogP. In addition to these 8 properties HBA, RB and PSA were also found to be significantly different between the SD versus Others datasets. Therefore, these properties can be predictive of suitability for commercial success via LBF or SD technologies according to the current commercial climate of both sets of drugs. While no clear trends for the properties of pKa (strongest acidic), MDS and pDose were differentiated between groups, thus, these properties did not appear useful in predicting suitability nor indicative of unsuitability for either formulation type. Between LBF and SD datasets

significant differences in drug properties were observed as SDs displayed significantly higher mean HBA, RB, MW and PSA, compared to LBFs.

Subsequently, a subset analysis was performed on BDDCS Class II/IV drugs (low solubility) to explore whether results would be altered by excluding high solubility drugs, typically delivered using conventional methods. This subset decreased the numbers in the LBF group by 22% (n = 38), the SD group by 19% (n = 30) and the Others group by 60% (n = 307). In terms of comparisons between LBF versus Others within this low solubility datasets, this resulted in the parameters of Ro5 ($p = 0.086$), MW ($p = 0.129$) and T_m ($p = 0.051$) being no longer significant, albeit marginally in the case of T_m. Conversely, differences in both MDS (** $p = 0.006$) and pDose (*$p = 0.026$) between LBF and Others gained significance in the low solubility dataset. In terms of comparisons between SD and Others, the low solubility subset did not result in loss of significance to any observation, while MDS (** $p = 0.003$), pDose (* $p = 0.037$) and HBD (* $p = 0.03$) also gained significance. The low solubility analysis was not shown to affect significant differences.

5 Discussion

Based on the statistical analysis of formulation types by drug properties the following general trends have been observed.

5.1 Molecular Weight (MW)

Drugs commercialised as both LBF and SD pharmaceutical products displayed significantly larger MW compared to those commercialised via traditional formulation approaches (i.e. Others). Comparatively, SDs displayed significantly greater mean MWs (586.6g/mol) versus LBFs (448.2g/mol) suggesting that while both LBFs and SDs express potential to accommodate high MW drugs, SD approach may offer greater opportunities at the higher MW range. Additionally, only LBF, not SD drugs, lost significance versus Others when a low solubility dataset was analysed, suggesting that as MW increases any benefits LBF confer for PWSDs are not as prevalent and preference for SD platforms prevails.

These results reflect drug development trends over recent decades of increasing MW of drug molecules in drug development pipelines [70-72]. In the two last decades, there has been consistent trends for higher MW drugs being brought to market, exemplified when in 2016 and 2017 for the first time, average MW for new FDA approved oral drugs exceeded 500g/mol [73], with widespread increases in MW observed not merely due to approval of a small proportion of very high MW drugs. Such trends fall outside both the Lipinski Ro5 and the "rule of three" for fragment based drug discovery [74]. Resultantly, this sharp increase has prompted questioning regarding the justification of MW as a property of "drug-likeness" [73].

The trend for high MW observed here should be considered in line with the earlier reported trend for increasing use of SD approaches in the last decade. It is unclear whether these reflect independent trends in technological advances of both SD and increasing drug candidate MW or complementarity of both. However, it is clear that SDs offer a more commercially successful track record for high MW drugs. As most recently evidenced by the high MW antiviral, enzyme inhibitor drugs being delivered commercially in this manner e.g. Cokiera®, Epclusa®, Zelboraf®. These results are broadly supportive of the general rule of thumb that molecules with a MW of >300 g/mol can more easily be transformed into an amorphous state [75]. Here, we uncovered only 2/37 drugs commercialised as SDs with MW <300 g/mol. It has also been suggested that comparatively high MW increases glass forming ability (GFA) of a drug [75, 76]. While a higher solubility advantage was also demonstrated for higher MW drugs as a result of *in silico* predictive modelling of the amorphous solubility advantage [77]. Resultantly, from our analysis MW provides a distinguishing property for potential commercial success between LBFs and SDs at the higher end of the MW scale.

5.2 Melting Point (T_m)

A significantly smaller mean T_m was found for LBF drugs (160.81°C) vs Others (181.18°C). This significance was lost, albeit marginally, when a low solubility dataset was analysed. When the variances of T_m among groups was analysed, the smallest spread of values was found amongst the SD group. While the lowest T_m values for

LBF and Others groups respectively were 38°C and 43°C, the lowest T_m of a drug produced as a SD was approximately double these figures (80.5°C). T_m is often cited as an important drug characteristic influencing solubility in lipid vehicles, as an indicator of the energy required to break intermolecular bonds and overcome the crystal lattice energy. Drugs possessing a high crystal lattice energy along with a moderate logP value (>2) are termed "brick dust" [61], typically possessing poor solubility in lipids due to limited capacity to dissociate from the solid form and are not ideal candidates for LBFs [7, 26]. Previous work has demonstrated, that addition of T_m improved computational predictions of drug solubility in triglyceride vehicles [21]. It has been reported that in order for reasonable solubility in lipid vehicles, a low to intermediate T_m was preferable, and a T_m <150^{0}C was proposed as a baseline for the selection of LBFs as potential enabling formulation approaches [77-80]. However, in this analysis more than half (i.e. 55%) of commercially licensed LBFs exceeded this commonly recommended value of 150°C. A subset analysis revealed however, that the mean maximum dosage strength was significantly lower for drugs exceeding this value (i.e. 148.62mg for drugs <150°C compared to 81.48mg for >150°C). Overall, this would suggest that while low to intermediate T_m may be still be recommended, particularly for higher dose products, in the case of low dose/highly potent drugs, a T_m in excess of 150°C may not be limiting.

T_m was not observed to be a predictor of SD commercial success. This was unexpected as T_m was previously demonstrated to be an important predictor for the solubility advantage for amorphous drugs [77], in addition to differentiating between GFA classifications of compounds [76]. T_m can also dictate the type of manufacturing method suitable for a particular SD commercial product due to heat unstable components and risks of chemical degradation [45], as well as being related to their glass transition temperature [81].

5.3 Lipophilicity (logP, clogP, $logD_{7.4}$)

Lipophilicity remains an important property of drug candidates in development over the last 15-20 years, due in part to the lipophilic molecular requirements of new drug targets [19, 82]. It is thought to be correlated with MW, yet it appears to be changing less overtime than other drug properties [71, 73]. A 2016 analysis of 1620 molecules patented around that time uncovered that around 50% had ligands displaying mean logP ≥4 [8]. As such, Leeson and Springthorpe have even suggested lipophilicty to be the most important drug property, where high lipophilicity can result in increased risks of multiple target binding and potential toxicology [71]. As expected LBF commercialised drugs displayed significantly higher measured logP, clogP and $logD_{7.4}$ values than drugs compounds in the Others dataset. High lipophilicity would be expected to facilitate sufficient drug loading capacity in lipid vehicles. It is commonly reported that "grease ball" drug molecules, displaying high lipophilicity and relatively low T_m are good candidates for LBFs [83], while the ability to facilitate lymphatic uptake by LBFs is optimised for highly lipophilic drugs (logP > 5) [84]. Overall, this finding suggests that drugs with logP values of approximately 4–5 are good candidates for commercial LBFs due to the mean logP value of 4.7 observed. Previously, Pouton and Porter have suggested a logP >5 demonstrates suitability for LBF as such drug compounds are incorporated into mixed micelles and absorbed efficiently [29]. Interestingly, the greatest variance in logP values was also found in the LBF group. This could be related to the diverse range of classes of

LBFs available [59], where differing quantities of lipophilic and hydrophilic excipients in the formulation offers greater versatility for incorporating drugs across a range of lipophilicities.

While SDs did display significantly higher lipophilicity than Others, LBFs and SDs could not be separated in terms of this parameter. This reflects analysis by Ditzinger et al. where 66% of SDs in literature displayed LogP values of 2-6 [7]. Previously, a logD cut off of ≤2.7 was suggested as a cut off for SD over LBF formulation class suitability in a decision tree tool [85]. However, our findings suggest that while lipophilicity provides potential to isolate drugs with potential for commercial success via LBF or SD delivery technologies, it does not differentiate between them. For example, earlier case studies of Kaletra®, and Norvir® containing highly lipophilic drugs (clogP ≥4.7) demonstrate that such drugs can be produced successfully as both LBFs and SDs. In these cases, despite high lipophilicity, the SD forms were ultimately more commercially favourable. While these provide just two examples, overall, these findings appear to challenge the commonly held belief that drugs with high logP values are more suited for LBFs and perhaps, begging the question if our rationale for assessing the utility of LBFs may be overly simplistic. As such, while previous research has demonstrated that the renowned ability of LBFs to eliminate the food effect does not always stand to scrutiny [50], the current results have also demonstrated that LBFs cannot be differentiated from SDs in terms of lipophilicity.

5.4 Aqueous Solubility (logS)

As expected, among the total dataset of drugs, aqueous solubility (expressed as logS) displayed a significantly lower solubility for both LBF and SD drugs versus Others. Interestingly, when excluding high solubility drugs from the dataset and reanalysed using only low solubility drugs, significances remained. This indicates that even within PWSD classes, LBF and SD technologies offer the opportunity to facilitate commercial development as oral drug products. In relating lipophilicity and hydrophilicity, Bergstrom et al. have previously suggested that a logP >3 is an indicator of reduced interaction with aqueous solvents [83]. In this analysis, our mean logP values for commercial LBFs (4.66) and SDs (4.16) both fell above this value. Such results are expected as both formulation technologies present a potential delivery solution for drugs encompassing the "poor solubility challenge".

5.5 Percentage Excreted Unchanged in Urine (%U)

Percentage drug excreted in urine also distinguished drugs suitable for both LBF and SD but not between the two delivery techniques. A significantly lower percentage of both LBF and SD drugs were excreted in urine compared to the Others dataset. This is not unexpected as drugs excreted in the urine unchanged are typically highly water soluble whereas PWSDs require metabolism into metabolites which are likely more polar and readily excreted [86]. However, a range of factors may influence the predictive ability of this property, including need for a bioavailability factor for orally delivered drugs coupled with the fact that that certain drugs or active metabolites may be excreted unchanged in bile not urine [49]. This property demonstrated that SD and LBF drugs

are less hydrophilic than Others, similar to our previous result of their higher lipophilicity and lower aqueous solubility.

5.6 Rotatable Bond Count (RB)

SD commercialised products displayed significantly higher mean RB count than both LBF and Others. Once again reflecting current trends in drug candidates, as bulk physical properties including MW and RB count have increased with time [71]. This finding compliments previous observations that compounds exhibiting high amorphous stability contain higher numbers of RBs [87]. Baird et al. have suggested that higher RB and molecular flexibility decreases probability of being incorporated into an ordered crystalline structure [76], and demonstrated that both high MW and high RBs are indicative of higher GFA and lower crystallisation tendency (i.e. Class III GFA). Elsewhere, the number of RB, providing a measure of molecular flexibility, has been suggested by Kuentz et al. to positively influence the amorphous solubility advantage of a drug [77]. Comparatively higher RBs (e.g. 5-10) were indicative of suitability for a SD formulation approach, and at a mechanistic level this most likely reflects the ability of good glass forming drugs to display prolonged supersaturation, relative to poor glass former which are at greater risk of precipitation from supersaturated solutions. It is also noteworthy that molecular flexibility was not predictive of a LBF approach. Again, at a mechanistic level LBF increase drug concentrations via promotion of solubilisation in the intraluminal fluids and hence the ability of the inherent amorphous stability of the drug is not a considered to be a factor influencing performance.

5.7 Hydrogen Bond Acceptors (HBA)

HBA count was observed to be a property which distinguished between suitability of SD commercial drugs versus both LBFs and others, with a significantly higher mean HBA found for SD drugs (i.e. 6.87). The importance of HBA count is reflected in the fact that more than double (24%) of SD drugs had greater than 10 HBA compared to LBF drugs (10%). Furthermore, when comparing only low solubility drugs the significance of the differences between SD and both LBFs and others was strengthened.

Hydrogen bonding interactions increase both stability and rigidity of the amorphous state by the formation of poorly packed aggregates which render crystal formation increasingly difficult [87]. Number of HBA has previously been significant in modelling both the potential for crystallisation of a drug, based on GFA class [88], as well as prediction of the solubility advantage for amorphous drugs [77]. In the latter, the number of HBAs was the most important descriptor after MW in amorphous solubility advantage prediction. Additionally, hydrogen bonding between the API and polymer excipients is an important feature aiding polymers to inhibit drug crystallisation and promote amorphous stability. Hydrogen bonding between the two have been observed in dispersions displaying lower tendency and highest resistance to crystallisation [89, 90]. Second, third and fourth generation SDs utilise polymer carriers, either alone or in the presence of other polymers or surfactants [7]. In

this analysis, polymers were found to be the most widely used excipients in commercial SDs for both crystalline and amorphous based solid dispersions.

5.8 Hydrogen Bond Donors (HBD)

Both HBD and HBA counts are important with regard to Lipinski Rule-of-5 violations, amorphous stability and hydrogen bonding interactions between polymeric stabilisers and drugs. However, in this case, HBD was not found to be a property distinguishable between LBF, SD or Others in our analysis of the full datasets. However, when only low solubility drugs were analysed, a significant difference was observed between SD and Others. Previously, amorphous stability was found to be moderately correlated with the number of HBDs upon previous examination of a group of PWSDs [87] and positively correlated with MW ($r^2 = 0.70$), previously discussed to be influential in Section 5.1. Thus, intensifying the significance of hydrogen bonding capacity in distinguishing suitability of drugs for SD commercial success.

5.9 Polar Surface Area (PSA)

The importance of hydrogen bonding capacity was once again reflected in the fact that PSA distinguished suitability of drugs for commercial SDs versus both LBFs and Others. Significantly higher mean values were found for the SD dataset (125.92 $Å^2$), versus LBF (79.68 $Å^2$) and Others (81.48 $Å^2$) which retained significance when only low solubility drugs were compared. The spread of values was also the smallest for SD drugs. Comparatively, drug development trends indicate the mean PSA of drugs has been increasingly significantly through the years [71, 73]. However, it is important to bear in mind that correlation does not imply causation as in this case, the increasing prevalence of new drug candidates displaying higher PSA as well as increasing use of SD technologies could represent independent trends in both cases or reflect complementarity of both. PSA was previously determined a significant descriptor in *in silico* modelling long term amorphous stability [87] and amorphous solubility gain [77]. For the later, the authors suggested a comparatively higher value for PSA as a property to prompt consideration for SD delivery. They found a range of 60-140 $Å^2$ being indicative of a high amorphous solubility gain. In our analysis, the mean PSA for SD commercial drugs was 125.9 $Å^2$, thus, within this range.

5.10 Lipinski Rule-of-5 Violations (Ro5)

We observed a significant association between drug group and prevalence of Ro5 violations. This 'drug likeness filter' states that, in general, an orally active drug has no more than one violation. Thus, in our analysis we used a cut-off of ≤1 (0, 1) or >1 violations (2, 3, 4). After this discrete numerical variable was recoded to a categorical variable, we observed both LBF and SD to be significantly different from Others in terms of Ro5 violations (p ** < 0.01, p *** < 0.001). As such, 30% of SD and 18% of LBF commercial drugs displayed >1 violation compared to 6% of Others (Supplementary Materials). Without question, the higher Ro5 violations observed mirrors the growing number of beyond Ro5 drugs candidates being produced in the search for biological selectivity for emerging biological targets [21]. It has previously been observed that only approximately

50% of all drug targets appear accessible by compounds within the Ro5 chemical space [91]. As such, extended Ro5 (eRo5) and beyond Ro5 (bRo5) compounds refer to those outside this defined chemical space [8]. Perhaps suggestive that standard drug likeness filters may appear overly conservative as more and more non Ro5 compliant compounds reach commercial development. As mentioned previously, complementary use of formulation likeness filters may provide accurate predictions of formulation success for such troublesome drug candidates, as commercial success has been already demonstrated through LBF and SD approaches.

5.11 Dosage Strength (pDose and MDS)

Although, the LBF dataset demonstrated the lowest mean MDS (118.59mg) and the smallest first quartile value among the three groups, no significant differences were observed between the three groups. Conversely, upon comparison of only low solubility drugs, both LBF and SD drugs demonstrated significantly lower MDS compared to Others ($p^{**} < 0.01$, $p^{**} < 0.01$). Any lower dosage levels could refer to higher potency where smaller doses are required. While conversely PWSD not formulated by enabling formulations may require dosage increases to compensate for low bioavailability. A dose of <100mg has previously been suggested as a significant factor to consider lipid-based drug delivery systems to dissolve the full dose. To overcome this perceived dose limitation LBF suspensions, along with the avocation of chase dosing [92] and use of ionic liquids have been suggested [93]. Previously, suitable drugs for LBF delivery have been proposed to be low dose drugs such as hormones, cytotoxic drugs or prolonged therapy drugs requiring dose titrations [15]. Linking to this, two of the BDDCS Class I drugs utilising LBFs commercially consisted of Vitamin D and its active metabolite with dosage levels in the microgram range (One-Alpha®, Thorens ®, Uvedose ®). Thus, dosage strength may also be a factor for previous observation that the second highest proportion of LBF commercial drugs are BDDCS class I.

We also examined dosage strength in terms of pDose. When only low solubility drugs were analysed both LBF and SD drugs displayed significantly smaller doses compared to Others ($p^{*} < 0.05$, $p^{*} < 0.05$). This was somewhat unexpected as a stated advantage of SDs over LBFs is in general, the potential for much higher dosage levels, as high API-to-polymer ratios can offer higher drug loadings, echoing the commercial product Kaletra® resulting in a decreased pill burden. However, this could be affected by whether a crystalline or amorphous-based solid dispersion is produced. Instability of the amorphous form or presence/absence of polymers could alter drug loading capacities of amorphous-based solid dispersions.

5.12 Non-Significant Properties

No trends in pKa were established. However, a previous meta-analysis of 61 articles regarding supersaturating drug delivery systems (SDDS) including SD and LBFs between 2010-2015 revealed weakly acidic drugs demonstrated the highest improvement in the oral bioavailability-related parameters in comparison to weakly basic or neutral drugs [94]. However, more extensive research is required as any effect of drug ionisation is difficult to analyse.

5.13 Properties of Drugs Commercialised via Both Bio-Enabling Formulation Technologies.

As stated previously, four drugs have been commercially developed using both LBF and SD technologies. These drugs are Fenofibrate, Nimodipine, Ritonavir and Lopinavir. Two drugs displayed >1 Ro5 violation and all four were BDDCS Class II. Mean logP, clogP and $logD_{7.4}$ values for these drugs were high with all drugs displaying low aqueous solubility. With regard to T_m, only one drug, Lopinavir, had a T_m above the aforementioned cut off for LBFs of 150°C (174.5°C). Thus, it can be suggested that for a drug to act as a commercial candidate for success via both technologies it should display an intermediate T_m (e.g. ~150°C) to increase likely solubility in the lipid system. Three of the four drugs displayed ≥10 RBs and PSA >120 $Å^2$. Thus, while these properties reflect suitability for SDs, they do not, in practice, limit the commercial potential of drugs for success with LBFs. MW ranged from 360.83–720.946 g/mol, demonstrating the ability of both technologies to accommodate drugs with a wide range of MW. The average number of HBA and HBD were similar to our previous values and mean %U was low (1.58%). Overall, it appears clear from the current commercial portfolio of products, that PWSD displaying rule-of-5 violations, higher PSAs, a high RB count, mid-range T_m, high HBA and HBD count and a low %U, provide potential candidates for commercial development with both LBF and SD technologies. While in terms of drug properties which can distinguish between LBF and SD platforms in terms of commercial success, this review has demonstrated that drug MW, PSA, RB and HBA count show significant differences between current LBF and SD commercial products.

6 Conclusion

This review examined physiochemical and molecular properties of the current commercial portfolio of drug products using LBF and SD formulations. A database of drugs commercially developed as LBFs and SDs was reviewed, prevalence of BDDCS class was determined and retrospective trends in drugs properties uncovered. It was established that drug properties could distinguish not only LBF and SD bio-enabled commercial drugs from Others but also distinguish between commercially successful LBF and SD drugs. The latter involved drug properties of MW, RB, HBA and PSA, indicating importance of size, molecular flexibility and hydrogen bonding capacity in formulation of SDs. In terms of well-established drug likeness filters, >1 violation of Lipinski's Ro5 was seen to be 5 and 3 times more prevalent for SD and LBF drugs, respectively, versus Others. While the T_m of 55% of commercial LBF drugs exceeded the often reported cut off of 150°C. A general trend toward increasing commercial development of SD formulations in recent years was observed. Encouragingly, many of the significant properties established reflect drug discovery trends of recent years, providing a positive outlook for potential of bio-enabling formulations to overcome solubility limitations. Furthermore, all drug properties included in the "Oral PhysChem Score" system i.e. MW, clogP, RB, Solubility and PSA, indicative of bio-pharmaceutical performance of a drug, were found to be significant in this analysis [95].

This is not a definitive nor exhaustive list, drugs which do not fit some properties mentioned may be successfully developed in the future and certain properties not deemed significant do have their part to play. Moreover, as the numbers of drugs encompassing commercial LBF and SD products continues to grow, alterations to these trends may develop as certain properties may emerge or become more influential over time. Additionally, it must also be acknowledged that other regulatory considerations such as drug efficacy, safety**,** instability or pharmaceutical commercial interest/priorities will also influence potential for commercial success. Utilizing and updating trends going forward can aid the continued growth of both LBF and SD commercial products. Retrospective assessments and formulation likeness filters possess capacity to inform potential developability, either as a LBF or SD commercial product, based on previously successfully drug candidates and success stories over the last few decades. As such, if trends of increasing MW, lipophilic, flexible, beyond Ro5, NCEs continue to stem from the discovery pipeline, the need for such bio-enabling formulations will also increase.

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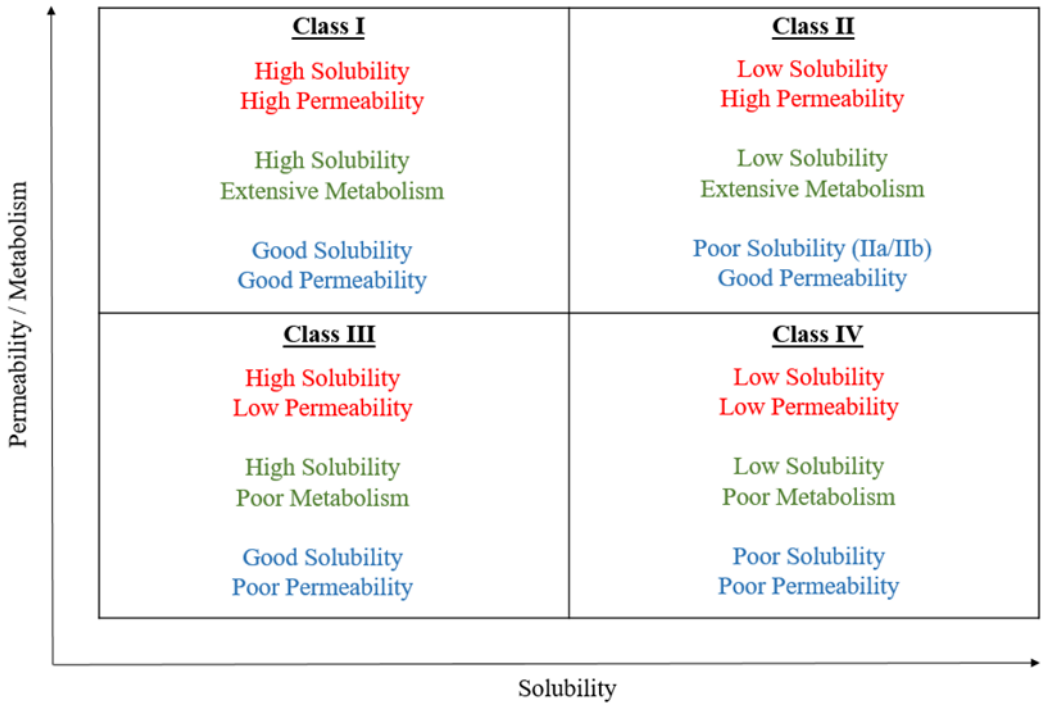


Figure 1: *Schematic representation of the various classification parameters for drugs using the BCS, BDDCS and DCS Classification systems. Red = BCS, Green = BDDCS, Blue = DCS. Drugs are further separated in DCS Class 2, IIa = dissolution rate limited, IIb = solubility limited. Scales and measurements per parameter are different depending on the classification system.*

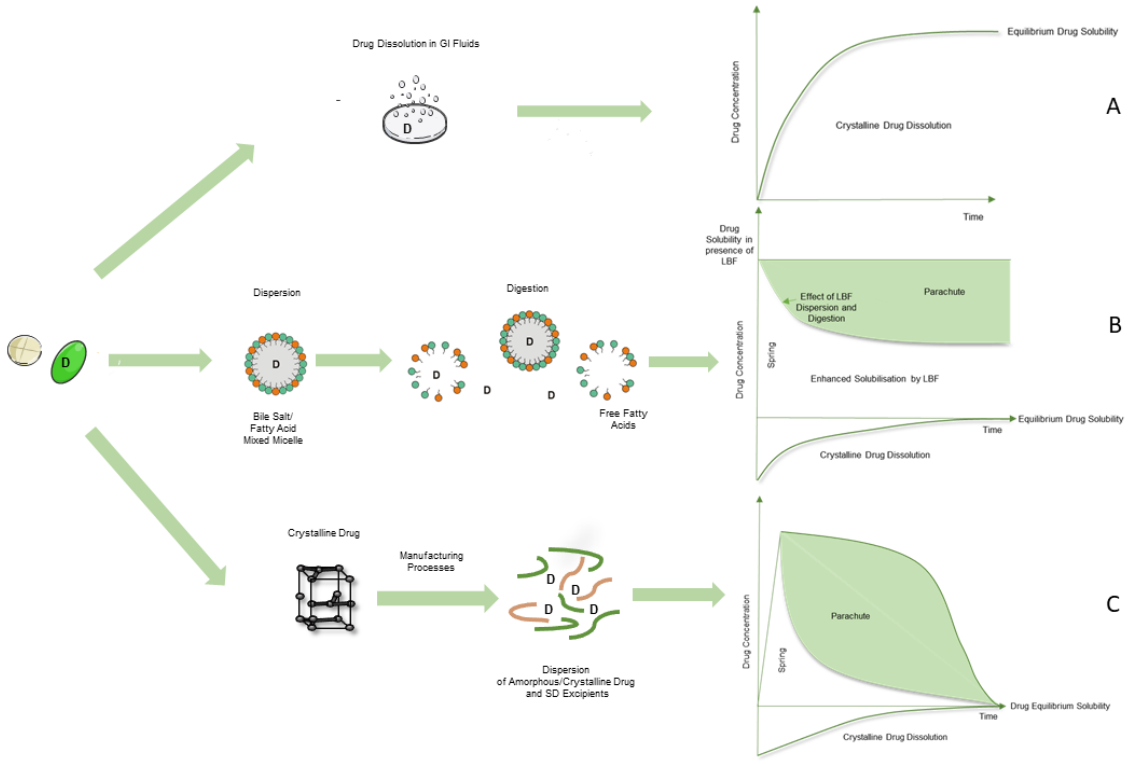


Figure 2: *Visual representation of modes of action of A) traditional immediate release oral drug products, B) LBF products, C) SD products. Adapted from Feeney et al.*[26] *and Williams et al.* [33].

Table 1: *Definitions of the drug molecular properties and physiochemical characteristics analysed in the statistical analysis.*

Property	Abbreviation	Definition
clogP	clogP	Logarithm of a molecules partition coefficient between n-octanol and using the method of Leo.
Hydrogen Bond Acceptors	HBA	Electronegative ion or molecule that must possess a lone electron pair in order to form a hydrogen bond.
Hydrogen Bond Donors	HBD	Heteroatom with at least one bonded hydrogen.
$logD_{7.4}$	$logD_{7.4}$	Partition coefficient of a drug at pH 7.4. This pH is utilised as this is the physiological pH of blood serum.
logP	logP	The measured partition coefficient of a molecule between an aqueous and lipophilic phases (n-octanol/water).
logS (mol/L)	logS	The 10-based logarithm of the solubility of a molecule mol/L.
Maximum Dosage Strength (mg)	MDS	The highest dosage strength licensed for a drug.
Melting Point (C°)	T_m	Temperature at which a solid changes state from solid to liquid.
Molecular Weight (g/mol)	MW	Molecular Mass of a drug.
pDose (mol/L)	pDose	$-\log_{10}$(Maximum Dose Strength) (molar).
Percentage Excreted Unchanged in Urine (%)	%U	The proportion of drug unchanged in the body and excreted in the urine.
pKa (Strongest Acidic)	pKa (Strongest Acidic)	The pH at which the drug is completely balanced between the charged and uncharged form. Strongest acidic refers to the strongest acidic group in the molecule.
Polar Surface Area ($Å^2$)	PSA	The sum of the fractional contributions to the surface area of all nitrogen and oxygen atoms calculated using the method of Clark.
Rotatable Bonds	RB	Any single bond, not in a ring, bound to a nonterminal heavy (i.e., non-hydrogen) atom.
Rule of Five Violations	Ro5	Number of Lipinski's Rule-of-Five violations which predicts poor absorption or permeation.

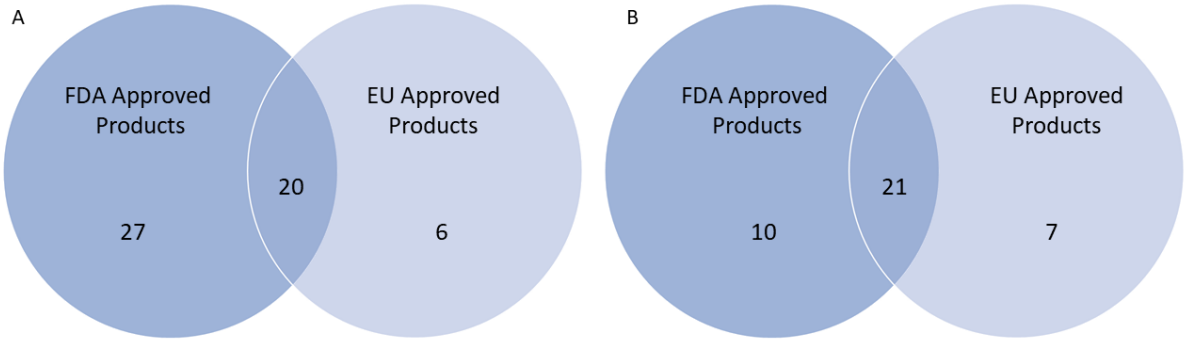


***Figure 3**: Venn Diagrams illustrating the numbers of LBF (A) and SD (B) commercial products authorised by the FDA and EU (EMA and HPRA).*

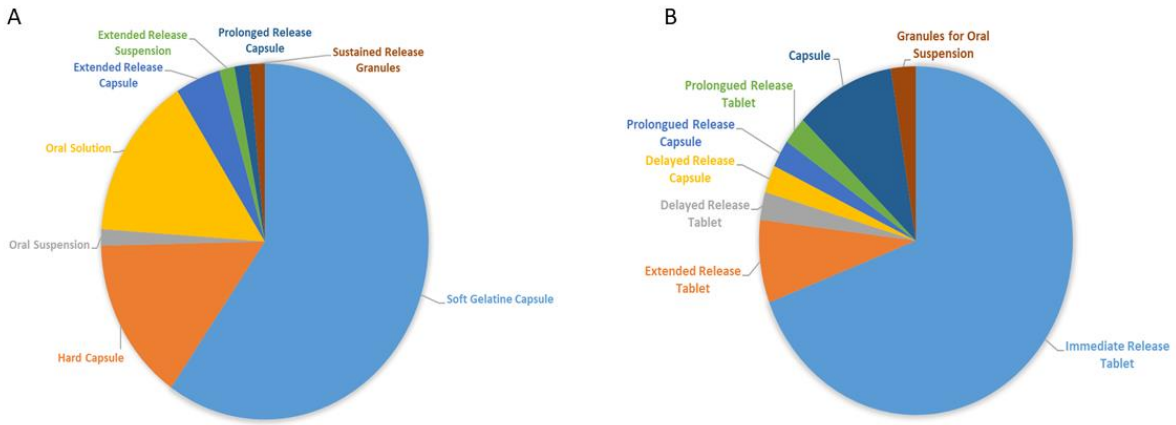


Figure 4: *Pie charts illustrating the different dosage forms products for LBF (A) and SD (B) commercial products.*

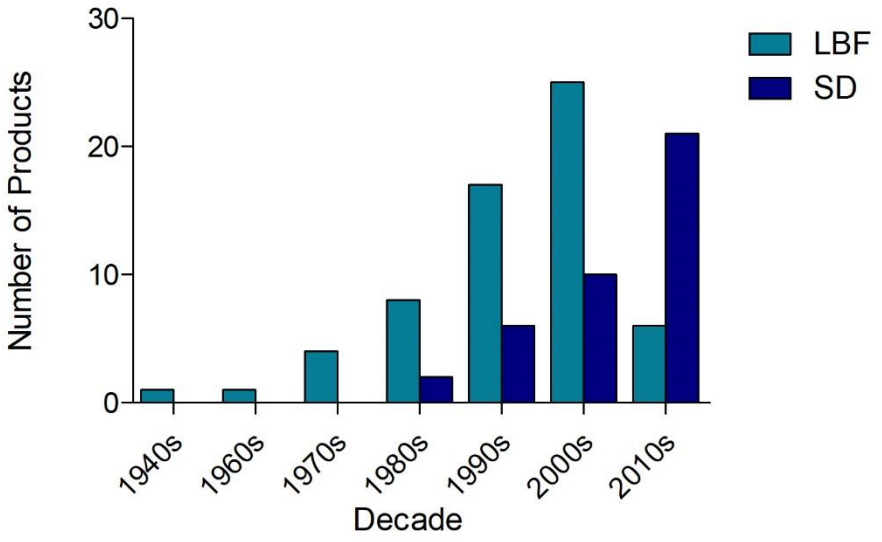


***Figure 5**: Grouped barchart illustrating the number of SD and LBF commercial products authorised by decade from 1940.*

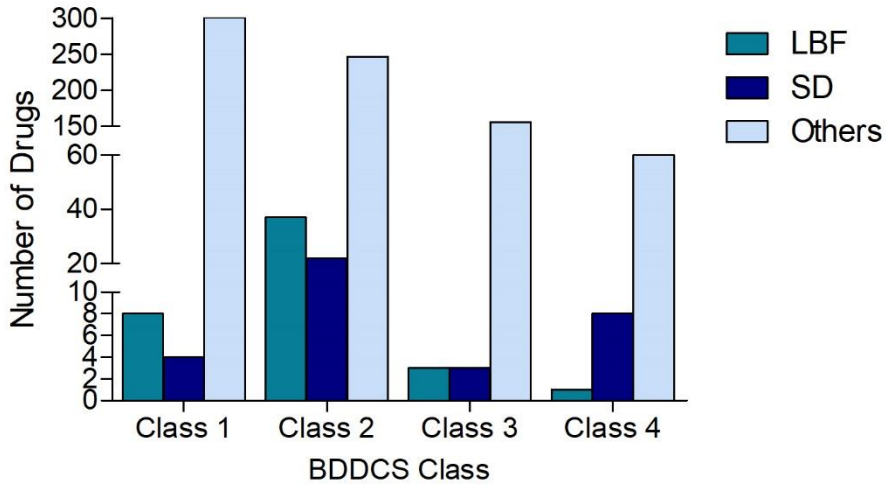
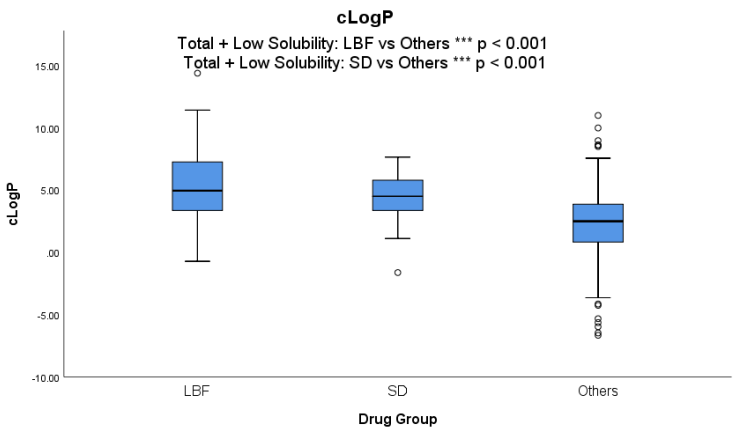
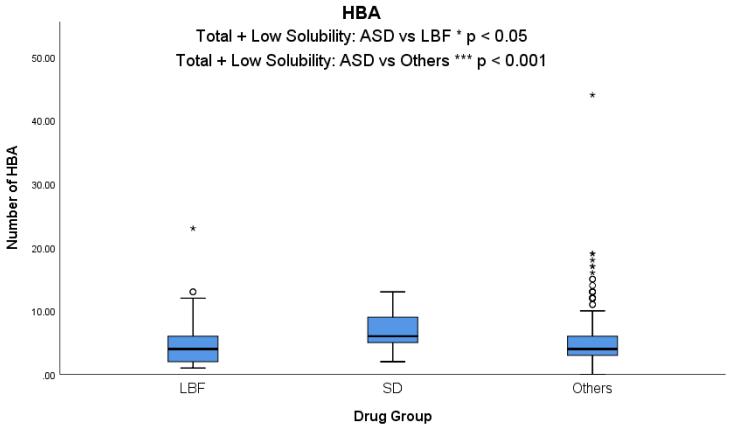
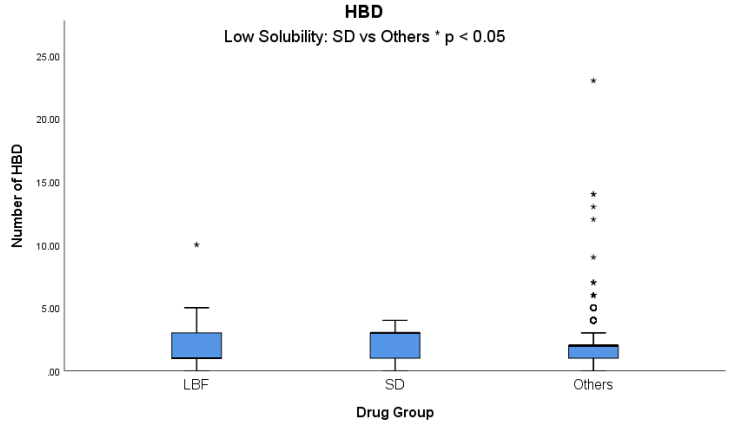
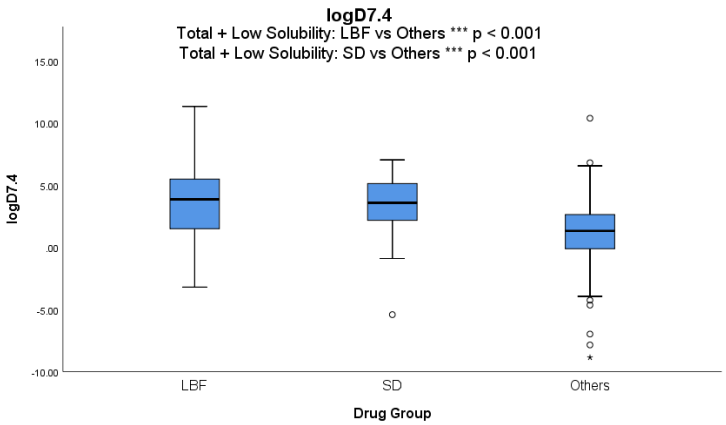


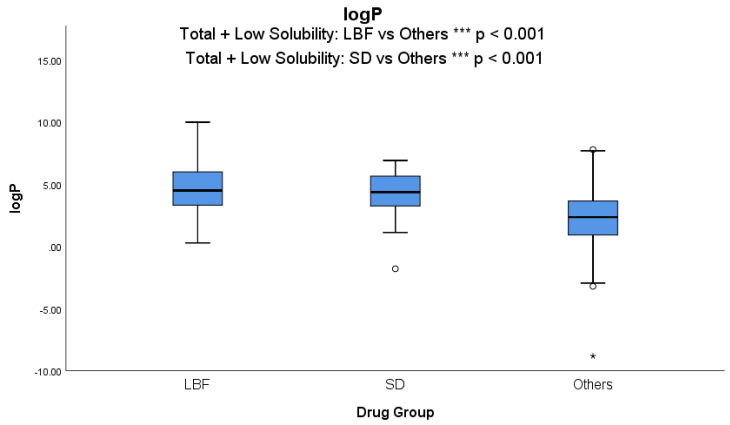
Figure 6: *Visual representation of the proportion of drug per dataset of LBF, SD and Others drugs in BDDCS Class I-IV.*

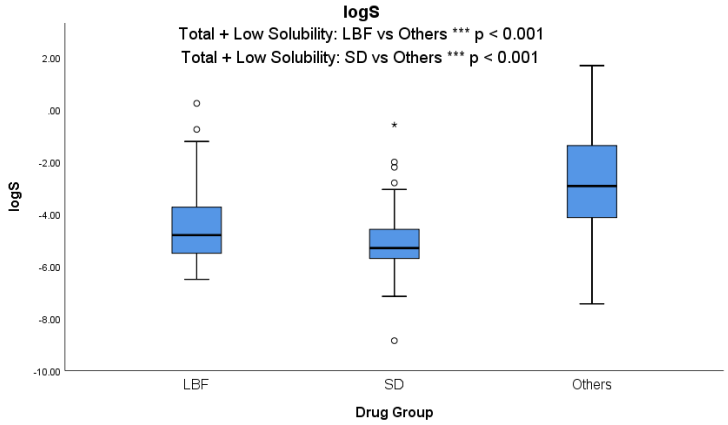

cLogP
Total + Low Solubility: LBF vs Others *** p < 0.001
Total + Low Solubility: SD vs Others *** p < 0.001
cLogP
15.00
10.00
5.00
.00
-5.00
-10.00
LBF
SD
Others
Drug Group

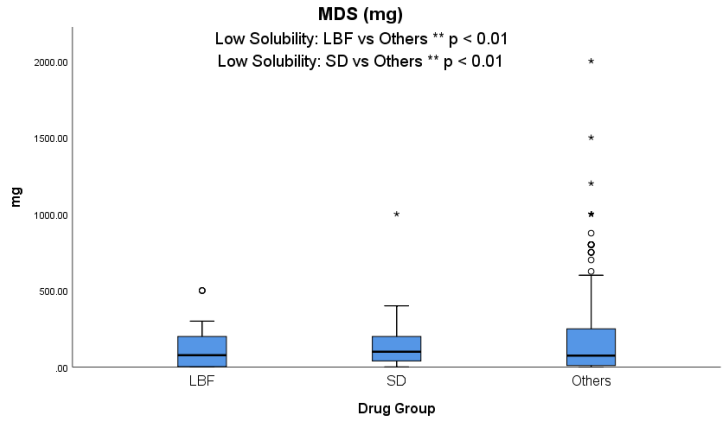

HBA
Total + Low Solubility: ASD vs LBF * p < 0.05
Total + Low Solubility: ASD vs Others *** p < 0.001
Number of HBA
50.00
40.00
30.00
20.00
10.00
.00
LBF
SD
Others
Drug Group

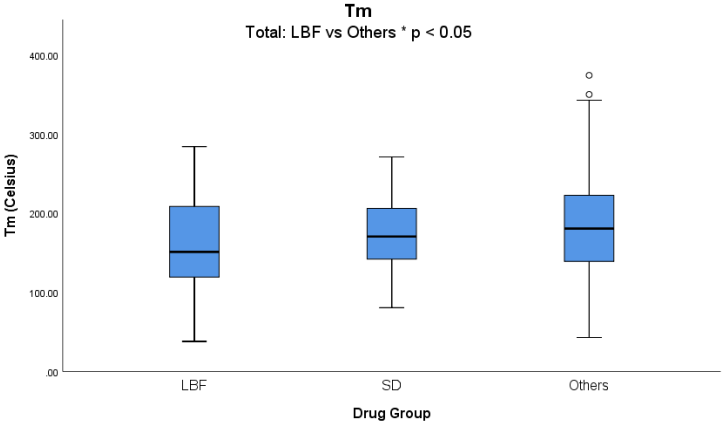

HBD
Low Solubility: SD vs Others * p < 0.05
Number of HBD
25.00
20.00
15.00
10.00
5.00
.00
LBF
SD
Others
Drug Group


logD7.4
Total + Low Solubility: LBF vs Others *** p < 0.001
Total + Low Solubility: SD vs Others *** p < 0.001
logD7.4
15.00
10.00
5.00
.00
-5.00
-10.00
LBF
SD
Others
Drug Group


logP
Total + Low Solubility: LBF vs Others *** p < 0.001
Total + Low Solubility: SD vs Others *** p < 0.001
logP
15.00
10.00
5.00
.00
-5.00
-10.00
LBF
SD
Others
Drug Group


logS
Total + Low Solubility: LBF vs Others *** p < 0.001
Total + Low Solubility: SD vs Others *** p < 0.001
logS
2.00
.00
-2.00
-4.00
-6.00
-8.00
-10.00
LBF
SD
Others
Drug Group


MDS (mg)
Low Solubility: LBF vs Others ** p < 0.01
Low Solubility: SD vs Others ** p < 0.01
mg
2000.00
1500.00
1000.00
500.00
.00
LBF
SD
Others
Drug Group


Tm
Total: LBF vs Others * p < 0.05
Tm (Celsius)
400.00
300.00
200.00
100.00
.00
LBF
SD
Others
Drug Group

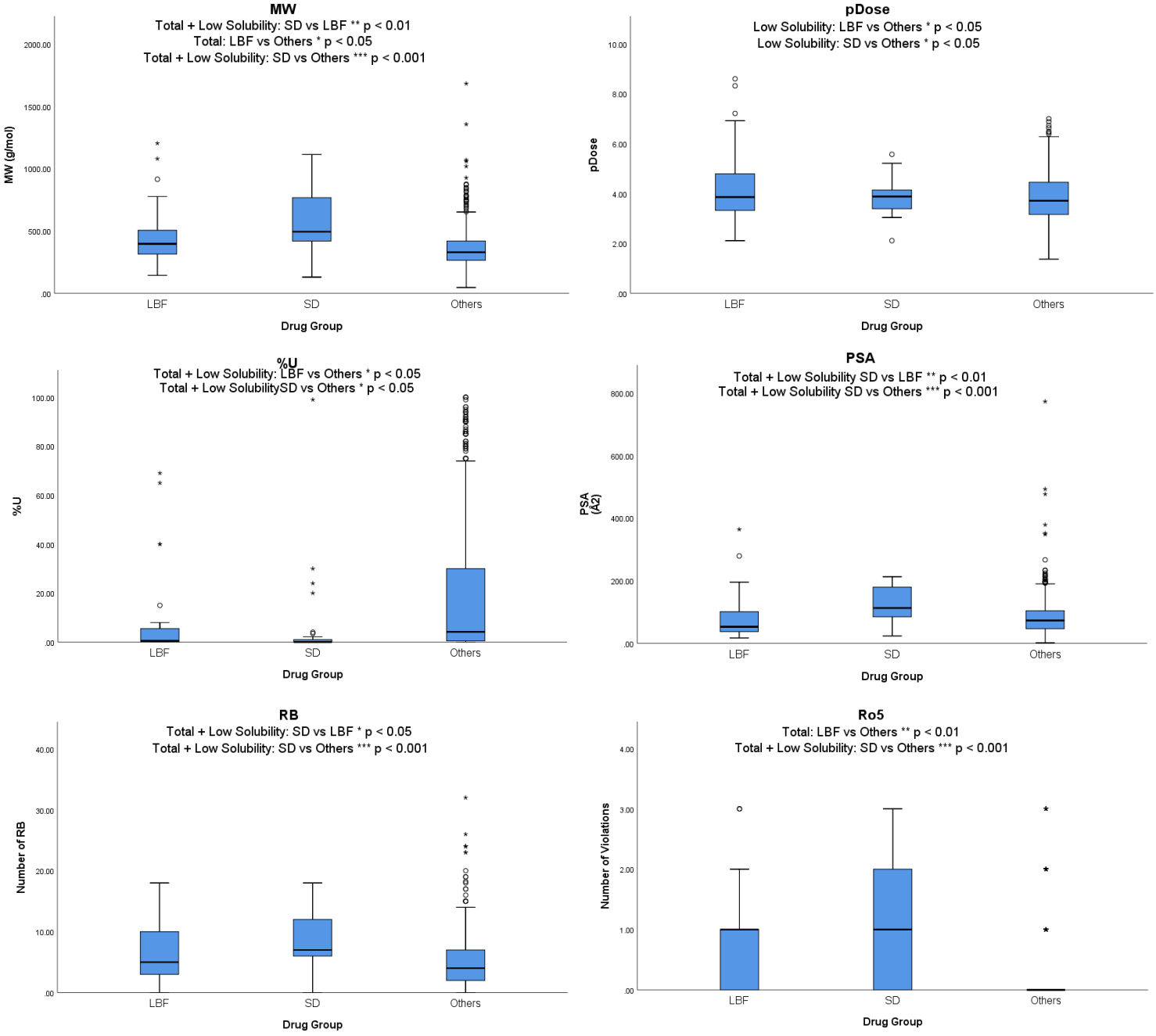


Figure 7: *Visual representation of the statistically significant differences found between LBF, SD and Others. p-values for the statistically significant pairwise comparisons are shown. "Total" refers to analysis with all BDDCS Classes. "Low Solubility" refers to analysis of only BDDCS Class II/IV. When both "Total" and "Low Solubility" are stated p-value refers to the "Total" result. The dark line in the middle of the boxes is the median. The bottom and top of the box indicates the 25th (Q1) and 75th percentile (Q3). The T-bars are inner fences/whiskers which extend to 1.5 times the box height. The points are outliers that do not fall in the inner fences. The asterisks are extreme outliers which have values greater than three times the height of the boxes*

Supplementary Materials

A Retrospective Biopharmaceutical Analysis of >800 Approved Oral Drug Products: Are Drug Properties of Solid Dispersions and Lipid-Based Formulations Distinctive?

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1: Results of Statistical Analysis comparing LBF, SD and Others using all BDDCS Classes.

2. Results of Statistical Analysis comparing LBF, SD and Others using BDDCS Class II/IV.

3. Tabular representation of SD commercial products.

4. Tabular representation of LBF commercial products.

1. Results of Statistical Analysis comparing LBF, SD and Others using all BDDCS Classes (Total).

Drug Property	Descriptors	LBF	SD	Others	Statistical Tests	p-value LBF vs SD	p-value LBF vs Others	p-value SD vs Others
clogP	*n*	49	37	763	Levene's Test	0.04	0.03	0.298
	Median	4.94	4.49	2.49	Welch's/t-test	0.14^{W}	0.00^{W}	0.00^{t}
	Mean	5.30	4.49	2.29	Mean Difference	0.82	3.01	2.20
	SD	2.97	2.04	2.37	95% Confidence Interval	(L) -3.17	(L) 2.14	(L) 1.42
	Q1, Q3,	3.32, 7,32	3.24, 4.49	0.81, 3.86		(U) 1.95	(U) 3.88	(U) 2.98
	Min, Max	-0.73, 14.36	-1.63, 7.63	-6.66, 10.97				
	Variance	8.85	4.15	5.613				
Hydrogen Bond Acceptors	*n*	49	37	763	Levene's Test	0.37	0.03	0.45
	Median	4	6	4	Bootstrap	0.011	0.85	0.00
	Mean	4.76	6.87	4.64	Mean Difference	-2.11	0.12	2.26
	SD of Mean	4.01	2.72	3.02	95% Confidence Interval	(L) -3.43	(L) -0.89	(L) 1.33
	Q1, Q3	2, 6	5, 9.5	3, 6		(U) -0.70	(U) 1.36	(U) 3.12
	Min, Max	1, 23	2, 13	0, 4				
	Variance	16.11	7.398	9.092				
Hydrogen Bond Donors	*n*	49	37	763	Levene's Test	0.77	0.45	0.714
	Median	1	3	2	Bootstrap	0.32	0.74	0.07
	Mean	1.92	2.27	1.82	Mean Difference	-0.35	0.09	0.45
	SD of Mean	1.86	1.43	1.78	95% Confidence Interval	(L) -1.05	(L) -0.39	(L) -0.05
	Q1, Q3	1, 3	1, 3.5	1,2		(U) 0.34	(U) 0.63	(U) 0.96
	Min, Max	0, 10	0, 4	0, 23				
	Variance	3.45	2.04	3.18				
$logD_{7.4}$	*n*	49	37	488	Levene's Test	0.15	0.003	0.7
	Median	3.87	3.59	1.34	Bootstrap	0.52	0.00	0.00
	Mean	3.82	3.46	1.25	Mean Difference	0.36	2.57	2.21
	SD of Mean	2.89	2.40	2.15	95% Confidence Interval	(L) -0.72	(L) 1.71	(L) 1.38
	Q1, Q3	1.48, 5.65	2.15, 5.26	-0.11, 2.65		(U) 1.45	(U) 3.43	(U) 2.98
	Min, Max	-3.2, 11.35	-5.4, 7.05	-8.86, 10.40				
	Variance	8.36	5.76	4.63				
logP	*n*	49	37	454	Levene's Test	0.22	0.45	0.33
	Median	4.50	4.37	2.36	Bootstrap	0.25	0.00	0.00
	Mean	4.66	4.16	2.22	Mean Difference	0.49	2.44	1.94
	SD of Mean	2.16	1.78	1.99	95% Confidence Interval	(L) -0.29	(L) 1.79	(L) 1.31
	Q1, Q3	3.31, 6.15	3.16, 5.69	0.92, 3.66		(U) 1.31	(U) 3.07	(U) 2.55
	Min, Max	0.28, 10	-1.80, 6.92	-8.83, 7.80				
	Variance	4.66	3.18	3.96				
logS	*n*	46	35	587	Levene's Test	0.24	0.28	0.008
	Median	-4.8	-5.3	-2.92	Welch's Test/ t-test	0.11^{t}	0.00^{t}	0.00^{w}
	Mean	-4.38	-4.95	-2.81	Mean Difference	0.58	-1.57	-2.15

Drug Property	Descriptors	LBF	SD	Others	Statistical Tests	p-value LBF vs SD	p-value LBF vs Others	p-value SD vs Others
	SD of Mean	1.64	1.49	1.73	95% Confidence Interval	(L) 0.58	(L) -2.09	(L) -2.63
	Q1, Q3	-5.54, -3.70	-5.7, -4.4	-4.14, -1.34		(U) 0.357	(U) -1.06	(U) -1.63
	Min, Max	-6.50, 0.25	-8.85, -0.57	-7.44, 1.70				
	Variance	2.70	2.22	2.968				
Maximum Dosage Strength (mg)	*n*	44	37	760	Levene's Test	0.79	0.39	0.46
	Median	62.5	100	75	Bootstrap	0.50	0.195	0.30
	Mean	118.59	144.33	195.79	Mean Difference	-25.75	-77.21	-51.46
	SD	141.02	181.56	761.68	95% Confidence Interval	(L) -106.33	(L) -160.1	-134.01
	Q1, Q3	1.94, 200	40, 200	10, 250		(U) 44.78	(U) -7.78	30.48
	Min, Max	0.0005, 500	1, 1000	0.04, 20000				
	Variance	19885.23	32964.28	580148.89				
Melting Point (^{O}C)	*n*	47	30	652	Levene's Test	0.01	0.20	0.05
	Median	151	170.5	180.5	Bootstrap	0.231	0.035	0.54
	Mean	160.81	175.97	181.18	Mean Difference	-15.18	-20.38	-5.21
	SD	64.14	44.83	58.8	95% Confidence Interval	(L) -39.26	(L) -39.91	(L) -22.22
	Q1, Q3	116.5, 211	141, 207.86	139, 222.5		(U) 8.98	(U) -1.14	(U) 11.81
	Min, Max	38, 284	80.5, 271	43, 374				
	Variance	4114.07	2009.88	3457.69				
Molecular Weight (g/mol)	*n*	49	37	763	Levene's Test	0.12	0.001	0.00
	Median	396.65	493.58	329.63	t-test/Bootstrap	0.009	0.011	0.00
	Mean	448.20	586.63	354.63	Mean Difference	-138.43	93.57	231.99
	SD of Mean	216.82	230.92	148.61	95% Confidence Interval	(L) -235.25	(L) 37.08	(L) 158.46
	Q1, Q3	314.61, 517.1	405.47, 785.47	263.79, 419.39		(U) -40.70	(U) 156.41	(U) 310.92
	Min, Max	144.21, 1202.61	129.17, 1113.2	46.07, 1681.91				
	Variance	47011.07	53322.02	22086.19				
pDose	*n*	44	37	760	Levene's Test	0.001	0.000	0.007
	Median	3.86	3.88	3.71	Bootstrap	0.115	0.063	0.737
	Mean	4.27	3.50	3.83	Mean Difference	0.407	0.45	0.04
	SD of Mean	1.49	0.66	0.90	95% Confidence Interval	(L) -0.07	(L) 0.36	(L) -0.18
	Q1, Q3	3.29, 4.94	3.37, 4,17	3.16, 4.45		(U) 0.91	(U) 0.90	(U) 0.26
	Min, Max	2.11, 8.60	2.11, 5,57	1.37, 7.00				
	Variance	2.21	0.44	0.82				
Percentage Excreted Unchanged in Urine (%)	*n*	40	33	667	Levene's Test	0.86	0.00	0.00
	Median	0.5	0.05	4.2	Bootstrap	0.70	0.01	0.03
	Mean	7.33	5.68	19.47	Mean Difference	1.65	-12.14	-13.79
	SD of Mean	16.5	18.24	27.78	95% Confidence Interval	(L) -7.21	(L) -17.07	(L) -18.77
	Q1, Q3	0.10, 5.75	0, 1.25	0.5, 30		(U) 9.23	(U) -6.41	(U) -7.18
	Min, Max	0, 69	0, 99	0, 100				
	Variance	272.16	332.84	771.91				
pKa (strongest acid)	*n*	46	29	624	Levene's Test	0.34	0.52	0.44
	Median	10.44	9.7	10.33	Bootstrap	0.38	0.73	0.41
	Mean	10.20	9.12	9.90	Mean Difference	1.08	0.30	-0.78

Drug Property	Descriptors	LBF	SD	Others	Statistical Tests	p-value LBF vs SD	p-value LBF vs Others	p-value SD vs Others
	SD of Mean	5.66	4.86	0.21	95% Confidence Interval	(L) -1.18	(L) -1.38	(L) -2.61
	Q1, Q3	0.27, 22	4.09, 12.63	4.77, 13.98		(U) 3.41	(U) 1.99	(U) 1.06
	Min, Max	4.75, 13.86	0, 19.90	-12.00, 19.96				
	Variance	32.07	23.57	26.99				
Polar	*n*	49	37	762	Levene's Test	0.82	0.12	0.26
Surface	*Median*	52.9	112.85	72.91	Bootstrap	0.003	0.85	0.00
Area	*Mean*	79.68	125.92	81.48	Mean Difference	-46.24	-1.91	44.33
(Å²)	*SD of Mean*	67.94	52.74	57.91	95% Confidence Interval	(L) -71.83	(L) -19.95	(L) 26.83
	Q1, Q3	37.3, 102.15	84.76, 180.59	46.53, 104.09		(U) -19.74	(U) 18.36	(U) 61.81
	Min, Max	17.10, 364.00	23.68, 212.97	1.18, 772.46				
	Variance	4616.27	2781.26	3340.33				
Rotatable	*n*	49	37	746	Levene's Test	0.95	0.013	0.024
Bonds	*Median*	5	7	4	Bootstrap	0.041	0.06	0.00
	Mean	6.6	8.76	5.2	Mean Difference	-2.14	1.41	3.56
	SD of Mean	4.82	4.67	4.02	95% Confidence Interval	(L) -4.20	(L) 0.06	(L) 2.04
	Q1,Q3	3, 10.5	5.5, 12.5	2, 7		(U) -0.09	(U) 2.81	(U) 5.04
	Min, Max	0, 18	0, 18	0, 32				
	Variance	23.2	21.8	16.17				
Rule of 5	*n*	49	37	763	Pearson Chi-Square/	0.22^{P}	0.006^{F}	0.000^{F}
Violations	*Mean*	0.82	1.03	0.269	Fischer's Exact Test			
	SD of Mean	0.88	0.96	0.62				

Results of the pairwise comparisons completed using BDDCS I-IV classification groups. B = Bootstrap, t = t-test, W = Welch's test, P = Pearson Chi-Square, F = Fischer's Exact Test. Bootstrap 95% Confidence Interval based upon 5000 stratified bootstrap samples. (L) and (U) refer to lower and upper 95% confidence limits. For non-categorical variables showing normal distribution, when Levene's test was not significant, 95% Confidence intervals and sig. Level for groups comparison were based on 'equal variance assumed' calculations i.e independent samples t-test (2 sided). When Levene's test was significant, 95% Confidence intervals and sig. Level for group's comparison were based on 'equal variance not-assumed' calculations i.e Welch's test. For non-categorical variables not showing normal distribution the bootstrap method was used (5000 samples). Categorical variables i.e. Ro5, were analysed using Chi-Square tests. If 1 or more cells had an expected count below 5, Fisher's exact test was employed. A p-value of 0.05 was used as the significance level for all tests. SD refers to Standard Deviation of the Mean.

Rule-of-5 Violations versus Drug Group Cross Tabulation (All BDDCS Classes):

			Drug Group			Total
			LBF	SD	Others	
Ro5	**No Greater than 1**	**Count**	40	26	714	780
		% of Group Total	81.6%	70.3%	93.6%	91.9%
	Greater than 1	**Count**	9	11	49	69
		% of Group Total	18.4%	29.7%	6.4%	8.1%
Total		**Count**	49	37	763	849
		% of Group Total	100.00%	100.00%	100.00%	100.00%

2**.** Results of Statistical Analysis comparing LBF, SD and Others using BDDCS Class II/IV (Low Solubility).

Drug Property	**Descriptors**	**LBF**	**SD**	**Others**	**Statistical Tests**	**p-value LBF vs SD**	**p-value LBF vs Others**	**p-value SD vs Others**
clogP	*n*	38	30	307	Levene's Test	0.16	0.005	0.33
	Median	4.99	5.05	3.36	Welch's/ t-test	0.21[W]	0.000[W]	0.000[t]
	Mean	5.62	4.92	3.31	Mean Difference	0.70	2.31	1.61
	SD of Mean	0.47	1.57	0.12	95% Confidence Interval	(L) -0.39	(L) 1.34	(L) 0.86
	Q1, Q3	3.76, 7.36	3.82, 6.02	2.19, 4.40		(U) 1.79	(U) 3.27	(U) 2.35
	Min, Max	-0.73, 14.36	1.91, 7.63	-2.42, 10.97				
	Variance	8.25	2.45	4.03				
Hydrogen Bond Acceptors	*n*	38	30	307	Levene's Test	0.97	0.36	0.37
	Median	4	6	4	Bootstrap	0.00	0.31	0.00
	Mean`	4.34	7	4.81	Mean Difference	-2.66	-0.47	2.19
	SD of Mean	2.88	2.56	2.60	95% Confidence Interval	(L) -3.90	(L) -1.40	(L) 1.26
	Q1, Q3	2, 6	5, 10	3, 6		(U) -1.39	(U) 0.58	(U) 3.16
	Min-Max	1, 13	3, 12	0, 18				
	Variance	8.29	6.55	6.78				
Hydrogen Bond Donors	*n*	38	30	307	Levene's Test	0.43	0.23	0.04
	Median	1	2.50	1	Bootstrap	0.09	0.81	0.03
	Mean	1.68	2.27	1.63	Mean Difference	-0.58	0.06	0.64
	SD of Mean	1.38	1.46	1.23	95% Confidence Interval	(L) -1.23	(L) -0.36	(L) 0.11
	Q1, Q3	1, 3	1, 4	1, 2		(U) 0.09	(U) 0.54	(U) 1.17
	Min-Max	0, 5	0, 4	0, 7				
	Variance	1.90	2.13	1.52				

Drug Property	Descriptors	LBF	SD	Others	Statistical Tests	LBF vs SD	p-value LBF vs Others	SD vs Others
$logD_{7.4}$	*n*	38	30	181	Levene's Test	0.04	0.02	0.30
	Median	3.92	4.05	2.85	Bootstrap	0.80	0.001	0.000
	Mean	3.90	4.04	4.04	Mean Difference	-0.14	1.82	1.96
	SD of Mean	2.85	1.67	2.01	95% Confidence Interval	(L) -1.21	(L) 0.92	(L) 1.28
	Q1, Q3	2.10, 5.58	2.75, 5.39	0.73, 3.52		(U) 0.94	(U) 2.74	(U) 2.66
	Min-Max	-3.20, 11.35	1.28, 7.05	-3.68, 10.40				
	Variance	8.12	2.79	4.04				
logP	*n*	38	30	175	Levene's Test	0.05	0.12	0.31
	Median	4.51	4.62	3.12	Bootstrap	0.56	0.00	0.00
	Mean	4.84	4.60	3.06	Mean Difference	0.24	1.78	1.54
	SD of Mean	2.05	1.30	1.66	95% Confidence Interval	(L) -0.54	(L) 1.08	(L) 1.02
	Q1, Q3	3.72, 6.29	3.63, 5.73	2.24, 4.18		(U) 1.03	(U) 2.49	(U) 2.07
	Min-Max	0.28, 10	2.18, 6.92	-1.56, 7.80				
	Variance	4.19	1.69	2.76				
logS	*n*	36	29	228	Levene's Test	0.74	0.93	0.63
	Median	-5.13	-5.4	-4.2	Bootstrap	0.24	0.00	0.00
	Mean	-4.91	-5.29	-4.23	Mean Difference	0.38	-0.69	-1.06
	SD of Mean	1.14	1.31	1.03	95% Confidence Interval	(L) -0.29	(L) -1.05	(L) -1.54
	Q1,Q3	-5.70, -4.2	-5.80, -4.90	-4.9, -3.44		(U) 1.03	(U) -0.29	(U) -0.56
	Min-Max	-6.5, -1.21	-8.85, -0.57	-7.44, -1.00				
	Variance	1.29	1.71	1.07				
Maximum Dosage Strength (mg)	*n*	35	30	307	Levene's Test	0.19	0.008	0.00
	Median	75	100	100	Bootstrap	0.96	0.008	0.003
	Mean	116.64	118.01	195.50	Mean Difference	0-1.37	-78.86	-77.50
	SD of Mean	133.81	104.11	209.24	95% Confidence Interval	(L) -57.57	(L) -126.11	(L) -120.90
	Q1, Q3	10, 200	37.5, 200	30, 300		(U) 57.13	(U) -30.98	(U) -32.83
	Min-Max	0.0005, 500	1, 400	0.45, 300				
	Variance	17904.70	10838.05	43781.20				
Melting Point (^{O}C)	*n*	36	24	257	Levene's Test	0.04	0.20	0.15
	Median	153	173.75	182	Welch's/t-test	0.25^{W}	0.051^{t}	0.77^{t}
	Mean	162.97	179.93	183.46	Mean Difference	-16.96	-20.49	-3.53
	SD of Mean	65.49	46.81	57.73	95% Confidence Interval	(L) -44.88	(L) -41.06	(L) -27.44
	Q1, Q3	117.88, 223.55	143.25, 211.63	141.75, 224.00		(U) 11.50	(U) 0.08	(U) 20.38
	Min-Max	38, 284	80.5, 271	52, 349.84				
	Variance	4288.33	2191.41	3332.99				
Molecular Weight (g/mol)	*n*	38	30	307	Levene's Test	0.17	0.007	0.000
	Median	398.64	581.65	375.87	Bootstrap	0.002	0.129	0.000
	Mean	449.49	618.37	394.59	Mean Difference	-168.88	54.91	223.79
	SD of Mean	207.06	215.47	138.62	95% Confidence Interval	(L) -266.68	(L) -7.11	(L) 145.70
	Q1, Q3	315.45, 530.36	431.08, 812.76	296.54, 451.62		(U) -68.55	(U) 127.64	(U) 306.04
	Min-Max	153.14, 1202.61	346.34, 1113.20	136.11, 1058.06				
	Variance	42874.38	46426.99	19214.60				
pDose	*n*	35	30	307	Levene's Test	0.004	0.000	0.04

Drug Property	Descriptors	LBF	SD	Others	Statistical Tests	p-value LBF vs SD	p-value LBF vs Others	p-value SD vs Others
	Median	3.86	3.95	3.51	Bootstrap	0.34	0.026	0.037
	Mean	4.18	3.93	3.67	Mean Difference	0.25	0.52	0.27
	SD of Mean	1.38	0.59	0.77	95% Confidence Interval	(L) -0.24	(L) 0.07	(L) 0.04
	Q1, Q3	3.38, 4.48	3.46, 4.21	3.09, 4.15		(U) 0.78	(U) 0.99	(U) 0.50
	Min-Max	2.11, 8.32	3.04, 5.57	2.29, 6.03				
	Variance	1.91	0.36	0.59				
Percentage Excreted Unchanged in Urine (%)	*n*	31	27	262	Levene's Test	0.13	0.001	0.000
	Median	0.5	0.03	1.5	Bootstrap	0.39	0.014	0.000
	Mean	3.98	1.36	1.36	Mean Difference	2.61	-7.77	-10.38
	SD of Mean	11.81	4.64	21.41	95% Confidence Interval	(L) -0.78	(L) -11.88	(L) -13.38
	Q1, Q3	0.05, 2.2	0, 0.5	0.29, 10		(U) 7.15	(U) -2.73	(U) -7.41
	Min-Max	0, 65	0, 24	0, 100				
	Variance	139.67	21.56	458.18				
pKa (strongest acid)	*n*	37	25	272	Levene's Test	0.23	0.14	0.70
	Median	10.6	9.33	10.29	Bootstrap	0.45	0.81	0.44
	Mean	10.11	9.04	9.85	Mean Difference	1.06	0.25	-0.81
	SD of Mean	0.99	5.01	5.13	95% Confidence Interval	(L) -1.68	(L) -1.78	(L) -2.89
	Q1, Q3	4.25, 14.04	3.99, 12.63	4.74, 13.78		(U) 3.78	(U) 2.4	(U) 1.25
	Min-Max	0.27, 22	0, 19.90	-12, 19.96				
	Variance	36.4	25.06	26.33				
Polar Surface Area ($Å^2$)	*n*	38	30	306	Levene's Test	0.56	0.22	0.05
	Median	55.4	116.43	76.15	Bootstrap	0.00	0.37	0.00
	Mean	74.63	130.08	82.85	Mean Difference	-55.45	-8.23	47.22
	SD of Mean	54.39	49.79	43.78	95% Confidence Interval	(L) -79.78	(L) -24.99	(L) 28.55
	Q1, Q3	37.3, 98.56	90.16, 182.69	54.8, 104.60		(U) -29.24	(U) 10.32	(U) 65.61
	Min-Max	20.23, 279	46.53, 204	1.18, 266.66				
	Variance	2957.95	2478.83	1917.02				
Rotatable Bonds	*n*	38	30	306	Levene's Test	0.76	0.04	0.13
	Median	5	7	5	Bootstrap	0.050	0.274	0.001
	Mean	6.53	8.8	5.62	Mean Difference	-2.27	0.90	3.18
	SD of Mean	4.88	4.39	4.10	95% Confidence Interval	(L) -4.46	(L) -0.65	(L) 1.51
	Q1, Q3	3, 11	5.75, 12.25	3, 7		(U) -0.08	(U) 2.53	(U) 4.87
	Min-Max	0, 18	3, 18	0, 24				
	Variance	23.8	19.27	4.10				
Rule of 5 Violations	*n*	34	27	239	Pearson Chi-Square/ Fischer's Exact Test	0.159^P	0.086^F	0.001^F
	Mean	0.9412	1.148	0.343				
	SD	0.8507	0.9488	0.6542				

Results of the pairwise comparisons completed using BDDCS II/IV classification groups. B = Bootstrap, t = t-test, W = Welch's test, P = Pearson Chi-Square, F = Fischer's Exact Test. Bootstrap 95% Confidence Interval based upon 5000 stratified bootstrap samples. (L) and (U) refer to lower and upper 95% confidence limits. For non-categorical variables showing normal distribution, when Levene's test was not significant, 95% Confidence intervals and sig. Level for groups comparison were based on 'equal variance assumed' calculations i.e independent samples t-test (2 sided). When Levene's test was significant, 95% Confidence intervals and sig. Level for group's comparison were based on 'equal variance not-assumed' calculations i.e Welch's test. For non-

categorical variables not showing normal distribution the bootstrap method was used (5000 samples). Categorical variables i.e. Ro5, were analysed using Chi-Square tests. If 1 or more cells had an expected count below 5, Fisher's exact test was employed. A p-value of 0.05 was used as the significance level for all tests. SD refers to Standard Deviation of the Mean.

Rule-of-5 Violations versus Drug Group Cross Tabulation (BDDCS Class II/IV)

			Drug Group			Total
			LBF	**SD**	**Others**	
Ro5	**No Greater than 1**	**Count**	31	20	279	330
		% of Group Total	81.60%	66.70%	90.90%	88.0%
	Greater than 1	**Count**	7	10	28	45
		% of Group Total	18.40%	33.30.%	9.10%	12.00%
Total		**Count**	38	30	307	375
		% of Group Total	100.00%	100.00%	100.00%	100.00%

3. Tabular representation of SD commercial products.

Trade Name	Drug	Dosage Form/Strength	Excipients*	Method of Manufacturer
Afeditab CR®	Nifedipine	Tablet (30mg)	Poloxamer/PVP	Spray Drying
Afinitor®	Everolimus	Tablet (2.5,5, 7.5, 10mg)	HPMC	Spray Drying
Astagraf XL®	Tacrolimus	Capsule (0.5, 1, 5mg)	HPMC	Wet Granulation
Belsomra®	Suvorexant	Tablet (5, 10, 15, 20mg)	Polyvinylpyrrolidone/ Vinyl Acetate Copolymer (Copovidone)	Melt Extrusion
Certican®	Everolimus	Tablet (0.25, 0.5, 0.75, 1mg)	HPMC	Spray Drying
Cesamet®	Nabilone	Capsule (1mg)	Povidone	Solvent Evaporation
Cokiera®	Dasabuvir/ Ombitasvir/ Paritaprevir/ Ritonavir	Tablet (200/8.33/50/33.33mg)	Copovidone	Melt Extrusion
Crestor®	Rosuvastatin Calcium	Tablet (5, 10, 20, 40mg)	HPMC	Spray Drying
Cymbalta®	Duloxetine	Capsule (30, 60mg (+20mg FDA))	HPMCAS	
Deltyba®	Delamanid	Tablet (50mg)	Hypromellose Phthalate (HPMCP)	
Envarsus XR®	Tacrolimus	Tablet (0.75, 1, 4mg)	HPMC	Melt Granulation
Epclusa®	Sofosbuvir/ Velpatasvir	Tablet (400/100mg)	Copovidone	Spray Drying
Eucreas®	Vildagliptin/ Metformin HCL	Tablet (50/850mg + 50/1000mg)	HPC	Hot Melt Extrusion
Fenoglide®	Fenofibrate	Tablet (40, 120mg)	PEG 6000, Poloxamer 188	Spray Melt
Galvumet®	Vildagliptin /Metformin HCL	Tablet (50/850mg + 50/1000mg)	HPC	Hot Melt Extrusion
Gris-PEG®	Griseofulvin	Tablet (125, 250mg)	PEG 400 and 8000, Povidone	Melt-Extrusion
Harvoni®	Ledipasvir/ Sofosbuvir	Tablet (90/400, 45/200mg)	Copovidone	Spray Drying
Incivek®	Telaprevir	Tablet (375mg)	HPMCAS	Spray Drying
Incivo®	Telaprevir	Tablet (375mg)	HPMCAS	Spray Drying
Intelence®	Etravirine	Tablet (25, 100, 200mg)	HPMC	Spray Drying
Isoptin SR-E 240®	Verapamil	Tablet (240mg)	HPMC/HPC	Spray Drying
Kaletra®	Lopinavir/Ritonavir	Tablet (100/25, 200/50mg)	PVP	Melt Extrusion
Kalydeco®	Ivacaftor	Tablet (75, 150mg)	HPMCAS	Spray Drying
Mavyret®	Glecaprevir/ Pibrentasvir	Tablet (40/100mg)	Copovidone (Type K 28)	Melt Extrusion
Modigraf®	Tacrolimus	Granules for Oral Suspension (0.2,1mg)	HPMC	Spray Drying
Nimotop®	Nimodipine	Tablet (30mg)	PEG	Spray Drying/ Fluid Bed
Nivadil®	Nilvadipine	Capsule (16mg,8mg)	HPMC	Spray Drying
Norvir®	Ritonavir	Tablet (100mg)	PVP VA 64	Melt Extrusion
Noxafil®	Posaconazole	Tablet (100mg)	HPMCAS	Melt Extrusion

Trade Name	Drug	Dosage Form/Strength	Excipients*	Method of Manufacturer
Onmel®	Itraconazole	Tablet (200mg)	PVP VA 64	Melt-Extrusion
Orkambi®	Lumacaftor/ Ivacaftor	Tablet (100mg/125mg, 200mg/125mg)	HPMCAS	Spray Drying
Prograf®	Tacrolimus	Capsule (0.5, 1, 3, 5mg)	HPMC	Spray Drying
Rezulin®	Troglitazone	Tablet (200, 300, 400mg)	PVP	Spray Drying
Samsca®	Tolvaptan	Tablet (15, 30 + 60mg)	HPMC	Granulation
Shui linjia	Silibinin	Capsule (70mg)	Lecithin	
Sporanox®	Itraconazole	Capsule (100mg)	HPMC	Fluid Bed Bead Layering
Stivarga®	Regorafenib	Tablet (40mg)	Povidone K25	
Venclexta®	Venetoclax	Tablet (10, 50, 100mg)	Copovidone	Melt Extrusion
Viekira XR®	Dasabuvir/ Ombitasvir/ Paritaprevir/ Ritonavir	Tablet (200/8.33/50/33.33mg)	Copovidone	Melt Extrusion
Votubia®	Everolimus	Tablet (2.5, 5, 10mg)	HPMC	Spray Drying
Zelboraf®	Vemurafenib	Tablet (240mg)	HPMCAS	Solvent/Anti-Solvent Precipitation
Zepatier®	Elbasvir/ Grazoprevir	Tablet (50/100mg)	TPGS, Copovidone, HPMC	Spray Drying
Zortress®	Everolimus	Tablet (0.25, 0.5, 0.75, 1mg)	HPMC	Spray Drying

Data obtained from FDA Drug Label (from Drugs @FDA database), European Summary of Pharmaceutical Characteristics (SPC), Health Products Regulatory Authority (HPRA) National Drug Authorisation SPC or Therapeutic Goods Administration (TGA) product information.
*Excipients listed refer only to selected relevant excipients from the total excipients of the drug products which contribute directly to the transformation and/or stability of a drug as a SD.

4. Tabular representation of LBF commercial products.

Trade Name	Drug	Dosage Form/Strength	Excipients*
Absorica®	Isotretinoin	Hard Gelatine Capsule (10,20,25,30,35,40mg)	Sorbitan Monooleate, Soybean Oil and Stearoyl Polyoxylglycerides
Accutane®	Isotretinoin	Soft Gelatine Capsule (10,20,40mg)	Beeswax, Hydrogenated Soybean Oil Flakes, Hydrogenated Vegetable Oil, Soybean Oil
Advil Cold and Sinus®	Ibuprofen	Liquid Gel Capsule (200mg/30mg)	Fractionated Coconut Oil, Poly Ethylene Glycol
Agenerase®	Amprenavir	Soft Gelatine Capsule (50, 150mg)	Polyethylene Glycol 1000 Succinate (TPGS), Polyethylene Glycol 400 (PEG 400), Propylene Glycol
Aloxi®	Palonosetron	Soft Gelatine Capsule (0.5mg)	Mono- and di-glycerides of Capryl/Capric acid, Glycerin, Polyglyceryl Oleate, Water, and Butylated Hydroxyanisole
Amitiza®	Lubiprostone	Soft Gelatine Capsule (8, 24mcg)	Medium-Chain Triglycerides
Aptivus®	Tipranivir	Soft Gelatine Capsule (250mg)	Macrogolglycerol Ricinoleate, Ethanol, Mono/diglycerides of Caprylic/Capric acid, Propylene Glycol.
Aptivus®	Tipranivir	Oral Solution (100mg/mL)	Macrogol, Polyethylene Glycol, Propylene Glycol, Mono/Diglycerides of Caprylic/Capric Acid, Polyoxyl 35 Caster Oil, Vitamin E Polyethylene Glycol Succinate (TPGS).
Avodart®	Dutasteride	Soft Gelatine Capsule (0.5mg)	Mono- and Diglycerides of Caprylic/Capric acid
Cipro®	Ciprofloxacin	Oral Suspension (250mg/mL, 500mg/5mL)	Medium Chain Triglycerides
Claravis®	Isotretinoin	Liquid Filled Hard Shell Capsule (10,20,30,40mg)	Hydrogenated Vegetable Oil, Polysorbate 80, Soybean Oil.
Clarityn®	Loratadine	Soft Gelatine Capsule (10mg)	Caprylic/Capric Glycerides, Glycerin, Polysorbate 80.
Convulex®	Valproic Acid	Soft Gelatine Capsule (150, 300, 500mg)	Macrogol 6000, Glycerol Monostearate 44-55 Type II
Depakene®	Valproic Acid	Soft Gelatine Capsule (250mg)	Corn Oil
Detrol La®	Tolterodine Tartrate	Extended Release Gelatine Capsule (2, 4mg)	Medium Chain Triacylglycerides, Oleic Acid, Gelatin.
Drisdol®	Ergocalciferol	Liquid Filled Hard Shell Capsule (1.25mg)	Glycerin, Soybean Oil, Edible Vegetable Oil.
Epadel®(1)	Ethyl Eicosapentaenoate	Soft Gelatine Capsule (500mg)	Alpha Tocopherol
Fenogal®	Fenofibrate	Hard Gelatine Capsule (200mg)	Lauryl Macroglycerides, Macrogol 20,000
Fortovase®	Saquinavir	Soft Gelatine Capsule (200mg)	Medium Chain Mono- and Diglycerides.
Gengraf®	Cyclosporin	Hard Gelatine Capsule (25, 100mg) (50mg discontinued)	Polyethylene Glycol, Polyoxyl 35 Castor Oil, Polysorbate 80, Propylene Glycol, Ethanol.

Trade Name	Drug	Dosage Form/Strength	Excipients*
Gengraf®	Cyclosporin	Oral Solution (100mg/mL)	Polyoxyl 40, Hydrogenated Castor Oil, Polysorbate 80, Propylene Glycol
Glakay®	Menatetrenone	Soft Gelatine Capsule (15mg)	Carnauba Wax, Hydrogenated Oil, Glyceryl Monooleate, PG Esters of Fa, Glycerin.
Hectorol®	Doxercalciferol	Soft Gelatine Capsule (0.5, 1, 2.5mcg)	Ethanol, Fractionated Triglyceride of Coconut Oil
Heminevrin®	Clomethiazole	Soft Gelatine Capsule (192mg)	Medium Chain Triglycerides, Glycerol
Hycamtin®	Topotecan	Liquid Filled Hard Shell Capsule (0.25, 1mg)	Hydrogenated Vegetable Oil, Glyceryl monostearate
Infree®	Indomethacin	Capsule (100, 200mg)	Cremophor RH 60
Juvela N®	Tocopherol Nicotinate	Soft Gelatine Capsule (200mg)	Carnauba Wax, Medium Chain Triglycerides, Glycol Esters of Fatty Acids, Glycerin.
Kaletra®	Lopinavir/ Ritonavir	Soft Gelatine Capsule (133.3mg/33.3mg)	Glycerin, Oleic Acid, Polyoxyl 35 Castor Oil, Propylene Glycol.
Kaletra®	Lopinavir/ Ritonavir	Oral Solution (80+20mg/mL)	Ethanol, Glycerin, Polyoxyl 40 Hydrogenated Castor Oil, Propylene Glycol.
Ketas®	Ibudilast	Sustained Release Granules (10mg)	Hydrogenated Castor Oil, Macrogol 6000, Cremophor RH 60.
Lamprene®	Clofazimine	Soft Gelatine Capsule (50, 100mg)	Beeswax, Glycerin, Lecithin, Plant Oils, Propylene Glycol.
Lipofen®	Fenofibrate	Hard Shell Capsule (50, 150mg) (100mg discontinued)	Gelucire 44/14, Polyethylene Glycol 20,000, Polyethylene Glycol 8000, Propylene Glycol
Lovaza®	Omega-3 Acid Ethyl Esters	Soft Gelatine Capsule (900mg/gram)	Soybean Oil.
Marinol®	Dronabinol	Soft Gelatine Capsule (2.5, 5, 10mg)	Sesame Oil.
MXL®	Morphine	Prolonged Release Capsule (30, 60, 90, 120,150,200mg)	Hydrogenated Vegetable Oil BP, Macrogol 6000 Ph Eur
Navelbine®	Vinorelbine	Soft Gelatine Capsule (20, 30, 80mg)	Anhydrous Ethanol, Glycerol Macrogol 400
Neoral®	Ciclosporin	Soft Gelatine Capsule (25, 50, 100mg)	Alpha-tocopherol, Ethanol, Propylene Glycol, Glycerol, Corn oil-mono-di-triglycerides, Macrogolglycerol hydroxystearate / Polyoxyl 40 hydrogenated castor oil.
Neoral®	Ciclosporin	Oral Solution (100 mg/mL)	Alpha–tocopherol, Ethanol, Propylene Glycol, Corn oil-mono-di-triglycerides, Macrogolgylcerol Hydroxystearate / Polyoxy 40 Hydrogenated Castor Oil.
Nimotop®	Nimodipine	Soft Gelatine Capsule (30mg)	Glycerin, Peppermint oil, Polyethylene Glycol 400
Norvir®	Ritonavir	Oral Solution (80 mg/mL)	Polyoxyl 35 Castor oil, Propylene Glycol, Ethanol.
Norvir®	Ritonavir	Soft Gelatine Capsule (100 mg)	Ethanol, Oleic Acid, Polyoxyl 35 Castor Oil.
Ofev®	Nintedanib	Soft gelatine capsule (100mg, 150mg)	Triglycerides (Medium-Chain), Hard Fat Lecithin (soya)

Trade Name	Drug	Dosage Form/Strength	Excipients*
One-Alpha®	Alfacalcidol	Soft Gelatine Capsule (1mcg)	Sesame Oil (refined)
Panimun Bioral®	Cyclosporin	Soft Gelatine Capsule (25, 50, 100mg)	Ethanol, Propylene Glycol, Corn Oil Mono/Di/Tri-Glycerides, Macrogolglycerol hydroxystearate / Polyoxyl 40 Hydrogenated Caster Oil, Ethanol.
Pentasa®	Mesalazine	Extended Release Capsule (250, 500mg)	Acetylated Monoglyceride, Castor Oil
Prometrium®	Progesterone	Soft Gelatine Capsule (100, 200,300mg)	Peanut Oil, Glycerin, Lecithin.
Rapamune®	Sirolimus	Oral Solution (1mg/mL)	Polysorbate 80 (E433), Phosal 50 PG (Phosphatidylcholine, Propylene Glycol, Mono-and Diglycerides, Ethanol, Soya Fatty Acids and Ascorbyl Palmitate).
Rayaldee®	Calcifediol	Extended Release Capsule (0.03mg)	Mixture of Lipophilic Emusifier with a HLB <7 and an absorption enhancer, oily vehicle - mineral oil, liquid paraffins or squalene.
Restandol Testocaps®	Testosterone	Soft Gelatine Capsule (40mg)	Castor Oil and Propylene Glycol Monolaurate (E477)
Roaccutane®	Isotretinoin	Soft Gelatine Capsule (10, 20mg)	Beeswax, Soya-Bean Oil (refined), Soya-Bean Oil (hydrogenated). Soya-bean Oil (Partially Hydrogenated)
Rocaltrol®	Calcitriol	Soft Gelatine Capsule (0.25, 0.5mcg)	Fractionated Triglycerides of Coconut Oil
Sandimmune®	Ciclosporin	Oral Solution (100 mg/mL)	Alcohol dissolved in Olive Oil, Ph. Helv./Labrafil M 1944 CS (Polyoxyethylated Oleic Glycerides) Vehicle
Sandimmune®	Ciclosporin	Soft Gelatine Capsule (25, 50 and 100mg)	Corn Oil, Linoleoyl Macrogolglycerides, Glycerol, Ethanol.
Selbex®	Teprenone	Hard Gelatine Capsule (50mg)	Alpha-tocopherol, Macrogol 6000
Solufen®	Ibuprofen	Hard Gelatine Capsule (200mg)	Gelucire 44/14
Sustiva®	Efavirenz	Oral Solution (30mg/mL)	Medium Chain Triglycerides
Targretin®	Bexarotene	Soft Gelatine Capsule (75mg)	Polysorbate 20, PEG400
Thorens®	Cholecalcifer-ol	Oral Drops Solution (10000IU/mL, 25000IU/2.5mL)	Refined Olive Oil
Tirosint®	Levothyroxine	Soft Gelatine Capsule (0.025, 0.05, 0.075, 0.1, 0.125, 0.15, 0.112, 0.137, 0.088, 0.174, 0.200, 0.013mg)	Glycerin
Uvedose®	Cholecalcifer-ol	Oral Solution (100,000IU/2mL)	Glycolyzed Polyoxyethylenated Glycerides
Vesanoid®	Tretinoin	Soft Gelatine Capsule (10mg)	Beeswax, Hydrogenated Soybean Oil Flakes, Hydrogenated Vegetable Oils and Soybean Oil
Vyndaqel®	Tafamidis	Soft Gelatine Capsule (20mg)	Macrogol 400, Polysorbate 20, Butylated hydroxytoluene
Xtandi®	Enzalutamide	Soft Gelatine Capsule (40mg)	Caprylocaproyl Polyoxylglycerides.
Zantac®	Ranitidine	Soft gelatine capsule (150, 300mg)	Medium Chain Triglycerides, Gelucire 33/01

Trade Name	Drug	Dosage Form/Strength	Excipients*
Zemplar®	Paricalcitol	Soft Gelatine Capsule (1, 2mcg)	Medium Chain Triglycerides (fractionated from coconut oil or palm kernel oil), Alcohol
Zipsor®	Diclofenac Potassium	Soft Gelatine Capsule (25mg)	ProSorb (proprietary combination of Polyethylene Glycol 400, Glycerin, Sorbitol, Povidone, Polysorbate 80, and Hydrochloric Acid), Isopropyl Alcohol, and Mineral Oil
Zmax®	Azithromycin	Extended Release Oral Suspension (27mg/mL)	Glyceryl Behenate

Data obtained from FDA Drug Label (from Drugs @FDA database), European Summary of Pharmaceutical Characteristics (SPC), Health Products Regulatory Authority (HPRA) National Drug Authorisation SPC or Medicines and Healthcare Products Regulatory Agency (MHRA) SPC unless otherwise stated.*Excipients listed refer only to selected relevant excipients from the total excipients of the drug products which include both lipophilic and hydrophilic excipients types as classified by the lipid formulation classification system.

References:

1. Hauss DJ. Oral lipid-based formulations. Advanced Drug Delivery Reviews. 2007;59(7):667-76.