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Review Article

Evolution of Choice of Solubility and Dissolution Media After Two Decades of Biopharmaceutical Classification System

Nadia Bou-Chacra,[1] Katherine Jasmine Curo Melo,[1] Ivan Andrés Cordova Morales,[1] Erika S. Stippler,[2] Filippos Kesisoglou,[3] Mehran Yazdanian,[4] and Raimar Löbenberg[5,6]

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Abstract. The introduction of the biopharmaceutics drug classification system (Biopharmaceutics Classification System (BCS)), in 1995, provided a simple way to describe the biopharmaceutics behavior of a drug. Solubility and permeability are among the major parameters, which determine the fraction dose absorbed of a drug substance and consequently its chances to be bioavailable. The purpose of this review is to summarize the evolution of the media used for determining solubility and dissolution and how this can be used in modern drug development. Over the years, physiologically adapted media and buffers were introduced with the intention to better predict the *in vivo* solubility and dissolution of drug substances. Water, buffer solutions, compendial media, micellar solubilization media, and biorelevant media are reviewed. At this time point, there is no universal medium available which can be used to predict every drug substance's solubility or a drug product's *in vivo* dissolution behavior. However, there have been many improvements and additions made to media to optimize their *in vivo* predictability; for example, the current phosphate concentrations in buffers seem to be too high to correlate with the carbonate buffer concentrations *in vivo*. Biorelevant media were updated to correlate them better with the composition of human intestinal fluids. The BCS was introduced into regulatory sciences as a scientific risk management tool to waive bioequivalence studies under certain conditions. Today's different guidance documents define the dose-solubility ratio differently. As shown for amoxicillin, this can cause more confusion than certainty for globally operating companies. Harmonization of BCS guidelines is highly desirable.

KEY WORDS: BCS; dissolution; IVIVC; solubility.

INTRODUCTION

The introduction of the biopharmaceutics drug classification system Biopharmaceutics Classification System (BCS), in 1995, provided a simple way to describe the biopharmaceutics behavior of a drug. Solubility and permeability are among the major parameters, which determine the fraction dose absorbed of a drug substance and consequently its chances to be bioavailable. Solubility in this context is reported as aqueous solubility. Regulatory guidance classify Active Pharmaceutical Ingredients (API) according to their solubility in aqueous buffers. However, human physiology in the gastrointestinal tract is complex and can have a profound impact on the *in vivo* solubility of a drug substance. Physiologically adapted media and buffers were introduced over the past decades with the intention to better predict the *in vivo* solubility of drug substances. Similarly, dissolution methodologies were originally developed as quality control methods with limited or sometimes no *in vivo* relevance. However, today's regulatory agencies prefer to see more *in vivo* clinical relevant dissolution specifications and a discriminating dissolution method, which can detect changes in the drug product's critical quality attributes. Product development in a Quality by Design approach is impossible without utilizing the fundamental principles of the BCS with *in vivo* relevant measurements and predictions. This highlights the gap between regulatory classification based on the BCS and scientific mechanistic information based on the

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[1] Faculty of Pharmaceutical Sciences, University of Sao Paulo, Sao Paulo, Brazil.
[2] United States Pharmacopeial Convention, Rockville, MD, USA.
[3] Merck & Co., Inc., Kenilworth, NJ, USA.
[4] Teva Branded Pharmaceutical Products R&D, West Chester, PA, USA.
[5] Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, AB, Canada.
[6] To whom correspondence should be addressed. (e-mail: raimar@ualberta.ca)

principles of the BCS needed to predict *in vivo* behavior/*in vivo* dissolution of APIs.

The purpose of this review is to summarize the evolution of the media used for determining solubility and dissolution and how this can be used in modern drug development. The literature search for this review paper was originally undertaken in September 2014 using four databases: ISI Web of Science, SciFinder, Scopus, and Google Scholar. These databases were carefully selected to allow identification of reports, dissertations, and conference contributions in addition to original studies published in scientific journals. No date or language restriction was applied to the searches. Update searches were subsequently performed in July 2016. The keywords and controlled languages were as follows: BCS, biorelevant media, dissolution, fasted state, fed state, drug solubility, intrinsic dissolution, simulated intestinal fluid, simulated gastric fluid, buffered dissolution media, apparent solubility, and dissolution rate. The total number of studies in this review was 51. Some of these studies utilized both methods (shake flask and dissolution testing) whereas 46 described using the shake flask method only and 20 studies used dissolution testing.

Drug solubility data for each media and its composition in the studies were extracted and tabulated. The information regarding the composition of dissolution media was also extracted from the official guidelines: European Medicines Agency (EMA), Food and Drug Administration (FDA), Health Canada, Brazilian Health Surveillance Agency (ANVISA), World Health Organization (WHO), and Brazilian, European, and United States pharmacopeias.

SOLUBILITY IN AQUEOUS MEDIA

From the biopharmaceutics perspective, aqueous solubility is an important primary physicochemical property of a drug substance. Solubility is defined as the amount of drug substance that dissolves into a solvent to achieve a saturated solution at constant temperature and pressure. Solubility is expressed in terms of maximum volume or mass of the solute that dissolves in a given volume or mass of a solvent (1).

The shake-flask method proposed by Higuchi and Connors (2) is today widely used in the determination of a drug's solubility. It determines the thermodynamic solubility of a drug substance after reaching equilibrium. An excess amount of drug substance is added to a specific medium at a specific temperature. Depending on the solubilization rate and the type of agitation used, equilibrium can be achieved within hours or days. The drug substance and the saturated solution can be separated via filtration or centrifugation during equilibration phase (3).

The United States Pharmacopeia (USP) describes solubility in more general terms and defines it as the number of parts by volume of solvent required to dissolve one part by weight of a solid, or one part by volume of a liquid (4) as described in Supplemental material 1.

Aqueous solubility as described by USP is normally reported as reference solubility in water at room temperature. However, in majority of cases, the pH value and the composition of a medium are important and can impact a drug substance's solubility; for example, functional groups, which are pH dependent, can be ionized and have a major impact on solubility (5).

Thus, solubility measured in water might not be indicative of solubility in the gastrointestinal tract, particularly for drugs, which are lipophilic and sparingly soluble.

WATER

The reviewed publications showed that different grades of water were used as media to determine the solubility of drug substance: double-distilled water (6–8); double deionized water (9), Milli-Q® purified water (10), 18.2 MΩ.cm/0.22 μm (11); Milli-Q®ultrapure water, conductivity less than 0.1 μS cm (12,13); ultrapure water Elix® Millipore (14); distilled water (5,15–21) deionized water (22–26); distilled, deionized, and filtered water (27); purified water (28–36); demineralized water (37). The type of water was not specified in 19 of 51 studies (37%) (38–56).

If analytical grade water used in assays for quality control has no specific pharmacopeial monograph, it still has to meet the requirements of the USP purified water definition. The USP lists in its general chapter 1231 (4) the following non-monograph waters: distilled water, freshly distilled water, deionized water, freshly deionized water, deionized distilled water, filtered water, high-purity water, ammonia-free water, carbon dioxide-free water, ammonia- and carbon dioxide-free water, deaerated water, recently boiled water, oxygen-free water, water for BET, organic-free water, lead-free water, chloride-free water, and hot water. Each of these water types has specific properties that are needed for a specific assay. For example, water properties like deairing can change the dissolution rate of a drug product, although solubility is not impacted by it. This is used in the Performance Verification Test of the USP. If the dissolution medium is not sufficiently deaired, air bubbles can attach to powder and API particles of the used prednisone tablets. The powder particle will then float in the medium and less coning occurs under the paddle. This increases the dissolution rate and the test might fail to meet the dissolution specification.

BUFFER SOLUTIONS

This literature review found that phosphate buffer solutions, in the range of pH 5.8–8.0, were employed in 32.6% of cases as medium for the shake-flask method (15 of 46 studies) (8,11,19,31,32,37,41–43,45,46,48,51,57,58) and in 40.0% as dissolution medium (8 of 20 studies) (10,11,22,24,51–53,56). Acetate buffer was used less frequently, in 4 of 46 studies (8.7%) (41,42,45,49) as medium for the shake-flask method and in 2 of 20 studies (10.0%) as dissolution medium (52,56). Phosphate and acetate buffer solutions, which were claimed to have similar osmolality and ionic strength as the physiological fluids, were the most employed buffer solutions to determine solubility (27.3% for the phosphate buffer and 9.1% for the acetate buffer).

The salt solubility of a drug depends not only on the concentration of the drug substance but also on that of the counter-ion. Buffers can introduce counter-ions with which the drug might precipitate due to lower solubility of the complex. On the other hand, high concentrations of the counter-ion can decrease the solubility of the salt, due to salting out effects. For example, sparingly soluble basic drugs, which are positively charged, can precipitate as phosphate salts in neutral or basic solutions due to pH change as reported by Kambayashi for dipyridamole and ketoconazole (59). Bergström reported similar solubility changes for a set of 25 drugs and described that a large variation in solubility was observed throughout the pH range. The

substance-specific solubility was linked to the uncharged and completely charged drug species and the phosphate ion (60). Völgyi reports the salt solubility of diprenorphine hydrochloride, codeine hydrochloride and phosphate, and lidocaine hydrochloride and phosphate. In this study, chlorine ions besides phosphate ions caused solubility changes when the pH was adjusted with hydrochloric acid to lower the pH of the media (61).

Under such conditions, drugs, especially those with surface-active properties, can form micelles or self-associated aggregates in the form of dimers, trimers, or higher-order oligomers (62). Many non-steroidal anti-inflammatory drugs, such as indomethacin, diclofenac, ibuprofen, ketoprofen, and naproxen, tend to self-associate by forming mixed-charged micelles or micelle-like structures (63). In such systems, the solubility-pH profiles cannot be accurately described with the Henderson-Hasselbalch eq. (62). Avdeef showed after revaluation of published data from Higuchi 1953 (64) that dimers of drug molecules can cause deviations from the Henderson-Hasselbalch equation using the pDISOL-X program. This method is based on Volgyi's publication for the estimation of solubility, which is independed from the Henderson-Hasselbalch eq. (19).

In this report, only 1 of 43 studies selected used the modified Hank's balanced salt solution (10,48), a bicarbonate-based buffer (Table I), for the shake-flask method. Krebs buffer, also a bicarbonate-based buffer, was used to determine drug solubility of ibuprofen (48) and as dissolution media for coated mesalazine tablets (65). This buffer was employed for intestinal absorption studies and provided an environment close to the physiological pH range and osmotic pressure. The disadvantage of the Krebs buffer is its sensitivity to storage conditions. Continuous sparking with 5% CO_2 and adding a layer of liquid paraffin on the top of the solution and/or the use of a completely sealed setup can stabilize the buffer (65).

McIlvaine buffer solutions with a citrate/phosphate buffer system were used in the range of pH 4.0 to 6.8 (6.5%), or 3 out of 46 studies used it for the shake-flask method (5,27,48) and in 2 out of 20 studies as dissolution media (10.0%) (5,27). Maleate (32), Britton-Robinson universal (19,25,39), and glycine buffers (31) were selected, respectively, in the rate of 2.2% (1 out of 46 studies), 6.5% (3 out of 46 studies), and 2.2% (1 out of 46 studies), for the shake-flask method.

As is evident, there are plenty of different buffer choices for measuring solubility. Future research has to demonstrate if one of them can be used as the universal first-choice medium. Phosphate buffer, which is currently the most often-used medium, fails to be predictive for *in vivo* solubility of many poorly soluble drugs due to its lack in solubilization capacity (66,67).

USP COMPENDIAL MEDIA

According to the FDA (68), simulated gastric fluid (USP-SGF) containing pepsin and the corresponding medium SGF without enzyme (SGFblank) or simulated intestinal fluid containing pancreatin (USP-SIF) and the corresponding medium without enzyme (SIF-blank) better reflect the physiologic conditions of the stomach and the small intestine compared to other buffers. The composition of USP-SGF and USP-SIF are listed in Supplemental material 2 (4). Our review found that SGF was used with the shake-flask method in 17.4% cases (8 of 46 studies) (13,15,17,21,26,40,41,49) and in 10.0% (2 of 20 studies) (13,17) to perform dissolution tests; however, this medium is often prepared and used without enzyme.

Dressman *et al.* (69) described the use of a fasted state simulated gastric fluid, which contains sodium taurocholate and lecithin to better simulate the composition of human gastric fluid.

Table I. Composition of Phosphate Buffer (PB) and Hank's (Bicarbonate Buffer Modified) Used in the Solubility Test

	PB Ph. Int. 3°	PB Ph. Eur. 8.0	PB Ph. Braz. 5°	PB USP 38	Hank's buffer
KH_2PO_4 (g)	34.00	1.36	–	1.36	0.06
NaOH (g)	–	0.18	–	0.18	–
Na_2HPO_4 (g)	35.30	–	28.8	–	–
K_3PO_4 (g)	–	–	11.45	–	–
$Na_2HPO_4{\cdot}12H_2O$ (g)	–	–	–	–	0.12
NaCl (g)	–	–	–	–	7.94
KCl (g)	–	–	–	–	0.40
D-glucose (g)	–	–	–	–	0.91
$MgSO_4{\cdot}7H_2O$ (g)	–	–	–	–	0.20
$NaHCO_3$ (g)	–	–	–	–	0.35
$CaCl_2{\cdot}2H_2O$ (g)	–	–	–	–	0.18
Deionized water (L)	10.00	0.20	1.00	0.20	1.00
Properties					
pH	6.80	–	–	6.80	6.80
Osmolality (mOsmol/kg)	–	–	–	115.00	–
Buffer capacity (mmol/L/pH)	–	–	–	18.60 ± 0.10	3.10 ± 0.20
Ionic strength (mol/L)	–	–	–	0.08	–

PB phosphate buffer, *Ph. Int.* Pharmacopeia International, *Ph. Eur.* European Pharmacopeia, *Ph. Braz* Brazilian Pharmacopeia, *USP* United States Pharmacopeia

Such media are generally referred to as biorelevant media and will be discussed later under the intestinal segments of the GI tract.

In the case of USP-SIF, the pH value was changed from originally pH 7.5 to pH 6.8 in USP 25 (70). If pH values exceeding 7.5 are used, scientific justification should be provided, since this is considered outside the physiologically relevant pH range (9). However, there are USP monographs for which the pH value is 8.0 and even higher (71). For dichlorphenamide, chlorothiazide, ethacrynic, methyldopa and chlorotiazide, reserpine and chlorothiazide, and ursodiol tablets, the dissolution medium is 8.0; for oxymetholone and glyburite (micronized) tablets, the pH of the dissolution medium is 8.5; for nalidixic acid tablets, pH 8.6; for glyburide (non-micronized) tablets, pH 9.5; and for sodium liothyronine tablets, pH 10 (71). SIF-blank was used in 8.7% of the cases (or 4 out of 46) studies (15,17,26,49) for shake flask and in 10.0% (2 out of 20 studies) (17,24) as dissolution medium.

Comparing SIF-blank and standard pH 6.8 phosphate buffer, e.g., International Pharmacopeia (72) (Tables II and III), shows that there can be differences in the raw materials used to make them. However, as shown by Stippler *et al.*, these buffers have similar properties including osmolality, ionic strength, and buffer capacity (72). In the same study, the media were considered interchangeable in the dissolution testing of ibuprofen, metronidazole, and indomethacin immediate-release solid oral dosage form. The study concluded that "only in specific cases where solubility is known to be affected by the cation does one need to be wary about substitution of the two cations for each other." This is in line with results reported by Almukainzi *et al.* (73). Here, the use of sodium and potassium buffers and SIF resulted in different disintegration times of cellulose-based hard shell capsules, which can result in different dissolution behaviors *in vitro*. In addition, Ropers *et al.* (74) reported the effect of Na+ and K+ counter-ions on the micelle formation of anionic surfactants like decyl and dodecyl sulfates. A decrease of the counter-ion binding in the order of Na+ > K+ was reported. Thus, the use of sodium buffer instead of a potassium buffer might avoid precipitation of the surfactant due to counter-ion interaction.

The present report shows that pH 6.8 phosphate buffer was the most commonly used medium (35.0%) in dissolution studies. Aqueous buffer solutions and the compendial media mimic typical pH conditions, ionic strength, and osmolality conditions in the stomach or small intestine. Thus, they do not represent all aspects of physiological conditions in the gastrointestinal (GI) tract (e.g., viscosity, surface tension) (75) and usually offer, at best, empirical *a posteriori* correlations with *in vivo* data (76). Also, the phosphate buffer failed to adequately discriminate and distinguish between products of torasemide, a class I drug according to the BCS, in a biowaiver approach. In this case, a medium at pH 5.0 discriminated better among these products and was superior to the FDA-recommended medium (75).

Recently, Krieg *et al.* (77) compared carbonate and phosphate buffers. Their results are detailed discussed under bicarbonate buffers. However, they point out that buffer concentrations are important factors when it comes to *in vivo* relevance. Additionally, the above-listed media cannot simulate the influence of food ingestion on drug release. Therefore, the development of adequate test media and methods for both, fasted and fed states, that mimic certain physiological conditions was obvious.

MICELLAR SOLUBILIZATION OF DRUGS

Micellar systems can enhance solubility of poorly soluble drug substances and increase their bioavailability (78). Zangenberg *et al.* (79) developed a dynamic lipolysis model, where the rate of the hydrolysis of triglycerides was controlled by the addition of Ca^{2+} ions. This model simulates postprandial *in vivo* conditions during the digestion and absorption of lipid-based formulations. They

Table II. Composition of Simulated Intestinal Fluid in Fasted and Fed State

Compound	FaSSIF	FaSSIF-V2	FeSSIF	FeSSIF Early	FeSSIF Middle	FeSSIF Late	FeSSIF-V2
Bile salt (taurocholate) (mM)	3.00	3.00	15.00	10.00	7.50	4.50	10.00
Phospholipid (lecithin) (mM)	0.75	0.20	3.75	3.00	2.00	0.50	2.00
Sodium dihydrogen phosphate (mM)	28.65	–	–	–	–	–	–
Acetic acid (mM)	–	–	144.00	–	–	–	–
Sodium chloride (mM)	105.85	–	173.00	145.20	122.80	51.00	125.50
Maleic acid (mM)	–	–	–	28.60	44 50	8.09	55.02
Sodium hydroxide (mM)	–	–	101.00	52.50	65.30	72.00	81.65
Glyceryl monooleate (mM)	–	–	–	6.50	5,00	1.00	5.00
Sodium oleate (mM)	–	–	–	40.00	30.00	0.80	0.80
Properties							
pH	6.5	6.5	5	6.5	5.8	5.4	5.8
Osmolality (mOsmol/kg)	270.00	180.00	635.00	400.00	390.00	240.00	390.00 ± 10
Buffer capacity (mEq/pH/L)	10.00	10.00	76.00	25.00	25.00	15.00	25.00

FaSSIF fasted state simulated intestinal fluid, *FaSSIF-V2* fasted state simulated intestinal fluid version two, *FeSSIF* fed state simulated intestinal fluid, *FeSSIF-V2* fed state simulated intestinal fluid version two

Table III. Comparison Performance of Biorevelant Media and Aqueous Buffers in Drug Solubility

Solubility (mg/mL)	Buffer	SGF	Relative Increase	Buffer	FeSSIF	Relative Increase	Buffer	FaSSIF	Relative Increase
Compound	pH 1.2			pH 5.0			pH 6.5		
Indomethacin	0.001	0.02	20.00	0.01	0.07	7.00	0.14	0.23	1.60
Sulindac	0.007	0.03	4.60	0.35	0.40	1.10	0.53	0.77	1.50
Ibuprofen	0.06	0.20	3.30	0.14	0.65	4.60	0.93	1.46	1.60
Napoxen	0.005	0.10	20.00	0.09	0.20	2.20	0.77	1.21	1.60

SGF simulated gastric fluid, *FeSSIF* fed state simulated intestinal fluid, *FaSSIF* fasted state simulated intestinal fluid

observed different dissolution profiles during lipolysis of probucol and danazol and linked this to their lipophilicity. Probucol has a log *P* value of over 10 and danazol, a value of 4.5 (79). The aqueous solubility of probucol depended on the partition of the drug between the lipophilic phase and the aqueous phase. The dissolution of danazol was found to be dependent on the solubilization capacity of the aqueous medium. This model was proposed as a method to investigate drug dissolution from formulations during lipolysis, simulating the fed state.

In a recent study, Ottaviani *et al.* (80) investigated the relationship between surfactants and their CMC (critical micellar concentration) on solubility enhancement of drug substances. The work shows that CMC is a better predictor in FaSSIF (fasted state simulated intestinal fluid) than lipophilicity (logD).

A study by Kaukonen *et al.* (81) compared the solubility of danazol and four other model drug substances between blank buffer solutions and micelles made from different triglyceride lipids. They investigated the impact of a digestion enzyme on the solubilization of poorly water-soluble drug substances (danazol, griseofulvin, diazepam, cinnarizine, and halofantrine). Data listed in Supplemental material 3 shows that mixed micelles composed of mono-, di-, and triglycerides, which form *in situ*, when the triglycerides are hydrolyzed, have a higher solubilization capacity compared to pure micelles or buffer only. The increases reported are ten times higher for griseofulvin, 17 for diazepam, 178 for danazol, 1600 for cinnarizine, and a staggering 10,720 for halofantrine.

This kind of digestion buffer system can be used to simulate lipid interactions with the intestinal environment on the solubility of a drug. However, such systems still do not give a complete picture of the factors impacting solubilization in the intestine.

BIORELEVANT MEDIA

In the last decade, biorelevant media have been extensively used to determine drug solubility and as dissolution media, especially for BCS class II compounds (14 studies or 25.0%) (8,9,13,22,27,33,35,42,44,45,47,51,54,55) as well as for BCS class I (4 studies or 7.1%) (33,34,49,51), class III (2 or 3.6%) (33,51), and class IV (2 or 3.6%) (33,51). As mentioned, biorelevant media contain generally components which are likely present in the human GI tract such as bile salts and lecithin aiming to mimic the physiological conditions in specific segments of the GI tract; thus, in these media, pH, osmolality, and surface tension are adapted to physiological values (75).

A precursor of biorelevant media was investigated by Macheras, Koupparis, and Tsaprounis in 1986 (82); Macheras, Koupparis, and Antimisiaris in 1988 (83); Macheras, Koupparis, and Antimisiaris in 1989 (84); Macheras, Koupparis, and Apostolelli in 1987 (85); and Macheras, Koupparis, and Antimisiaris in 1990 (86). They evaluated the dissolution profiles of drug products using milk. Macheras, Koupparis, and Tsaprounis in 1986 investigated drugs were nitrofurantoin, piroxicam, indomethacin, prednisolone, diazepam, dicumarol, and griseofulvin. The use of this medium aimed to simulate the conditions of the fed state. The first generation of biorelevant media FaSSIF and FeSSIF (fed state simulated intestinal) was published by Galia *et al.* (87). These authors, similarly to Macheras, Koupparis, and Tsaprounis, evaluated the dissolution profiles of acetaminophen in milk corroborating the findings previously published. The biorevelant media FaSSIF and FeSSIF were updated later on and are now known as FaSSIF-V2 and FeSSIF-V2. The main difference between FaSSIF and FaSSIF-V2 is the reduced amount of lecithin in FaSSIF-V2 as compared with FaSSIF (88). The difference between FeSSIF and FeSSIF-V2 is that the second-generation medium includes two digestion components: glyceryl monooleate and sodium oleate. Both are known to enhance the solubility and dissolution of poorly water-soluble drugs. Table II shows the composition of the different versions of FaSSIF and FeSSIF (87).

Ionization and lipophilicity play an important role in solubilization of drugs in FaSSIF-V2, compared to aqueous buffer solutions. The solubility of the strong basic drug substances showed an enhanced solubility in FaSSIF-V2 probably due to favorable electrostatic interactions with the negatively charged media. For the ionized acid drug substances, the solubility was not improved using FaSSIF-V2 compared to aqueous buffer solutions (32).

The solubility of representative acid and basic and neutral compounds, respectively mefenamic acid, ketoconazole and paracetamol, and metoprolol and danazol, was measured using FaSSIF or FaSSIF-V2. FaSSIF-V2 provided lower drug solubility values than FaSSIF for basic and neutral drugs. For acid drugs, which are ionized in the intestine, pH plays a more important role. The use of both fasted state media, FaSSIF and FaSSIF-V2, provides a wider range to test a drug's solubility. The results of a commercially available FaSSIF-V2 were equivalent to those for FaSSIF-V2 prepared using methylene chloride as described in the literature (88).

Several studies have shown that drug solubility in these biorelevant media is increased compared to the solubility determined in aqueous buffer solutions (Table III), as a result of enhanced wetting and/or micellar solubilization of poorly soluble drug substances (26,32,55,89–91). Yazdanian and collaborators (2004) investigated NSAID (non-steroidal anti-inflammatory drug) in a study and showed an increased drug solubility when FeSSIF and FaSSIF instead of buffers 0.1 N HCl (pH 1.2), 0.02 M citric acid (pH 5.0) and 0.02 M Na_2HPO_4, and 0.02 M NaH_2PO4 (pH 7.4) were used (90). Rinaki *et al.* developed a dynamic GI absorption model and showed that such solubility data generated in biorelevant media can be used as guidance for the formulation scientist in the development phase (92).

Studies from Wei and Löbenberg (55) and Okumu *et al.* (89) showed that the purity of the used lecithin and bile salts impact the solubility of drugs like glyburide (Supplemental material 4) and montelukast sodium (Supplemental material 5) (55,89). Glyburide has a higher solubility when the purity of the lecithin and bile salts is low while montelukast sodium has a higher solubility when more than 95% pure lecithin and sodium taurocholate was used.

Recently, the composition and physicochemical properties of biorelevant media and human intestinal fluids (HIF) were reviewed by Fuchs and Dressman (2014) (93). The report indicated that the type of phospholipids and bile salts used to compose a biorelevant medium must be considered. The authors proposed that a free fatty acid as a lipolysis product of lecithin should be added. The addition of low concentrations of cholesterol would also be appropriate.

An example of such media was published by Khoshakhlagh *et al.* (94). They conclude that the addition of cholesterol to FaSSIF results in a physiologically adapted model fluid FaSSIF-C, which increases the solubility of poorly soluble drugs. The composition of FaSSIF-C can further be adapted and differentiated to gender-specific compositions.

Today, there are a number of different biorelevant media available representing different segments of the GI tract. They range from the stomach to the colon.

Fasted and fed state simulated gastric fluids were introduced as biorelevant media to simulate the dissolution behavior of drugs, which should be taken with or without food and dissolve in the stomach. The composition of these media is presented in Table IV (95).

Fotaki *et al.* (96) and Chen *et al.* (97) published studies using simulated colonic fluid (SCoF) (Table V). The difference is the buffer system. SCoF1 has a phosphate buffer while SCoF2 has an acetic acid buffer.

In a recent study, the solubility of 17 model drugs (Supplemental material 6) was compared between simulated biorelevant media and real human intestinal fluids. The study compared fasted HIF, fed human intestinal fluid (HIF fed) with blank FaSSIF and FeSSIF, and FaSSIF and FeSSIF, respectively (33). FaSSIF and FeSSIF were prepared with crude (low-quality) taurocholate. The comparison shows that the simulated media can be considered biorelevant for intestinal solubility estimation and gives a better estimate compared to the simple buffers when poorly soluble drugs are evaluated. They also tested different concentrations of d-α-tocopheryl polyethylene glycol 1000 succinate (TPGS) in phosphate buffer. The correlation was not as good as for FaSSIF and FeSSIF (33).

In the present literature review, biorelevant media were used in 12 studies of 56 (21.4%). The biorelevant media selected were as follows: FaSSIF (21,29,30,33,36,40,44,48,54,57); FeSSIF (21,29,33,40,48,54); fasted HIF and fed HIF (33); LQ-FaSSIF (55); and FaSSIF-V2 (32).

Other studies used media containing milk with different fat contents, protein, carbohydrates, and amino acids to mimic a digested meal and added bile components to enhance the solubility of itraconazole compared to simulated gastric fluid (26).

Table IV. Simulated Gastric Fluids in Fasted and Fed State

Composition	FaSSGF	FeSSGF			SGF
		Early	Middle	Late	
Lecithin (μM)	20				
Sodium taurocholate (μM)	80				
Pepsin (mg/mL)	0.1				
Sodium chloride (mM)	34.2	148	237.02	122.6	3.2
Acetic acid (mM)			17.12		50
Sodium acetate (mM)			29.75		
Orthophosphoric acid (mM)				5.5	
Sodium dihydrogen phosphate (mM)				32	
Milk/buffer		1:0	1:1	1:3	
Hydrochloric acid (mL)					7
Hydrochloric acid/sodium hydroxide q.s.	pH 1.6	pH 6.4	pH 5.0	pH 3.0	
Properties					
Buffer capacity (mmol/L/ΔpH)		21.33	25	25	
pH	1.6	6.4	5	3	1.2
Surface tension (mN/m)	42.6				33.7
Osmolality (mOsm/kg)	120.7	559	400	300	180

FaSSGF fasted state simulated gastric fluid, *FeSSGF* fed state simulated gastric fluid, *SGF* simulated gastric fluid

Table V. Composition of Simulated Colonic Fluid 1 (SCoF1) and Simulated Colonic Fluid 2 (SCoF2)

Composition	SCoF1	SCoF2
Potassium chloride (g)	0.20	–
Sodium chloride (g)	8.00	–
Potassium phosphate monobasic (g)	0.24	–
Sodium phosphate dibasic (g)	1.44	–
Acetic acid (g)	–	10.20
Sodium hydroxide (g)	–	6.20
Deionized water to (L)	1.00	1.00
Properties		
pH	7	5.8
Osmolality (mOsmol/kg)	–	295
Buffer capacity (mEq/L/pH)	–	29.1
Ionic strength	–	0.16

SCoF1 simulated colonic fluid 1, *SCoF2* simulated colonic fluid 2

As seen, different biorelevant media are available to assess drug solubility in different segments of the GI tract. However, they are still variable in their purity and batch-to-batch consistency. High-purity grades of bile salts are expensive. Additionally, they pose an analytical challenge due to their complex composition and require time-consuming and complicated procedures (98). However, at this time point, biorelevant media as described above seem to be the best starting point to estimate *in vivo* solubility and estimate *in vivo* dissolution behavior of poorly soluble drugs.

DRUG DISSOLUTION

In 1897, Noyes and Whitney found that "the rate at which a solid substance dissolves in its own solution is proportional to the difference between the concentration of that solution and the concentration of the saturated solution" (99). Today, dissolution testing is used in pharmaceutical performance testing to determine the rate and extent of drug release from a dosage from, e.g., a tablet. Therefore, the choice of the experimental medium composition has to be based on scientific knowledge and experience (100). In this review, we focus on media evolution in dissolution testing.

WATER

When purified water is selected as a dissolution medium and not used as a solvent to determine a drug's solubility, it might have to be treated to reduce the dissolved air by suitable means, according to the USP Chapter 711 (101). Deaerated water is mentioned in USP chapter 1092 (102); the suggested methods for deaerating include warming the dissolution media to 41 °C, followed by vacuum filtration through a 0.45-μm pore-size-rated membrane, and vigorously stirring the filtrate while maintaining vacuum. This review showed that 6 of 20 studies (9,14,16,22,23,34) used water as dissolution medium. Only one study mentioned the degassing procedure (14).

Pure water as dissolution medium has some drawbacks. For example, its characteristics can change during the test due to the influence of the active ingredients or excipients. In addition, water might not provide sink conditions for poorly soluble drugs. Sink conditions are defined as at least three times the volume necessary to obtain a saturated solution of the tested drug dose (103). In the pharmaceutical industry, dissolution testing was historically used as a quality control method for batch release and as a development tool to assess different formulations (104).

BICARBONATE BUFFER

Lately, the use of bicarbonate buffer gained interest due to their similarity with the physiological buffer systems. The use of pH 6.8 physiological bicarbonate buffer, derived and modified from Hank's balanced salt solution, allowed the differentiation between enteric coatings of tablets. Compared to the *in vitro* release in compendia phosphate buffers, which was rapid, the carbonate buffers differentiated significant differences in drug release between different coating materials, which correlated with disintegration results (105).

Varum *et al*. (106) introduced a bicarbonate buffer, which is based on Hanks' balanced salt solution. The pH 5.6 buffer was highly unstable and had to be maintained by an Auto pH™ System. The purpose of this buffer was to mimic the conditions of the proximal small intestine. The study showed that dissolution behavior of different coated formulations could be predicated *in vitro* using this buffer but not when phosphate buffer was used (Supplemental material 7).

Similarly, the dissolution behavior of mesalazine enteric-coated tablet has shown that the use of bicarbonate buffer provides improved predictive power compared to compendial phosphate buffers (107). However, Boni *et al.* (108) emphasized that the bicarbonate buffer has to be freshly prepared to produce reproducible dissolution profiles. The improved *in vivo* relationship of bicarbonate buffers seems to be due to a complex and dynamic interplay between the concentration of hydrogen carbonate, carbonic acid, and the amount of dissolved and solvated carbon dioxide, as well as the ambient partial pressure of carbon dioxide. These features allow simulating dynamic intraluminal pH changes in the physiological range. This can be achieved in a single experiment without the need to alter the ionic strength of the solution by using an automated system (109).

As mentioned before, Krieg *et al*. (77) compared carbonate and phosphate buffers and its correlation of *in vitro* dissolution of weak acids and bases. The study concluded: "It appears that low phosphate buffer concentrations (1–25 mM) are often more physiologically relevant and may better simulate the impact of bicarbonate buffer on the dissolution of weak acid drugs. For weak base drugs, extremely low phosphate buffer concentrations (<2 mM) would be needed to match physiologically relevant bicarbonate buffer." They point out that the currently used phosphate buffers have too high salt concentrations and do not correlate to the *in vivo* present carbonate buffer strengths. The authors recommend following the low buffer concentrations to gain better understanding of the impact of phosphate buffer strength on dissolution.

BIORELEVANT MEDIA

Biorelevant media are not only used to determine the solubility of a drug but are also used to perform dissolution tests. However, their analytical properties, price, and

variability in composition exclude them from being used as routine quality control media. Several studies have shown that a dissolution test using biorelevant media for poorly soluble drugs seems to be able to mimic the *in vivo* dissolution better compared to other media (55,85,110–112). If the *in vitro* dissolution matches the *in vivo* dissolution then computer simulations might use the dissolution profiles as input function into pharmacokinetic models. This allows establishing *in vitro*/*in vivo* correlations (IVIVC). Examples for IVIVCs using dynamic dissolution conditions and biorelevant media combined with software applications were published by Jantratid *et al.* (110). They identified a food effect for diclofenac sodium MR pellets using FaSSIF and FeSSIF. In addition, the correlation between fraction dose absorbed *vs*. fraction dose dissolved was superior if a dynamic dissolution flow-through model was used.

Wei and Löbenberg (55) showed that dynamic pH changes in biorelevant dissolution media impact the dissolution behavior of glyburide tablets and reported similar results when dissolution data were used as input function into simulation software. The dissolution data could predict *in vivo* observed clinical data using GastroPlus™, a software which uses the Advanced Compartmental Absorption and Transit model. Sunesen *et al.* (111) investigated the behavior of danazol under fasted and fed conditions, using biorelevant media. The authors found that by using a flow-through dissolution method, it was possible to achieve an IVIVC under these conditions. Okumo *et al.* (89) showed that a dynamic pH change of the dissolution media generated a release profile for montelukast sodium tablets which was able to predict the observed pharmacokinetics when used as input function into GastroPlus software. Fang *et al.* (113) fine-tuned the dynamic dissolution protocol and applied it to food effect studies and as a screening tool in early drug development.

However, FaSSIF and FeSSIF are not always predictive. For example, the absorption and *in vivo* behavior of griseofulvin were not revealed by these media (54). In this case, MREVID 2 (medium reflecting *in vivo* dissolution) was proposed as a new *in vitro* dissolution medium to mimic the *in vivo* dissolution behavior of poorly water-soluble drugs better. The proposed media contains 7.5 times more sodium taurocholate and phosphatidylcholine compared to FaSSIF. The maximum drug concentration of griseofulvin was 9.15 μg/mL in FaSSIF and 3.8 times higher using MREVID 2 (35.42 μg/mL) (54).

SURFACTANTS

Today, regulatory agencies like the FDA 2015 (114) request that product specifications focus on clinical relevance and this might include dissolution specifications. However, biorelevant media are not practical in routine quality control due to their properties and therefore other surfactants have to be considered instead. The choice and type of surfactant are in most cases based solely on the fact that they will facilitate drug dissolution and might increases *in vivo* predictability.

The physicochemical characteristics of a surfactant, ionic strength of the medium, and nature of the buffer system depend on the type of drug under investigation such as in the case of mefenamic acid. The solubility of this drug is affected by a change in ionic strength when sodium lauryl sulfate (SLS) is used. Differently, cetyltrimethylammonium bromide (CTAB) did not show the same effect. In general, CTAB, SLS, and polysorbate 80 are common choices for cationic, anionic, and non-ionic surfactants (Table VI) (115).

Crison *et al.* (116) described an experiment where dissolution rate and solubility of piroxicam (PX) were estimated by a simple additive model for the effect of pH and surfactant SLS 0.5, 1.0, and 2.0 (*w*/*v*%). The dissolution rate was directly proportional to the diffusivity of the drug-loaded micelle, and any change in the formation of the micelle impacted the dissolution process. The total drug solubility was determined by a sum of the values for the individual species, which were PX, PX−, and [PX] micelle. The proposed model was able to predict the dissolution and the solubility of ionizable water-insoluble drug as functions of pH and surfactant concentration (5). Moreover, the purity of the surfactant also must be investigated due to its significant influence in the size and loading capacity of micelles, which results in changes in solubility and dissolution rate (117).

As seen, the purity of a surfactant is an important quality attribute to obtain reproducible results. Polysorbate 80 typically has a structure that contains approximately 20 groups of polyoxyethylene (POE) per molecule. However, its synthesis process yields not only the desired monoesters but also some by-products. The analysis of polysorbate 80 using reverse-phase-HPLC and mass spectrometry revealed a complex mixture of polymeric species containing POE groups. The surfactant contained not only polyoxyethylene sorbitan monooleate (PSM) but also a number of POE intermediates such as polyoxyethylene sorbitan (PS), polyoxyethylene sorbitan dioleates (PSD), polyxoyethylene sorbitan trioleates (PStri), and polyoxyethylene sorbitan tetraoleates (PSTetra) (118). Furthermore, the fatty acid composition is approximately 70% oleic acid with several other fatty acids, which is not always the same. Therefore, other surfactants with higher purity and better-controlled composition should be considered for dissolution testing.

Polyoxyethyleneglycol dodecyl ether, commercially known as Brij 35, was used in some studies as surfactant for dissolution testing (95). The hydrophobic segment of this surfactant is of similar size and structure as the one of polysorbate, but Brij 35 has an unbranched hydrophilic PEO chain and has a single long-chain fatty acid. By choosing the number of (OE) group *vs*. the length of the hydrocarbon

Table VI. Commonly Used Surfactants for Dissolution Testing

Surfactant type	Anionic surfactants	Neutral surfactants	Cationic surfactants
Commonly used surfactants	Sodium lauryl sulfate, sodium deoxycholate	Polysorbate 20, Polysorbate 80, X-100, Myri-52; Brij-35	Cetyl trimethylammonium bromide (CTAB), cetylpyridinium chloride (CPC)

chain, the analyst can find the right property of the surfactant to be used in dissolution method development. This might overcome variability observed with polysorbate-based surfactants (119).

In predictive dissolution testing, the micelles composed of surfactant molecules mimics the bile acid aggregates in the small intestine; the surfactant facilitates the diffusion and transport of the free solute into the bulk medium. Since dissolution is a combined effect of solubility and diffusivity, the micelle size will have an effect on the dissolution rate of molecules when different surfactants are used (120).

REGULATORY VIEW OF BIOPHARMACEUTICS DRUG CLASSIFICATION SYSTEM AND SOLUBILITY

The Biopharmaceutics Drug Classification System (BCS) determines solubility of a certain drug dose within the pH range of the gastrointestinal tract in up to 250 mL medium. The 250 mL refer to the volume of water, which is taken with the dosage form when administered orally (121).

The BCS assumes that a drug is highly soluble if a certain dose is soluble in 250 mL or less in an aqueous medium within the physiological pH range. The drug substance will then dissolve instantly after administration (122,123).

However, different FDA guidance documents use different pH ranges to determine the solubility of drug substances: e.g., the biowaiver guideline from 2000 determines the solubility of the highest dose strength in 250 mL or less of aqueous media, over the pH range of 1–7.5 at 37 ± 1°C (124), while the CEDER guide from 1997 uses pH 1.0–8.0 (69), an FDA's draft guidance from 2015 on "Dissolution Testing and Specification Criteria for Immediate-Release Solid Oral Dosage Forms Containing Biopharmaceutics Classification System Class 1 and 3 Drugs" uses pH 1 to 6.8 (113).

Other global guidance documents such as Brazilian Health Surveillance Agency (ANVISA) and Health Canada guidance use the pH range of pH 1.2 to 6.8 (125,126). This pH range was accepted over the years as the most appropriate pH range best reflecting the *in vivo* conditions of the gastrointestinal tract. Today's different guidance documents use the 250 mL medium, but unfortunately define the dose tested differently.

The 2000 FDA guidance (124) and the 2015 draft guidance (127) measure the solubility of the highest (dose) strength in 250 mL of aqueous medium (67,111,119,120). In contrast, the EMA guidance documents (128), WHO Technical Report (2015) (129), and Health Canada (126) require determining the solubility of the highest single dose administered, which in certain cases can be two or more units in 250 mL (115). This shifts many drugs into the "poorly soluble" classification category.

Sediq *et al.* (130) evaluated the impact on the BCS classification related with dose-solubility ratio (D/S) (expressed in volume mL) of 27 drugs using the new dose definition. A reclassification of some drugs, where a biowaiver monograph was published prior to 2015 by the International Pharmaceutical Federation (FIP), was necessary. The FIP compendium currently contains over 40 monographs (131). The criterion change did not alter the BCS classification, as well as the recommendation of biowaivers, for 22 drug substances. However, for drugs such as acetazolamide, metoclopramide hydrochloride, verapamil hydrochloride, prednisolone, and prednisone, the highest single doses administered were as follows: 500 mg (D/S = 406 mL), 20 mg (D/S = 472 mL), 240 mg (D/S = 500 mL), 100 mg (D/S = 412 mL), and 100 mg (D/S = 752 mL), respectively. The needed volume to dissolve the dose is above 250 mL. These results modify the biopharmaceutical classification of these drug substances and their eligibility for a biowaiver. The authors concluded that a case-by-case review is required for drug substances close to the solubility limit (250 mL). The use of the EMA criterion may alter the classification of a class I drug to class II and for a class III drug to class IV, rendering them ineligible for the biowaiver procedure (130). Bioequivalence studies normally do not compare the highest administered dose but the highest dose strength.

Thus, Daousani and Macheras (132) suggest the suppression of the "highest single oral dose recommended for administration" concept in the EMA's "Summary of Product Characteristics" (133). Because dissolution kinetics are dose dependent, the dissolution requirement (% dissolved at a specified time) may differ from the dose concepts used by FDA and EMA (132). These authors consider that it is scientifically acceptable to perform the dissolution tests based on the dose used in the actual practice to guide dose selection criteria for bioequivalence studies.

The 2015 changed WHO criterion (134) considers a "highly soluble drug" when the highest single therapeutic dose as determined by the relevant regulatory authority is soluble in 250 mL or less of aqueous media, over the pH range of 1.2–6.8, at 37 ± 1°C. According to this new report, the drug substance accepted for a biowaiver procedure has to be evaluated using an *in vivo* equivalence study, at the highest marketed strength.

On the other side, Yazdanian *et al.* (90) argued that the solubility criteria used by FDA for weak acids are too stringent because acids do not dissolve well in the stomach but will be highly soluble in the intestine, which is the site of drug absorption. According to their study, 15 out of the 18 tested acidic NSAIDs have to be classified as class II compounds when the solubility criteria of pH 1.2 to 7.4 are applied. However, 15 drugs could be classified as a class I drug based on the pH 7.4 solubility alone. The authors suggest that a pH solubility range between 5.0–7.4 should be applied to acetic compounds, when they are classified according to the BCS (90). The rationale of this study was integrated in the 2006 WHO biowaiver guideline (129), which allowed biowaivers for weak acids. Unfortunately, this was removed in the 2015 guideline (134).

The solubility criterion is one of two parameters to classify drug substances according to the BCS. Today, amoxicillin is a BCS class I drug substance according to the WHO list of essential drugs (135,136). EMA classifies it as BCS class II drug substance due to the highest dose criterion and FDA as BCS class IV drug substance due to differences in the permeability criterion.

Overall, the BCS is a scientific approach to oral bioavailability and was introduced into regulatory sciences as a scientific risk management tool to waive bioequivalence studies under certain conditions as first done by the FDA SUPAC guideline (137). It is unfortunate that since then different guidelines have introduced slightly different

definitions. As shown for amoxicillin, this causes more confusion than certainty for globally operating companies.

As seen, there is room for harmonization between the different guidance documents to have the same BCS class assigned for a drug substance globally, since solubility does not change just because it was determined in different countries.

FINAL CONSIDERATIONS

Herein was presented the evolution of media and buffers in the determination of a drug substance's solubility and promising trends in developing predictive dissolution media. The type of surfactant used as a potential alternative to biorelevant media has to be carefully considered. At this time point, there is no universal medium available which can be used to predict every drug substance's solubility or a drug product's *in vivo* dissolution behavior. However, there have been many improvements and additions made to dissolution media to optimize their *in vivo* predictability. The right choice of a dissolution media to predict clinical relevant dosage form attributes is still done on a case-by-case basis. Also, the dissolution apparatus has a huge impact on the shape of the dissolution profiles; however, this was not part of this review. While establishing an IVIVC for every drug molecule sounded impossible some years ago, all current developments in media composition, dissolution apparatus design, and computer simulations suggest that it might be possible in the future. Examples of how such integrated software-guided approaches can look like have been published in the past (55,85,110,138). However, precise mechanistic understanding of the dissolution processes *in vitro* and *in vivo* is imperative to set clinical relevant dissolution specifications and to link *in vitro* dissolution to clinical outcomes.

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