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Review article

Simulated, biorelevant, clinically relevant or physiologically relevant dissolution media: The hidden role of bicarbonate buffer

Daniela Amaral Silva[a], Jozef Al-Gousous[b], Neal M. Davies[a], Nadia Bou Chacra[c], Gregory K. Webster[d], Elke Lipka[e], Gordon Amidon[b], Raimar Löbenberg[a,*]

[a] Faculty of Pharmacy & Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada
[b] College of Pharmacy, University of Michigan, Ann Arbor, MI, United States
[c] Faculty of Pharmaceutical Sciences, University of Sao Paulo, Sao Paulo, SP, Brazil
[d] Research and Development, AbbVie Inc., North Chicago, IL, United States
[e] TSRL, Ann Arbor, MI, United States

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ABSTRACT

In-vitro dissolution testing of pharmaceutical formulations has been used as a quality control test for many years. At early drug product development, in vivo predictive dissolution testing can be used for guidance in the rational selection of candidate formulations that best fit the desired in vivo dissolution characteristics. At present, the most widely applied dissolution media are phosphate-based buffers and, in some cases, the result of dissolution tests performed in such media have demonstrated reasonable/acceptable IVIVCs. However, the presence of phosphates in human GI luminal fluids is insignificant, which makes the use of such media poorly representative of the in vivo environment. The gastrointestinal lumen has long been shown to be buffered by bicarbonate. Hence, much interest in the development of suitable biorelevant in vitro dissolution media based on bicarbonate buffer systems has evolved. However, there are inherent difficulties associated with these buffers, such as maintaining the pH throughout the dissolution test, as CO_2 tends to leave the system. Various mathematical models have been proposed to analyze bicarbonate buffers and they are discussed in this review. Approaches such as using simpler buffer systems instead of bicarbonate have been proposed as surrogate buffers to produce an equivalent buffer effect on drug dissolution on a case-by-case basis. There are many drawbacks related to simpler buffers systems including their poor in vivo predictability. Considerable discrepancies between phosphate and bicarbonate buffer dissolution results have been reported for certain dosage forms, e.g. enteric coated formulations. The role and need of bicarbonate-based buffers in quality control testing requires scientific analysis. This review also encompasses on the use of bicarbonate-based buffers as a potentially in vivo predictive dissolution medium for enteric coated dosage forms.

1. Introduction

In-vitro dissolution testing of pharmaceutical formulations has been used as a quality control test for many years. During the drug development process, it is often used to optimize formulations according to a desired release profile [1]. Additionally, dissolution experiments can also be used with a prognostic purpose of the dosage form's performance in the gastrointestinal tract, known as in vivo predictive dissolution testing. [2]. Drug dissolution in the gastrointestinal (GI) fluids is a prerequisite for drug absorption and subsequent pharmacokinetic and pharmacodynamic response. An in vitro dissolution test reflects the in vivo performance of a drug product when the in vitro dissolution rate is corresponding to the in vivo dissolution rate. This is the basis to establish an in vitro-in vivo relationship/ correlation (IVIVR/ IVIVC) [3,4]

At early drug product development, in vivo predictive dissolution testing can be used for guidance to rational selection of candidate formulations that best fit the desired in vivo dissolution characteristics. Such an approach can later serve as a surrogate for clinical studies by requesting a biowaiver [1].

In order to achieve this, in vitro dissolution test methods of oral products should be reflective of the in vivo situation, establishing

* Corresponding author at: 11361 – 87 Avenue, Room 3-142-K, Edmonton, AB T6G 2E1, Canada.
E-mail address: raimar@ualberta.ca (R. Löbenberg).

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conditions that closely reflect the physiological environment of the gastrointestinal tract (GIT) [3]. Nevertheless, this is rather difficult to achieve in practice due to the inherent physiological complexity and variability of the GIT. Gastrointestinal transit time, unsteady hydrodynamics and changing fluid contents are a complex physiological

$$HCl + NaHCO_3 \rightarrow NaCl + H_2O_{(l)} + \underset{\uparrow\downarrow}{CO_{2\,(g)}} \; CO_{2(aq)} \rightleftarrows H_2CO_{3(aq)} \rightleftarrows H^+_{(aq)} + HCO_3^-{}_{(aq)} \quad (1)$$

system to attempt to experimentally mimic [3,5–10]. It is important for the predictive in vitro dissolution test media to closely match the pH, buffer species and concentration, bile salts/ lipid content, electrolytes and enzymes of the GI fluids [3].

At present, the most widely applied dissolution media are phosphate-based buffers and, in some cases, the result of dissolution tests performed in such media have demonstrated reasonable/acceptable IVIVCs [1,3,11]. This is true for dosage forms in which the choice of dissolution buffer is essential in achieving IVIVC. However, the concentration of phosphates in human GI luminal fluids is insignificant, which makes the use of such phosphate-containing media poorly representative of the in vivo environment. Thus, these media might fail to reflect in vivo characteristics including ionic strength, buffer capacity, fluid volume and viscosity [6,12–15].

The gastrointestinal lumen has long been shown to be buffered by bicarbonate, which maintains the pH gradient along the GIT [3,16]. Hence, much interest has been drawn to the development of suitable biorelevant in vitro dissolution media [3,7,17–21]. This review focuses on the use of bicarbonate-based buffer in clinically relevant dissolution tests and as a potentially biorelevant media as well as key determinants to in vivo predictive dissolution testing.

2. Intestinal lumen environment - what are we trying to reproduce in a dissolution vessel?

2.1. Physiology overview of gastrointestinal secretions

There are different anatomical components that make up the gastrointestinal tract (GIT) with different functions, such as production of mucus and secretion of digestive enzymes. Complex glands and organs (salivary glands, pancreas and liver) assist with the digestion and emulsification of food. Secretions coming from the pancreas and the liver are emptied into the upper part of the small intestine (duodenum) through the pancreatic and hepatic duct. These two ducts join together immediately before the duodenum.

The pancreatic secretions are composed of various digestive enzymes and a large volume of sodium bicarbonate solution. The bicarbonate ions are important in neutralizing the acidity of the content coming from the stomach [22]. On the other hand, the hepatic secretions are primarily composed of bile. When secreted into the duodenum, the bile plays an important role in fat digestion and absorption. Similarly to the pancreatic secretion, a sodium bicarbonate solution is added to the initial bile [22]. This solution is secreted by epithelial cells in the ducts. This additional quantity of bicarbonate ions supplement the bicarbonate ions in the pancreatic secretion for neutralizing the acid that empties into the duodenum from the stomach.

In addition to the hepatic and pancreatic secretion, the intestinal fluids are also composed of secretions by the epithelial cells of the duodenum. These secretions are an alkaline mucus to protect the duodenal wall from the highly acidic gastric juices. This mucus contains a large excess of bicarbonate ions, which adds to the bicarbonate ions from pancreatic and hepatic secretion in neutralizing the hydrochloric acid entering the duodenum from the stomach. [3,16,22–28].

Consequently, the net result is in the duodenum follows the neutralization equation (Eq. (1)):

The carbonic acid promptly dissociates into carbon dioxide (CO_2) and water. The CO_2 can be absorbed into the systemic circulation and released through the respiratory system. In this way, a neutral solution of sodium chloride is left in the duodenum and the acid contents from the stomach become neutralized [22].This results in an overall effect where the luminal fluids of the small intestine are predominantly buffered by bicarbonate [29].

3. Buffer species - in vitro considerations

Even though the human small intestinal fluid is buffered primarily by bicarbonate buffer, this buffer has been rarely used in dissolution studies [3,30]. This is mainly due to the challenges involved with carrying dissolutions tests using bicarbonate buffer.

3.1. Peculiarities of the bicarbonate buffer

In a bicarbonate buffer system, carbon dioxide (CO_2) has an inherent tendency to leave the aqueous solution (Eq. (1)) and, consequently, the medium has to be continuously purged with CO_2 gas at a constant rate. This maintains the concentration of $CO_{2(aq)}$ in solution in an equilibrium with HCO_3^-, avoiding a pH increase [3,30]. Additionally, both the escape and sparging of $CO_{2(g)}$ in the medium can potentially form bubbles in the medium, which can affect the dissolution process by building bubbles on the surface of the dosage form or powder particles and altering surface tension.

Different models of physiological bicarbonate buffers have been proposed, such as Hanks and Krebs buffers, varying in composition (Table 1) [11]. Hanks buffer composition is similar to the proximal small intestine with respect to electrolyte composition. Nevertheless, modifications to the Hanks balanced salt solution (pH 7.4) is needed to match the physiological pH of 6.8 and to adjust its low buffer capacity (1 mmol/L/ΔpH) to the human jejunal fluids (3.2 mmol/L/ΔpH) [29,31]. This can be accomplished by following the Henderson–Hasselbalch equation (Eq. (2)), i.e. adjusting the concentration of the acid

Table 1
Composition of different bicarbonate buffer systems.

Buffer component (mM)	Hanks buffer[11]	Krebs buffer[31]
KH_2PO_4	1.18	0.441
$Na_2HPO_4{\cdot}2H_2O$	–	0.337
$NaHCO_3$	24.97	4.17
NaCl	118.07	136.99
KCl	4.69	5.37
$CaCl_2$	2.52	1.26
$MgSO_4{\cdot}7H_2O$	1.18	0.812
Ionic Strength	0.161	0.155
Buffer Capacity (mmol/L/ΔpH)	3.7	1.0

(H_2CO_3) and its conjugate base (HCO_3^-) by purging $CO_{2(g)}$ into the medium, which shifts the equilibrium (Eq. (1)) towards formation of $H_2CO_{3\ (aq)}$, thus decreasing the pH of the buffer system [11,29,31–33].

$$pH = pKa + log\frac{[HCO_3^-]}{pCO_2} \quad (2)$$

Another example of bicarbonate-based buffer is the Krebs buffer, which has a different salt composition and buffer capacity than Hanks buffer (Table 1) [31]. Krebs buffer resembles the distal small intestine and approximates the ionic composition and buffer capacity of human small intestinal luminal fluids [11,34]. Nevertheless, the system still has to be stabilized in terms of maintaining the pH and $CO_{2(aq)}$. Purging $CO_{2(g)}$ into the medium is one way of accomplishing it. Garbacz et. al. investigated the pH shift caused by CO_2 loss in different bicarbonate buffer systems, including Krebs buffer. The authors reported that the evaporated CO_2 can be partly substituted by sparging the bicarbonate buffer with gas mixtures, such as 5% (vol/vol) CO_2 and N_2 [33]. When appropriate partial pressure of CO_2 is applied, such purging maintains the bicarbonate equilibrium in the buffer solution, which, in turn, prevents the upward shift in pH. Another way to maintain the desired pH level is to prevent the CO_2 escape. Fadda et. al. (2009) applied strategies such as the addition of liquid paraffin layer above the dissolution media and a completely sealed set-up made of a nylon lid that is impermeable to gas. The authors also investigated the approach of sparging the medium with $CO_{2(g)}$ and concluded that all the three approaches were successful.

However, the buffering capacity of the bicarbonate buffer in bulk is higher for a sparged system compared to a sealed or paraffin-covered system (Al-Gousous et al, 2019).This is because in a sparged system, mass transfer of CO_2 between gas and aqueous phases is allowed. As a result, for weak acid dissolution, accumulation of dissolved CO_2 is limited, and, for weak base dissolution, net loss of dissolved CO_2 is limited. Consequently, a sparged system is more capable of resisting changes in bulk pH resulting from drug dissolution, as was observed by Fadda et al (2009) [34]. Taking into account that CO_2 is absorbed through intestinal mucosa, it would be recommended to use a sparged system for cases where significant shifts in bulk pH due to drug dissolution is expected. However, as explained later in Section 3.1.2, this enhanced buffer capacity in bulk does not typically translate into enhanced buffer capacity in the boundary diffusion layer.

Bicarbonate buffer can also be made by dissolving the appropriate amount of sodium carbonate and/or sodium bicarbonate in deionized water and sparging it with CO_2 (Eq. (1)) or a mixture of compressed air and carbon dioxide while monitoring the pH with a pH meter and CO_2 concentration with a suitable electrode [30,32]. The ionic strength of the solution can be adjusted by adding sodium salts, such as NaCl and Na_2SO_4 [35].

Furthermore, bicarbonate buffer can also be made in situ by continuously sparging $CO_{2(g)}$ or a mixture of 100% dry compressed air and 100% CO_2 at a fixed partial pressure into a 0.9%(w/v) NaCl solution. The pH of the solution can be adjusted by addition of NaOH [36,37].

The sparging of gas into the medium can vary in many aspects, such as the rate in which the gas is purged, the position of the tube in the vessel and the gas(es) mixture composition sparged into the system [3,30,32–34,36,38]. Different sparging rates have been reported and there is no consensus on what rate should be used for greatest efficiency. Simply purging the medium to equilibrate to the desired pH before commencing the experiment is not enough, due to the $CO_{2(aq)}$ decrease (evaporation) the bicarbonate buffer is only stable if continuous sparging occurs. For instance, Boni et. al. (2007) used a sparging rate of 400 ml/min until the desired pH was achieved and during the dissolution experiment the flow rate was adjusted appropriately for the surface area, buffer concentration, pH and volume of media [1].

McNamara et. al. (2003) used a sparging rate of 300 ml/min to equilibrate the medium to the desired pH and a rate range of 250–500 ml/min during the dissolution itself [37]. The authors also investigated different partial pressures of $CO_{2(g)}$ in the sparging gas set at 5, 10, 15, and 20% CO2 %atm which correspond to 6.4, 12.9, 19.3, and 25.8 mM HCO_3^-, respectively. Thus, higher partial pressures of $CO_{2(g)}$ in the sparging gas lead to higher concentrations of $CO_{2(aq)}$ and bicarbonate in the dissolution medium. It was observed that increasing bicarbonate concentration at pH 6.8 increased the dissolution rate and flux for a low-solubility acidic drug (indomethacin), whereas for a low-solubility basic drug (dipyridamole) no increase in dissolution was observed at pH 6.8. Nevertheless, at pH 5 dipyridamole dissolution was significantly impacted by increasing the concentration of $CO_{2(g)}$ in the sparging gas.

Al-Gousous et al. (2018) evaluated different setups in which the tube sparging the gas in the medium was either at a 5 cm depth in the medium or moved up so that its opening would only touch the surface of the liquid [30]. The authors reported that buffer capacity enhancement is not only dependent upon the tube position, but also on sparging rate as well as the titration rate. Accordingly, Boni et. al. (2007) conducted the dissolution experiments supplying the carbon dioxide above the liquid level to avoid noticeable bubble formation in the medium caused by inflow and evaporation of gas [1]. Both authors reported that finer bubbles can be produced by using a gas inlet frit instead of direct sparging.

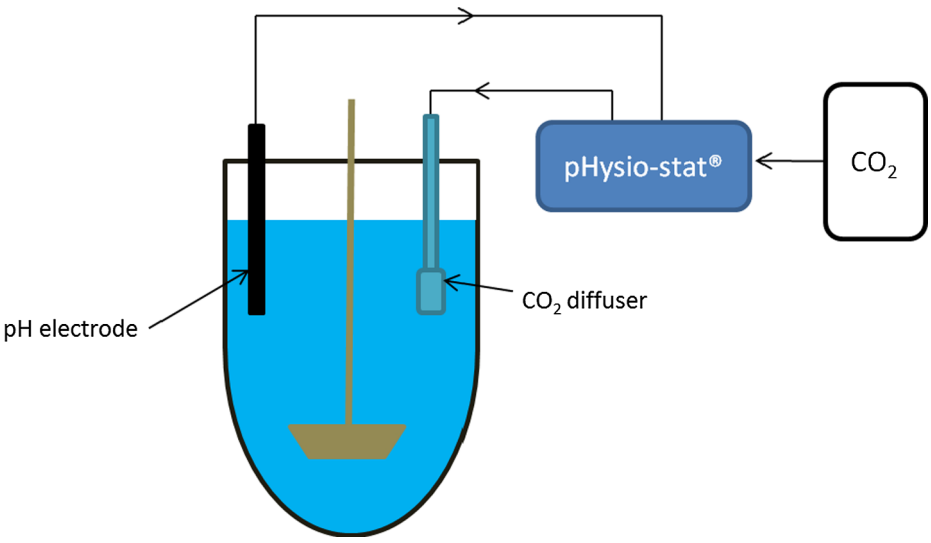

Fig. 1. Schematic illustration of the pHysio-stat device. (Adapted from Garbacz et. al., 2013).

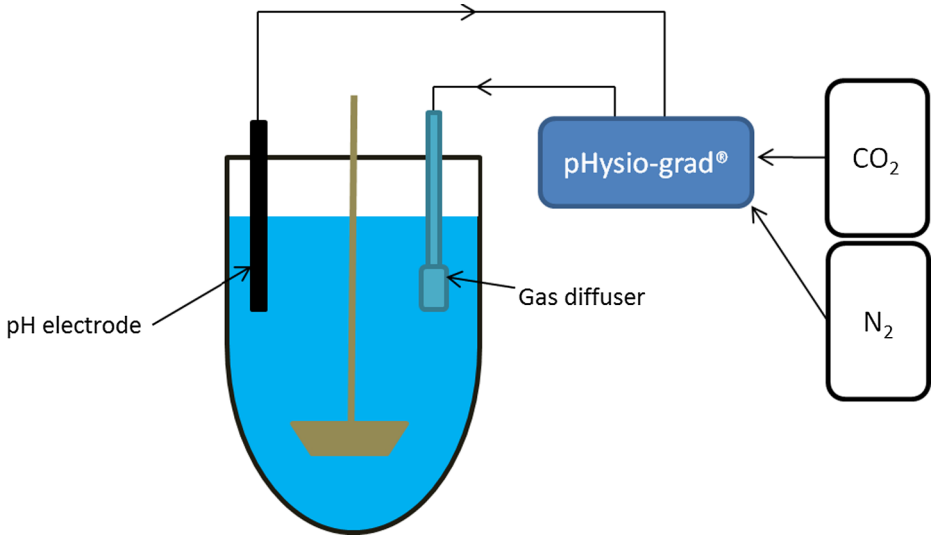

Fig. 2. Schematic illustration of the pHysio-grad® device. (Adapted from Garbacz et. al., 2014).

3.1.1. Automated systems

Different automated systems to monitor the pH and regulate bicarbonate buffers have been proposed in the literature. Garbacz et. al. (2013) developed a device called "pHysio-stat®" to adjust the bicarbonate buffer pH in a dissolution vessel [33]. The system is composed of a pH electrode, a gas diffuser, a digital microcontroller and a valve system, as illustrated in Fig. 1. In this setup the pH electrode and the gas diffuser remain at a 35 mm depth in the medium during the dissolution test. Throughout the experiment, the potential of the electrode is measured and the CO_2 introduced into the dissolution medium via the diffuser is regulated accordingly.

The authors concluded that the pHysio-stat® system was able to monitor and adjust the pH in bicarbonate buffers, thus being a useful tool for routine applications in dissolution tests based on bicarbonate buffers.

The pHysio-stat® system (Garbacz et al., 2013) was further developed to a system (pHysio-grad®) that enabled dynamic adjustment and media pH change by purging CO_2 or an inert gas into the dissolution medium [32]. The system composition was similar to the previous one, but with an additional proportional valve, used for dosing N_2 or CO_2, as illustrated in Fig. 2. In this setup the pH electrode and the gas diffuser remain at a 45 mm depth in the medium during the dissolution test.

Merchant et al. described a system (Auto pH System™) that is also triggered by a pH feedback from the dissolution vessel (Fig. 3) [38,39]. The pH probe is connected to a source of CO_2 gas (pH decreasing gas) and helium (pH increasing gas), and the system is controlled by a control unit. The sparged Helium displaces the dissolved CO_2 which will then result on an increased pH by shifting the equilibrium towards $CO_{2(g)}$ (Eq. (1)). Changes in the bicarbonate buffer pH will cause the appropriate gas to be supplied into the dissolution vessel, providing a dynamic pH adjustment during testing.

3.1.2. Understanding the bicarbonate–CO_2 equilibrium

The solubility of CO_2 in water depends on its partial pressure and medium temperature with Henry's constant being ~24 mM/atm at 37 °C [36]. When dissolved in water CO_2 reversibly hydrates to form carbonic acid (H_2CO_3) which deprotonates forming bicarbonate ion as follows in Eq. (3):

$$CO_{2(aq)} + H_2O_{(l)} \underset{\text{Dehydration}}{\overset{\text{Hydration}}{\rightleftharpoons}} H_2CO_{3(aq)} \rightleftharpoons HCO_3^- + H^+ \quad (3)$$

The intrinsic pKa for H_2CO_3 dissociation ($pK_a^{H_2CO_3}$) is ~3.5 [40]. However, during potentiometric titration, the equilibrium that is established between H_2CO_3 and CO_2 results in the apparent pKa

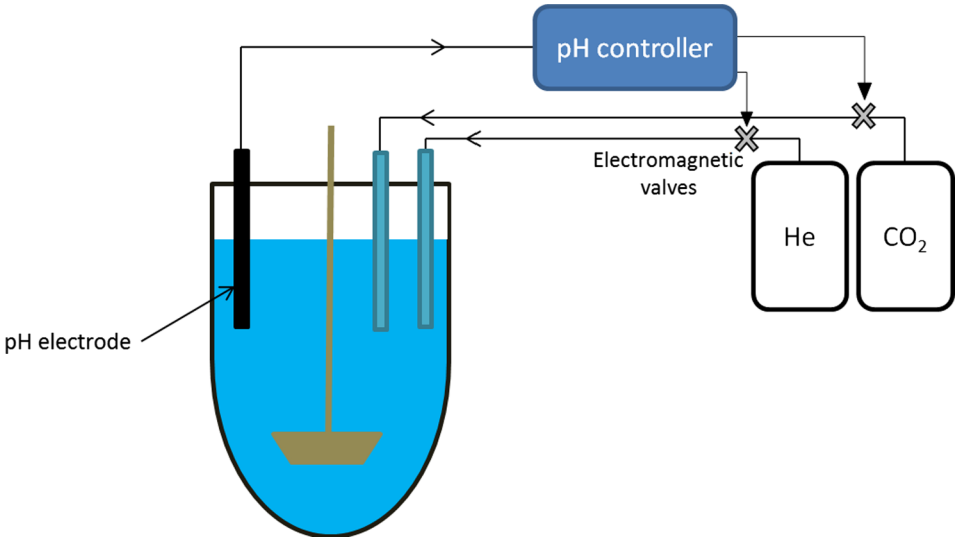

Fig. 3. Schematic illustration of the Auto pH System™ device. (Adapted from Goyanes et. al., 2015).

($pK_a^{potentiometric}$) being equal to 6.35 since:

$$K_a^{potentiometric} = \frac{[HCO_3^-][H^+]}{([CO_2] + [H_2CO_3])} = \frac{[HCO_3^-][H^+]}{[H_2CO_3]} \times \frac{[H_2CO_3]}{([CO_2] + [H_2CO_3])} = K_a^{H_2CO_3} \times \frac{1}{1 + k_d/k_h} \quad (4)$$

where k_d is the rate constant for the dehydration reaction and k_h is the rate constant for the hydration reaction (Eq. (4)). This $pK_a^{potentiometric}$ will govern the pH of a bulk solution of the bicarbonate buffer, since the mixing processes limit the rate of neutralization processes in bulk, which in turn are slower than the interconversion between carbon dioxide and carbonic acid. Therefore, it would appear in bulk as if carbon dioxide were the conjugate acid with carbonic acid being merely a short-lived intermediate. However, in the diffusion layer at the solid–liquid interface of a tablet, the situation is different [41].

There, in contrast to the extremely rapid proton transfer reactions, the CO_2-H_2CO_3 interconversion is not faster than diffusional processes (under normal hydrodynamic conditions) to a degree that would allow it to reach equilibrium in this layer. As a result, the relative contribution of carbonic acid and carbon dioxide to the buffer flux and so to the buffering action in the boundary layer will not be reflective of the equilibrium situation present in bulk. Consequently, in the boundary layer, the buffering action of bicarbonate will not correspond to that of a pKa 6.35 buffer, and the buffer will act there as if its pKa were lower than that. In other words, the apparent effective pKa governing the buffering action of bicarbonate in the diffusion layer will not be the potentiometrically determined value of 6.35 but lower. According to a recently published model this apparent effective pKa (at 37 °C and ionic strength of 0.15 M) would be equal to [41]:

$$3.3 + \log\left(1 + \frac{D_{CO_2}}{D_{H_2CO_3}} \times \frac{k_d}{k_h + \left(\frac{2D_{CO_2}}{h^2}\right)}\right) \quad (5)$$

where D_{CO_2} and $D_{H_2CO_3}$ are the diffusion coefficients of carbon dioxide and carbonic acid respectively and h is the boundary layer thickness (Eq. (5)).

Accordingly, its buffering capacity in the diffusion layer against the dissolving drug/excipient will be lower, since the effective pKa values is shifted away from the intestinal pH range of 6–7.5. This means that while the buffer capacity of bicarbonate is enhanced in bulk, it is weakened in the diffusion layer, which further adds to the complexity of the system. This is of particular significance for enteric coated dosage forms. For, based on the equation above, in a 30 μm-thick diffusion layer, the apparent effective pKa of bicarbonate would be around 4.6, which will make it difficult for proximal intestinal bicarbonate molarities to maintain the surface of a dissolving enteric polymer at pH values exceeding 5.5. Therefore, obtaining prompt release from enteric-coated dosage forms at bicarbonate molarities present in the proximal small intestine is difficult as shown by data in literature [42].

3.2. Phosphate buffer

Dissolution testing for quality control (QC) as a performance test is used to ensure lot-to-lot consistency and batch compliance to the defined specifications for the drug product [43–45]. For this purpose, compendial dissolution media (simple media), such as phosphate buffers, are used in most cases [43,46]. Nevertheless, considering the concept of biorelevant media, phosphate buffers are not physiologically relevant, since the buffering system in the human intestines is bicarbonate-based. Even though, many phosphate-based dissolution media have been proposed to be biorelevant, such as the USP simulated intestinal fluids (SIFs) (Table 2), which were developed to simulate the GI pH and bile salts concentration (discussed in the next section) [3,7,17–21]. According to the FDA, simulated intestinal fluid with pancreatin (USP-SIF) and without enzyme (SIF-blank) better reflect the physiologic conditions of the small intestine than other buffers [11,47].

The different pharmacopoeias recommend different salts to make buffers. In the USP, SIF-blank and phosphate buffer pH 6.8 are made with the potassium salt, whereas the International Pharmacopoeia (Ph. Int.) recommends the use of sodium salt [43,48]. Nevertheless, osmolality, ionic strength, and buffer capacity are similar between these buffers, as shown by Stippler et al. [48]. The author considered the media to be interchangeable for the dissolution test of the tested drugs (ibuprofen, metronidazole, and indomethacin - immediate-release solid oral dosage form). Substitution of the two cations (Na+ and K+) is only necessary in cases where solubility is known to be affected by the cation. This is also true for surfactant containing media. Ropers et al. reported that surfactant precipitation can occur as a result of counterion interaction. The use of sodium buffer instead of a potassium buffer seems to avoid this issue [11,49]. The counterion effect on surfactants has a lot to do with their micelle formation in aqueous media. The counterions of surfactant polar head groups have strong influence on their packing and thermodynamic behavior because each particular type of counterion possess different binding energy to the respective head group, causing structural changes which affect the surfactant self-assembly process.

The disintegration of HPMC capsules containing carrageenan as gelling agent is also affected by the type of cation used in the buffer.

Table 2
Composition of Simulated Intestinal Fluids.

Buffer component	USP** PB	USP** SIF	IntPh 3 PB[#]	FaSSIF[+]	FaSSIF V2[+]	FeSSIF[+]	FeSSIF V2[+]
KH_2PO_4	50 mM	6.8 g	3.4 g	–	–	–	–
Na_2HPO_4			3.53 g	–	–	–	–
NaH_2PO_4			–	3.438 g	–	–	–
NaOH	qs ad pH 6.8	15.4 mM	–	qs ad pH 6.5	34.8 mM	4.04 g	81.65 mM
Pancreatin		10 g	–				
Bile salt (taurocholate)	–	–	–	3 mM	3 mM	15 mM	10 mM
Phospholipid (lecithin)	–	–	–	0.75 mM	0.2 mM	3.75 mM	2 mM
Acetic acid	–	–	–	–	–	8.65 g	–
NaCl	–	–	–	6.186 g	68.62 mM	11.874 g	125.5 mM
Maleic acid (mM)	–	–	–	–	19.12 mM	–	55.02 mM
Glyceryl monooleate (mM)	–	–	–	–	–	–	5 mM
Sodium oleate (mM)	–	–	–	–	–	–	0.8 mM
Deionized water		qs 1L	qs L	qs L	qs L	qs L	qs L
Buffer Capacity (mmol/L/ΔpH)	29[++]	18.4[#]	18.6	~12	10	~72	25
Osmolarity (mOsmol/kg)	–	113	115	~270	180 ± 10	~670	390 ± 10
pH	6.8	6.8	6.8	6.5	6.5	5	5.8

References: [+] [69]; * [70] ** [71] [#] [46] [++] [72].

Potassium ions are a gelling promoter for carrageenan, which causes delay in capsule opening along with increased variability of dissolution. Hence, the presence of potassium cations in the dissolution media hinders drug release from such capsules [50–53]. This issue can be easily overcome by avoiding the use of potassium salt in the test media.

Almukainzi et al. reported the impact on disintegration time of cellulose-based hard shell capsules based on the use of sodium and potassium buffers and SIF. Different salts caused different disintegration times of capsules, which will likely cause differences in dissolution behavior [54].

Furthermore, adding enzymes to the dissolution medium can be technically challenging when testing gelatin capsules. Gelatin can cross-link in the presence of aldehydes, or in high temperature and humidity conditions. Cross-linking is characterized by a covalent bonding between gelatin chains which creates water insoluble pellicles/membranes on the internal or external surface of the capsule shell during the dissolution test. Cross-linking can cause slower drug release from the gelatin capsule or even no release altogether. Several examples of cross-linking are reported in the literature [55–58].

3.2.1. Biorelevant media

As mentioned before, biorelevant media were made to simulate the GI tract pH and components likely to be found in the human GI tract, such as bile salts and lecithin. Osmolality, pH and surface tension are adapted to physiological values [59]. Food can have an impact on a drug's *in vivo* dissolution and further absorption. In the fed state the physiological environment of the GIT differs in many ways, such as prolonged gastric emptying time, increased stomach pH, increased bile secretion into the small intestine, and increased hepatic blood flow, which can affect drug metabolism. In order to obtain meaningful in vitro dissolution results, the media used should reflect the in vivo dissolution environment and account for such factors and changes [60].

In 1998, Dressman et. al. proposed the first generation of biorelevant media know as fasted state simulated intestinal fluid and fed state simulated intestinal fluid (FaSSIF and FeSSIF, respectively) (Table 2). The dissolution tests performed using such media aimed to be an in vitro method that would serve as a surrogate for in vivo release [43,61]. Later on FaSSIF and FeSSIF were updated and are now described as FaSSIF-V2 and FeSSIF-V2 [11,62] (Table 2). FaSSIF-V2 contains a reduced amount of lecithin [43,63] and FeSSIF-V2 contains two additional digestion components: glyceryl monooleate and sodium oleate.

Biorelevant media has been used both in solubility tests and dissolution experiments [11]. Several studies have reported successful in vitro/in vivo correlations (IVIVC) using biorelevant media for poorly soluble drugs. Biorelevant media seems to be able to mimic the in vivo dissolution more effectively compared to other media [64–67]. On the other hand, the purity of the surfactants present in biorelevant media highly impact the solubility and dissolution of certain drugs [68,69]. Other factors such as the preparation methods can also impact the dissolution testing results. Kloefer et al. investigated different media preparation methods and observed that standard preparation methods resulted in reproducible dissolution profiles. However, the different methods yielded differences in the micelle sizes which may impact the dissolution behavior of other drugs [70]. The current composition of biorelevant media falls deficient in some aspects, such as the fact that only taurocholic acid is present as the only bile salt, when, in fact, it represents only 20% of the in vivo bile salt content. Moreover, lysolecithin, a naturally occurring phospholipid in the small intestine, is also not included in both FaSSIF and FeSSIF [14]. Hence, due to their analytical properties, price, and variability in composition biorelevant media are not currently used as routine quality control media [11]. In addition, such media may not be accepted by regulatory agencies based on the fact that a full release may not be achieved, even though it seems to be physiologically relevant. In such cases, addition of surfactant is needed to meet the requirements, causing the method to be no longer physiologically relevant.

Bicarbonate-containing biorelevant media for poorly soluble drugs is also technically challenging due to the foaming encountered when sparging the medium as a consequence of the surfactants present.

4. Buffer capacity

Buffer capacity is the efficiency of a buffer system to resist changes in pH [31,71]. It is calculated as the amount of acid or base added per unit of buffer volume per unit of pH change (molar concentration/volume/ΔpH) [30].

Buffer capacity (β) is usually calculated according to Eq. (6):

$$\beta = \Delta AB/\Delta pH \quad (6)$$

where AB is the mol/l increment of the amount of acid or base added to produce a pH change of Δ pH in the buffer [31,71].

The more concentrated a buffer is, the higher its buffer capacity. The buffer capacity of the human intestinal fluid ranges from 2.4 to 5.6 μmol/mL/ΔpH and conventional buffer systems such as FaSSIF and USP SIF fail to reproduce such characteristics. FaSSIF (pH 6.5) and USP SIF (pH 6.8) have strong buffer capacities (Table 2), which is, respectively, 5 and 7.7 times higher than the buffer capacity of human intestinal fluids [72–74].

Due to such high buffer concentration (USP SIF: 50 mM and FaSSIF: 29 mM) it is likely to overestimate the dissolution of BCS II weak acids, particularly drugs with pKa values less than 6.5. Therefore, in spite of the fact that biorelevant media such as USP SIF buffer and FaSSIF may reflect the small intestine fluids pH, the buffer composition and concentration also significantly impacts the dissolution behaviour of BCS II weakly acidic drugs. Moreover, the discrepancy between the buffering capacity of bicarbonate in bulk and in the boundary layer (as explained in Section 3.1 and 3.1.2) also needs to be taken into account. Hence, not only the pH but, as importantly, the buffer species and concentrations should be carefully considered when making in vivo predictive dissolution media, especially in the case of poorly soluble and ionizable drugs. Sheng et. al. (2008) evaluated the difference between the phosphate buffers and the gastrointestinal bicarbonates in dissolution of ketoprofen and indomethacin and observed that even with FaSSIF (lower phosphate buffer concentration of 29 mM) the dissolution of ketoprofen and indomethacin demonstrated a higher rate than in the bicarbonate, that is, in vitro dissolution testing with either USP SIF or FaSSIF was overestimating the true dissolution rates of both drugs in vivo [3]. There are many other reports in the literature about differences in dissolution rate when varying the buffer capacity [35,75–77]. Ashford et al. compared the in vitro release characteristics of tablets coated with Eudragit S in different buffers varying the buffer's capacity and composition and observed that increasing phosphate concentration also causes a dissolution rate increase [78]. Hamed et. al. (2016) tested carvedilol (BCS IIb - weak base) in phosphate buffer with varying capacities and observed that lowering the buffer capacity resulted in a decrease in carvedilol solubility and dissolution rate [79].

In a high buffer capacity medium there is an abundance of the buffer conjugate base species in the diffusion layer of a dissolving drug particle. In the case of BCS class IIa drugs (weak acids), a prompt neutralization of H^+ at the solid–liquid interface occurs, preventing a pH shift in the microclimate around the dissolving particle. As a result, the pH in the diffusion layer is similar to the bulk solution pH, which can lead to higher dissolution rates [80].

When considering in vivo predictive dissolution media both species and capacity are equally important. As already mentioned, the human intestine is chiefly buffered by a bicarbonate buffer system. The preparation of physiologically relevant bicarbonate buffer is complex, a generally slow process, and there is the potential formation of gas bubbles at the solid–liquid interface, which can affect the dissolution of drug product/particles. Hence, the use of a non-bicarbonate based surrogate buffer that produces equivalent buffer effect on drug

dissolution may be preferable [3,81].

Phosphate is usually the buffer of choice and it is also the buffer proposed by US FDA to be used for in vivo biowaivers [81,82]. Since its pKa of 6.8 falls right within the pH range of the small intestine, phosphate is a suitable buffer to be considered for physiologically relevant dissolution tests. Phosphate buffer is present in both USP SIF at pH 6.8, and FaSSIF at pH 6.5 with concentrations/buffer capacities of 50 mM/29 mM/ΔpH and 29 mM/15 mM/ΔpH, respectively (Table 2) [81,83,84].

On the other hand, the average concentrations/buffer capacity of bicarbonate buffer in the small intestine are approximately 6–20 mM/2.5–8.5 mM/ΔpH at a pH of 6.5 [8–10,81,85–88]. But, as discussed before, the buffer capacity of bicarbonate buffer at the diffusion layer does not correspond to that in bulk. As a result, lower buffer capacities would be necessary for the surrogate phosphate buffer to be equivalent to bicarbonate buffer, and an additional external pH control may be needed to maintain the bulk solution pH [81].

Krieg et al. (2015) studied several different weak acid and weak base drugs and reported that it is possible to match the dissolution rate of weak acid/base drugs in bicarbonate buffer systems to phosphate buffer [81]. This is a complex interdependence of buffer pH and pKa, drug pKa and solubility, and diffusion layer thickness. For weak acid drugs, the authors observed that phosphate buffer concentrations between 1 and 25 mM are more physiologically relevant and may translate the impact of bicarbonate buffer on their dissolution. This means that the dissolution rate of the drug in phosphate buffer 1–25 mM matches the drug dissolution rate in a physiologically relevant bicarbonate buffer. For weak base drugs, very low phosphate buffer concentrations of < 2 mM would be necessary to match bicarbonate buffer. This study concluded that, in light of their findings, the current phosphate buffer concentrations used in dissolution testing (50 mM) does not seem to accurately reflect the dissolution media and conditions of the human intestine fluids that the drug is exposed to.

Sheng et. al. (2009) also evaluated the difference between phosphate buffer and bicarbonate buffer in the dissolution of ketoprofen and indomethacin [3]. The author recommended the use of phosphate buffers of 13–15 mM and 3–4 mM for ketoprofen and indomethacin, respectively, to reflect the in vivo dissolution of both drugs in gastrointestinal bicarbonates, with special applications to the development of buffer systems for BCS II weak acids, which might allow later on the development of in vitro biowaiver dissolution methodology.

5. Dissolution tests in phosphate buffer *versus* bicarbonate buffer

There are many cases in the literature reporting differences in the dissolution profile of various drugs and dosage forms when tested in phosphate buffer vs. bicarbonate buffer [3,29,31,34,37,81,89–91].

McNamara et. al. investigated the use of stable bicarbonate buffer to characterize the dissolution of low-solubility ionizable drugs [37]. The authors reported that dissolution of indomethacin in phosphate-based buffers (SIF and FaSSIF) with controlled pH yielded higher intrinsic dissolution rates than what can be expected at the same physiologic pH (pH 6.8), overestimating what occurs in vivo in a bicarbonate buffer system. Though SIF and FaSSIF may mimic the intestinal physiologic pH, the buffer composition and concentrations may not be physiologic, impacting the dissolution of ionizable compounds.

Karkossa and Klein assessed the drug release from commercial immediate-release (IR) and enteric-coated (EC) aspirin tablets in media with different composition and ionic strength [35]. The authors conducted a systematic study in phosphate buffer pH 6.0 and 6.8 at three different ionic strengths of 75 mM, 150 mM and 300 mM, and in bicarbonate buffer also pH 6.0 and 6.8 at three different ionic strengths of 10 mM, 85 mM and 235 mM. For the IR tablets, dissolution was > 85% within 15 min in all cases independent of the media composition and pH, indicating very rapid dissolution. The tested EC tablets presented a highly variable drug release performance and it was affected by both media pH and buffer species. In all cases, the release profile in a bicarbonate buffer system displayed longer lag times compared to phosphate-based buffers. After the coating had dissolved, the drug release was complete (100%) in bicarbonate buffer and at least > 85% in phosphate buffers. In both buffer systems, higher ionic strength resulted higher release rate. The authors remarked that changes in the drug release behavior were not attributed to the tablet core, but to the functional coating of the EC tablets. Hence, it was concluded that the dissolution behavior of enteric coating materials strongly depends not only on the pH but also on the dissolution medium composition (buffer species and ionic strength).

The impact of the buffer system utilized to test EC dosage forms has important implications. Rudolph et al. tested the release of 5-aminosalicylic acid formulations coated with Eudragit S in phosphate-based biorelevant media to simulate biological surfactants in intestinal fluids [31,83,90]. No differences in drug release of Eudragit S coated formulations were observed, even with increasing ionic strength. Even though the prediction of in vivo dissolution processes of poorly soluble drugs can be enhanced in such media [31,92]; it does not simulate the buffer composition of the GIT, failing to represent the in vivo performance of a given dosage form. Liu et al. tested the dissolution of prednisolone tablets coated with various enteric polymers in both pH 6.8 phosphate and modified Hanks bicarbonate buffer [29]. The authors observed rapid and comparable dissolution profiles for the various polymers in pH 6.8 phosphate buffer. In the bicarbonate-based buffer, drug release was delayed and marked differences between the various coated tablets were observed. The in vitro bicarbonate dissolution results demonstrated a better fit with the *in vivo* observed data [29,43]. Similarly, Ibekwe et al. 2006 tested the drug release of prednisolone tablets coated with different Eudragit polymer systems in phosphate buffer and Hanks buffer [93]. The authors also observed similar drug release from the polymer coated tablets in the phosphate compendial media, whereas in the physiological buffer the drug release differed and was slower for all the coated tablets compared to the compendial buffer. Chan et al. also observed significantly faster drug release rate in phosphate buffer than in Hank's solution (bicarbonate-based) for EudragitS100 coated capsules [91].

Fadda and Basit investigated the drug release profiles of commercial Eudragit S coated mesalazine tablets (Asacol MR, Mesren MR and Ipocol) in different media: phosphate and physiological bicarbonate buffers (Hanks and Krebs) [31]. Similarly to the above cited studies, the drug release profiles were substantially faster in phosphate buffer compared to physiological bicarbonate buffers. The buffer salts and concentrations in the two physiological buffers resulted in different dissolution profiles for the tested products.

Therefore, there is the need to adequately choose the ionic composition of dissolution media to match as closely as possible the intestinal fluid composition. The differences encountered in the dissolution profiles in phosphate vs. carbonate buffer can have relevant pharmaceutical implications. For instance, there are many reports in the literature of non-responsiveness or even “resistance” to aspirin when enteric coated (EC) products are administered [94–97]. Studies have shown a decreased bioavailability (BA) of EC aspirin both in healthy volunteers and in patients and they do not recommend the use of EC aspirin in conditions requiring rapid onset of action [94,96]. Failure of enteric coated formulations is a long known problem, dating back to 1964, where EC aspirin tablets did not pass the USP disintegration test, which was used to assess its physiologic availability [98]. This problem has continued to persist with many cases of inadequate BA of EC products found in the literature: Wagner et. al. 1973, Maree et. al. 2005, Cox et. al. 2006, Grosser et. al. 2013, Bhatt et. al. 2017 [95,96,99–101]. A particularly striking case was the report of slow release aspirin in the elderly [102]. The study measured the plasma salicylate concentrations of a group of 77 elderly and no salicylate was detected in 26 of 77 patients. At the time, poor compliance was considered as one of the possible explanations for the undetected salicylate

plasma level. However, the test was repeated in a subgroup to ensure compliance. In three of the six patients, absence of detectable plasma salicylate was confirmed. Hence, there is strong evidence that this is a clinical drug product performance issue that has not yet been resolved.

The study conducted by Karkossa and Klein revealed that aspirin release from marketed EC products was strongly affected by the buffer species [35]. The lag times before onset of drug release in phosphate-based buffers ranged from 10 to 20 min, whereas in bicarbonate-based buffers with the same pH, lag times of ~60 min were observed. Correlating the observations made in the above cited studies with in-vitro dissolution profiles obtained from standard tests using compendial buffers indicates that such in-vitro dissolution profiles are not predictive of the in-vivo release behavior of EC formulations. The poor outcome of the in-vitro experiments can be attributed to the buffer species and concentrations used in compendial dissolution tests [31,32,35,91,93,103–105]. Hence, while resistance is claimed with EC aspirin formulations, the reduced BA could rather be linked to the dissolution behavior of the coating materials in the GI fluid.

In 1988 Bochner et. al. assessed the pharmacokinetics of Aspirin in man when administered in solution, modified release tablet (EC) and intravenously. The formulation and route of administration profoundly influenced several pharmacokinetic parameters of aspirin, with a 6-fold decrease in Cmax, 1.8 fold decrease in AUC and 12-fold increase in Tmax for the modified release tablet compared to the oral solution [106]. Further on Bochner et. al. (1991) compared the pharmacokinetics of four commercially available oral aspirin formulations, in which two of the formulations were rapid release and the other two were EC formulations [107]. The authors observed marked differences in the plasma concentration-time profiles between the rapid release compared to the EC formulations. Interestingly, a comparison between the rapid release formulations, demonstrated no significant differences in Tmax were found, whereas Tmax was significantly prolonged for the EC formulations, and it presented great variability in the plasma concentration vs time profiles.

An additional factor that needs to be taken into account when comparing dissolution in bicarbonate to that in phosphate is that some drugs the possibility of $CO_{2(g)}$ generation when bicarbonate reacts with a drug that has a combination of low pKa and high intrinsic solubility [35,42]. This could lead to the solid dosage form experiencing an additional disintegrating force in bicarbonate that is is difficult to simulate using phosphate [35,42].

6. Applicability in the industry

A biorelevant dissolution method is the one that attempts to mimic the different physiological environments that the drug will encounter throughout its passage in the GI tract. The overall goal is guidance during formulation selection and optimization. Nevertheless, this does not necessarily mean that the method will be predictive of clinical outcomes. As the formulation development advances, a superior dissolution method can be development, which is able to model the in vivo performance more accurately yielding a good IVIVC/IVIVR. Hence, such a dissolution test is clinically relevant; i.e. it links the in vitro data with in vivo pharmacokinetic performance data, creating an IVIVC or IVIVR [108]. When a level A IVIVC can be achieved then this method is predictive of the in vivo drug release in humans.

Bicarbonate buffer often falls under the biorelevant umbrella, contributing to an efficient design of drug formulations [109]. Accordingly, the aforementioned studies demonstrate that bicarbonate buffer has its place and importance during the drug development process. Considering the differences and outcomes when using phosphate and bicarbonate buffers the role and need of the latter should be revisited in a QC manner in cases in which it models in vivo performance more accurately, such as EC formulations [29,110].

7. Clinical reports

There are many different EC products from various classes of drugs that require further experimental scrutiny. A compilation of delayed release (enteric coated) products listed as Reference Listed Drug (RLD) by the FDA is shown in Table 3. According to the FDA, an RLD is “an approved drug product to which new generic versions are compared to show, among other things, that they are bioequivalent. A drug company seeking approval to market a generic equivalent must refer to the RLD in its Abbreviated New Drug Application (ANDA)”. Biowaivers are not applied to EC products. However, caution has to be taken as to which EC formulation is to be used in a bioequivalence study. Similar dissolution profiles in phosphate buffer may not render bioequivalence, as pointed out by Gelderen et. al., that compared the relative BA of four different diclofenac EC products [111]. The authors reported that only one generic product was fully bioequivalent with the reference product Voltaren. The European Pharmacopeia test at the time did not detect any differences between the products. Elkoshi et. al., evaluated the bioequivalence of two enteric-coated formulations of omeprazole, Losec® (reference) and Omepradex® (test) [112]. Surprisingly, the two products differed in both their rate and extent of absorption after a single dose and following multiple doses. The products failed the bioequivalence test for area under the plasma concentration-time curve (AUC) and maximum plasma drug concentration (Cmax) after a single and multiple doses. The authors concluded that the two products may not be considered either therapeutically equivalent or interchangeable.

Many other EC products drawbacks have been reported for various drugs. Inadequate BA due to delayed pharmacokinetics and poor absorption led to non-interpretable therapeutic drug monitoring results, for mycophenolate sodium, an antiproliferative agent used in kidney transplantation [111]. Edaravone EC pellets, a drug used for acute ischemic stroke, had its BA 9 times lower than gastric retention pellets and almost 5 times lower than a solution preparation [111]. Interestingly, > 90% release was obtained in the in vitro release experiment with phosphate buffer pH 6.8. For some drugs, such as omeprazole and rasagiline, the delayed release and immediate-release formulations presented similar AUC, nevertheless, there were marked differences in Cmax and Tmax, which may delay the onset of action for such formulations [113,114]. Studies done with drugs such as flurbiprofen and sulfapyridine presented much lower BA when administered in an enteric coated formulation and were not within the bioequivalence range [115,116].

Failure to dissolve the enteric coat may present disturbing outcomes as severe as fecal impaction. In many cases, ammonium chloride formulations caused gastrointestinal obstruction leading to patient hospitalization [117–119]. Hence, the product safety in such cases may be a concern. Also, awareness of toxicological manifestations related to the use of non-steroidal anti-inflammatory drugs (NSAIDs) haven been raised, once it is possible that modified release formulations may increase the exposure of active drug to the distal GI regions [120,121].

8. Conclusion

Herein was presented an overview of promising trends in developing in vivo predictive dissolution media by means of using bicarbonate-based buffer systems. When assessing a dosage form’s performance, the buffer media must be carefully considered. Currently, many studies are conducted in non-bicarbonate buffer systems, such as the so called “biorelevant” media. However, there have been many drawbacks related to these systems likely due to their sometimes limited in vivo predictability.

Bicarbonate-based buffers can be superior in predicting the in vivo behavior of certain dosage forms, like enteric coated formulations. This is possible owing to its composition, which resembles the intestinal fluids in terms of buffer species and buffer capacity. Nonetheless, the inherent difficulties associated with bicarbonate buffers make it

Table 3
Delayed release drug products listed as Reference Listed Drug (RLD) by the FDA Orange book.

Active Ingredient	Proprietary Name	Dosage Form	Applicant Holder
AMOXICILLIN; CLARITHROMYCIN; OMEPRAZOLE	OMEPRAZOLE AND CLARITHROMYCIN AND AMOXICILLIN	CAPSULE, TABLET, CAPSULE, DELAYED RELEASE	GASTROENTERO LOGIC LLC
ASPIRIN; OMEPRAZOLE	YOSPRALA	TABLET, DELAYED RELEASE	GENUS LIFE SCIENCES INC
CHOLINE FENOFIBRATE	TRILIPIX	CAPSULE, DELAYED RELEASE	ABBVIE INC
CROFELEMER	MYTESI	TABLET, DELAYED RELEASE	NAPO PHARMACEUTICALS INC
CYSTEAMINE BITARTRATE	PROCYSBI	CAPSULE, DELAYED RELEASE	HORIZON PHARMA USA INC
DEXLANSOPRAZOLE	DEXILANT	CAPSULE, DELAYED RELEASE	TAKEDA PHARMACEUTICALS USA INC
DICLOFENAC SODIUM; MISOPROSTOL	ARTHROTEC	TABLET, DELAYED RELEASE	GD SEARLE LLC
DIDANOSINE	VIDEX EC	CAPSULE, DELAYED REL PELLETS	BRISTOL MYERS SQUIBB CO
DIMETHYL FUMARATE	TECFIDERA	CAPSULE, DELAYED RELEASE	BIOGEN IDEC INC
DIVALPROEX SODIUM	DEPAKOTE	CAPSULE, DELAYED REL PELLETS	ABBVIE INC
DIVALPROEX SODIUM	DEPAKOTE	TABLET, DELAYED RELEASE	ABBVIE INC
DOXYCYCLINE HYCLATE	DORYX	TABLET, DELAYED RELEASE	MAYNE PHARMA INTERNATIONAL PTY LTD
DOXYLAMINE SUCCINATE; PYRIDOXINE HYDROCHLORIDE	DICLEGIS	TABLET, DELAYED RELEASE	DUCHESNAY INC
DULOXETINE HYDROCHLORIDE	CYMBALTA	CAPSULE, DELAYED REL PELLETS	ELI LILLY AND CO
ERYTHROMYCIN	ERYC	CAPSULE, DELAYED REL PELLETS	MAYNE PHARMA INTERNATIONAL PTY LTD
ESOMEPRAZOLE MAGNESIUM	NEXIUM	CAPSULE, DELAYED REL PELLETS	ASTRAZENECA PHARMACEUTICALS LP
ESOMEPRAZOLE MAGNESIUM	NEXIUM	FOR SUSPENSION, DELAYED RELEASE	ASTRAZENECA PHARMACEUTICALS LP
ESOMEPRAZOLE MAGNESIUM; NAPROXEN	VIMOVO	TABLET, DELAYED RELEASE	HORIZON MEDICINES LLC
ESOMEPRAZOLE STRONTIUM	ESOMEPRAZOLE STRONTIUM	CAPSULE, DELAYED RELEASE	R2 PHARMA LLC
FLUOXETINE HYDROCHLORIDE	PROZAC WEEKLY	CAPSULE, DELAYED REL PELLETS	ELI LILLY AND CO
LANSOPRAZOLE	PREVACID	CAPSULE, DELAYED REL PELLETS	TAKEDA PHARMACEUTICALS USA INC
LANSOPRAZOLE	PREVACID	TABLET, ORALLY DISINTEGRATING, DELAYED RELEASE	TAKEDA PHARMACEUTICALS USA INC
MESALAMINE	DELZICOL	CAPSULE, DELAYED RELEASE	ALLERGAN PHARMACEUTICALS INTERNATIONAL LTD
MESALAMINE	ASACOL HD	TABLET, DELAYED RELEASE	ALLERGAN PHARMACEUTICALS INTERNATIONAL LTD
MESALAMINE	LIALDA	TABLET, DELAYED RELEASE	SHIRE DEVELOPMENT INC
MYCOPHENOLIC ACID	MYFORTIC	TABLET, DELAYED RELEASE	NOVARTIS PHARMACEUTICALS CORP
NAPROXEN	EC-NAPROSYN	TABLET, DELAYED RELEASE	ATNAHS PHARMA US LTD
OMEPRAZOLE MAGNESIUM	PRILOSEC	FOR SUSPENSION, DELAYED RELEASE	COVIS PHARMA BV
PANCRELIPASE (AMYLASE;LIPASE;PROTEASE)	CREON	CAPSULE, DELAYED RELEASE	ABBVIE INC
PANCRELIPASE (AMYLASE;LIPASE;PROTEASE)	PANCREAZE	CAPSULE, DELAYED RELEASE	VIVUS INC
PANCRELIPASE (AMYLASE;LIPASE;PROTEASE)	PERTZYE	CAPSULE, DELAYED RELEASE	DIGESTIVE CARE INC
PANCRELIPASE (AMYLASE;LIPASE;PROTEASE)	ZENPEP	CAPSULE, DELAYED RELEASE	FOREST LABORATORIES INC
PANTOPRAZOLE SODIUM	PROTONIX	FOR SUSPENSION, DELAYED RELEASE	WYETH PHARMACEUTICALS LLC
PANTOPRAZOLE SODIUM	PROTONIX	TABLET, DELAYED RELEASE	WYETH PHARMACEUTICALS LLC
POSACONAZOLE	NOXAFIL	TABLET, DELAYED RELEASE	MERCK SHARP AND DOHME CORP
PREDNISONE	RAYOS	TABLET, DELAYED RELEASE	HORIZON PHARMA INC
RABEPRAZOLE SODIUM	ACIPHEX SPRINKLE	CAPSULE, DELAYED RELEASE	CERECOR INC
RABEPRAZOLE SODIUM	ACIPHEX	TABLET, DELAYED RELEASE	EISAI INC
RIFAMYCIN	AEMCOLO	TABLET, DELAYED RELEASE	COSMO TECHNOLOGIES LTD
RISEDRONATE SODIUM	ATELVIA	TABLET, DELAYED RELEASE	ALLERGAN PHARMACEUTICALS INTERNATIONAL LTD
SULFASALAZINE	AZULFIDINE EN-TABS	TABLET, DELAYED RELEASE	PHARMACIA AND UPJOHN CO
ESOMEPRAZOLE MAGNESIUM	NEXIUM 24 HR	CAPSULE, DELAYED RELEASE	ASTRAZENECA LP
ESOMEPRAZOLE MAGNESIUM	NEXIUM 24 HR	TABLET, DELAYED RELEASE	ASTRAZENECA LP
LANSOPRAZOLE	PREVACID 24 HR	CAPSULE, DELAYED REL PELLETS	GLAXOSMITHKLINE CONSUMER HEALTHCARE
OMEPRAZOLE	OMEPRAZOLE	TABLET, DELAYED RELEASE	DEXCEL PHARMA TECHNOLOGIES LTD
OMEPRAZOLE	OMEPRAZOLE	TABLET, ORALLY DISINTEGRATING, DELAYED RELEASE	DEXCEL PHARMA TECHNOLOGIES LTD
OMEPRAZOLE MAGNESIUM	PRILOSEC OTC	TABLET, DELAYED RELEASE	ASTRAZENECA PHARMACEUTICALS LP

difficult for routine dissolution testing. Hence, using simpler buffer systems as surrogate to produce equivalent buffer effects on drug dissolution remains preferred. Given inherent obstacles and drawbacks, each product has to be studied on a case-by-case basis.

Understanding the in vivo dissolution process may assist in setting clinically relevant in vitro dissolution testing methodologies. There is a major opportunity in utilizing bicarbonate-based buffers for in vivo predictive dissolution of EC dosage forms and further studies are still needed to assess its potential in a QC environment.

9. Disclosure

Gregory K Webster is an employee of AbbVie may own AbbVie stock. AbbVie helped sponsor and fund the study; contributed to the design; participated in the collection, analysis, and interpretation of data, and in writing, reviewing, and approval of the final publication. The other authors declare no conflicts of interest related to this work.

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