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Drug release from matrix tablets: physiological parameters and the effect of food

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Abstract

Introduction: As dissolution plays an important and vital role in the drug- delivery process of oral solid dosage forms, it is, therefore, essential to critically evaluate the parameters that can affect this process.

Areas covered: The consumption of food as well as the physiological environment and properties of the gastrointestinal tract, such as its volume and composition of fluid, the fluid hydrodynamics, properties of the intestinal membrane, drug dose and solubility, pK_a, diffusion coefficient, permeability and particle size, all affect drug dissolution and absorption rate. There are several dissolution approaches that have been developed to address the conditions as experienced in the in vivo environment, as the traditional dissolution being a quality control method is not biorelevant and as such do not always produce meaningful data. This review also describes the development of a systematic way that differentiates between robust and non-robust formulations by varying the effects of agitation and ionic strength through the use of the automated United States Pharmacopeia type III Bio-Dis apparatus.

Expert opinion: With the improved understanding of the physiological parameters that can affect the oral bioperformance of dosage forms, strides have, therefore, been made in making dissolution testing methods more bio- logically based with the view of obtaining more in vitro–in vivo correlations.

Keywords: agitation rate, biodissolution, drug release, effect of food, hydrophilic matrices, ionic strength

Highlights

- Understanding all the physiological parameters can serve as a basis for designing dissolution testing methods and systems that can more fully represent the gastrointestinal (GI) tract in humans and allow more *in vitro-in vivo* (IVIVC) correlations to be obtained thereby improving the oral bioperformance of dosage forms.
- Simulation of GI conditions is essential to adequately predict the in vivo behaviour of drug formulations.
- The choice of appropriate media for in vitro tests is crucial to their ability to correctly forecast the food effect in pharmacokinetic studies.
- Several methods of dissolution testing have been conducted and are still ongoing that seek to further understand and develop media and dissolution methods to better represent the in vivo conditions and to aid in the better prediction of in vivo drug release.
- Systematic change of agitation method and ionic strength evaluation may be used as additional tools in allowing for the identification of potential fed and fasted effects on drug release from hydrophilic matrices in the drive for developing dissolution methodologies that are more relevant in helping to achieve more IVIVC.

1. Introduction

Dissolution plays a very important and critical part in the drug delivery process as pharmaceutical solid oral dosage forms must undergo this process in the gastrointestinal (GI) tract before they can be absorbed and reach the systematic circulation. An efficient understanding of this dissolution process allows the development of dosage forms that are robust and can perform well. Dissolution testing is a quality control (QC) procedure employed in pharmaceutical product development and is of a great importance in the selection and facilitation of candidate formulations for *in vitro-in vivo* correlations (IVIVC) [1,2].

Reproducible and reliable correlations between in vitro and in vivo human clinical studies remain a challenge to scientists due to several reasons. Human subjects for formulation development are almost impossible due to ethics. Extensive costs and completion of marketing timelines are also problematic [3]. There is, therefore, a need for developing and understanding in vitro drug dissolution models as they are very important. It is important to ensure that the developed in vitro methodology has the ability and power to predict in vivo characteristics. This approach serves as a valuable tool in the early stage of profiling lead compounds to optimise the drug products in the late stage of drug development.

The determination of the solubility of the active pharmaceutical ingredient (API) and the drug products' dissolution profile is to ensure a close link to the solubility and dissolution in vivo, thus enabling a predictive in vitro system for solubility and dissolution. The knowledge of in vitro predictive solubility and dissolution in establishing and optimising drug product compositions and manufacturing processes can be further used as input parameters for in-silico modelling and simulation. This in turn helps reduce guesswork and improves the prediction accuracy [3].

Drug dissolution and absorption rate are thus dependent on properties of the physiological environment and properties of the drug itself with parameters such as the dimension of the GI tract, volume and composition of fluid, the fluid hydrodynamics, properties of the intestinal membrane, drug dose and solubility, pKa, diffusion coefficient, permeability and particle size all playing a key role [4]. In an attempt to bridge the gap between the in vitro and in vivo dissolution and absorption, the Biopharmaceutics Classification System provides guidance for predicting in vivo performances of drug substances based on the drugs solubility, permeability and *in-vitro* results from testing [5]. This review looks to summarise the physiological parameters that can affect drug release, discuss food effect on drug release and some of the dissolution methods used in trying to predict in vivo dissolution behaviour. This review will also look at a simple in vitro methodology developed by Asare-Addo et al. by varying agitation in ascending and descending sequences as a systematic process for potentially discriminating fasted and fed states to represent the various levels of agitation to mimic the fed and fasted states in man [6-10].

2. Physiological parameters

In the GI tract, the small intestine comprises of the duodenum, jejunum and ileum. The large intestine is divided into the cecum, colon and rectum. Ritschel [11] reported that the jejunum and ileum had similar absorbing areas and that these areas were significantly larger than the other segments of the GI tract. Also, generally, there is a better absorption of drugs in the upper GI tract and this has to do with the significant higher surface absorbing area in the upper GI tract. Drug transport across the intestinal epithelium in each segment of the GI tract is non-uniform and tends generally to decrease as the drug moves along the GI tract.

Absorption/permeation is what ultimately carries orally administered drugs into the intestinal membrane to be transferred to the bloodstream. As drug absorbance/permeation is different

in the different parts of the GI tract, the residence time of a drug in each segment of the GI tract can significantly affect the performance/absorption/permeability of an oral controlled dosage form.

The GI fluid is a complex and dynamic mixture of components from a number of sources within the GI tract and its composition can have a huge impact on the solubility and dissolution of poorly soluble APIs [12]. Gastric fluid is a com- position of saliva, gastric secretions, dietary food and liquid and secretions from the liver [4]. The composition of the fluid in the upper small intestine, however, is made up of chime from the stomach, secretions from the liver, the pancreas and the wall of the small intestine. This fluid composition is affected by fluid compartmentalisation, mixing patterns, permeation through the intestinal wall and the transit down the intestinal tract. Physiological characteristics such as pH, bile salts, gastric-emptying rates, buffer species, hydrodynamics, shear rates and intestinal motility can significantly impact dis- solution and absorption [4,13]. The methods for the aspiration of gastric or intestinal fluids and characterising them are vast and well documented in literature. This is not covered in this review and interested readers are directed to Bergstrom et al. [12] and all the references therein.

The pH in the GI tract is a function of many variables such as time, prandial condition, meal volume and content and the volume of secretion. This varies along the GI tract (Figure 1). The pH strongly influences the solubility of weak electrolytes by determining their ionisation states. When a pH is such that a drug is in its ionic form, the drug behaves like a strong electrolyte and the drugs solubility becomes usually high as compared to its non-ionised form [4]. Drug products with pKa values especially in the physiological range thus have dis- solution rates that are affected greatly by pH. Sheng et al. [14], Li et al. [15] and Phaechamud and Ritthidej [16] have all showed this to happen for different types of dosage forms such as immediate and modified release.

Typical median values for the gastric pH in the fasted state ranges between 1 and 2 with pH values of 1.7 -- 3.3 (median of 2.5) also reported [17-24]. Dressman et al., [24] interestingly found that 68% of the time, gastric pH remained below pH 2 and that for 90% of the time, it remained below 3. Fasted pH values for the upper small intestine have been reported to range between 4 and 8 with typical values around 6.5 [23, 25-27]. Others have reported pH of the duodenum to range between 5.6 and 7 with median values of 6.3 [19,22,26,28-31]. The pH values ranging from 6.5 to 8 in ileum have been reported in the fasted state [32,33], whereas pH values for the jejunum ranging from 6.5 to 7.8 with a median value of 6.9 have been reported [20]. Shortly after ingesting a meal, gastric pH values have been shown to rise to about 6 -7 which decreases back to fasting levels again after about 1- 4 h depending on conditions such as meal composition, amount and pH [21]. Gastric pH in the fed state ranges from 2.7 to 6.4 [21,22]. Typical median values are around 5 during the later postprandial state for the small intestine [33,34]. Pre- treatment of a meal in the stomach means that the pH of the intestinal fluids is not as affected to the same extent as gastric fluids as such fed state fluid in the duodenum have been reported to be between 5.4 and 6.5 [12,19,21,22,28,35-37]. Persson et al. [38] found the pH in fed jejunal fluids to be 6.1. Buffer capacity of the GI fluid is also known to affect the dis- solution rate. This particularly is the case for ionisable drugs. The higher the buffer capacity, the more the buffer influences the pH changes at the drug--liquid interface [39]. Fadda et al. [40] studied the solubility of two drugs with different physicochemical properties in luminal fluids obtained from various regions of the human GI tract to determine the most important luminal parameters influencing their solubility. They found the solubility of 5-aminosalicylic acid to significantly change down the GI tract with buffer capacity being the most important determinant of its solubility. They found buffer capacity to increases down the GI tract [40]. This was, however, from one patient suffering from polyposis [40]. There was a buffer capacity (mM/L/DpH) transition from 6.4 in the

ileum to 28.6 in the ascending colon, reaching 44.4 mM/L/DpH in the transverse/descending colon. They attributed the high buffer capacity of colonic fluids to the presence of short-chain fatty acids (SCFAs), which predominantly consisted of acetate, propionate and butyrate, produced by the breakdown of carbohydrate by anaerobic microflora. Cummings et al. [41] measured the levels of SCFA from small bowel contents weighing 291 g (range = 156 -- 508 g) and large bowel contents weighing 174 g (range = 83-421) from six subjects after autopsy was done on average 3 h 20 min after death and showed a decrease to occur from the ascending colon (123 ± 12 mmol/kg) progressively to the transverse (117 ± 9 mmol/kg) and descending colon (80 ± 17 mmol/kg). The concentration of SCFA, however, appears to increase despite their decreasing levels in the large intestine as a result of the lower proportion of fluid in the luminal content [40]. Another explanation is that, the absorption of SCFA is linked to the accumulation of bicarbonate in the lumen, which is explained by the presence of an acetate-- bicarbonate exchange at the surface of the mucosal cells [40,42-44]. Three studies determined the buffer capacity of gastric fluid to range between 13.3 and 19.0 mM/DpH with a median value of 14.3 [12,20,22,26]. Buffer capacity values ranging from 2 to 13 mM/L/pH have also been reported for the small intestine in the fasted state [26,38]. The buffer capacity is higher in the fed state as compared to the fasted state for gastric (19.5 mM/pH), duodenal (24 -- 30 mM/pH) and jejunal fluids (13.9 mM/pH) [12,19,22,37,38,45].

Reported values in the fasted for gastric osmolarity, duodenal fluids and the fluids in the jejunum have been reported to range between 119 and 221 mOsm with a median value of 202 mOsm, 137 and 224 mOsm with a median value of 197 mOsm and 200 and 300 mOsm with a median of 280 mOsm, respectively [12,18,20,22,23,26,28,45,46]. Values in the fed state for gastric osmolarity are to be 388 mOsm, with duodenal fluids osmolarity ranging from 276 and 416 mOsm [12,19,22,28,45]. Just like the buffer capacity, osmolarity values

tend to be higher in the fed state as compared to the fasted state. Jantratid et al. [47] showed that the osmolarity in the distal duodenum increases slightly after a meal intake during the first 120 min and then gradually equilibrates to isosmotic. Clarysse et al. [28] also found variability in osmolality to be higher in the fed state as compared to the fasted state. They also found fasted state values to be hypo-osmotic or close to isosmotic with a median value of 224mOsm/kg. They found that in fat-enriched fed states or fed states, values suggested hyperosmoticity during the first 3 h postprandially.

Viscosity is quite complex due to the Newtonian or non- Newtonian behaviours of either simple fluids or biological fluids. For the reason of complexity, measured values of GI fluid viscosity for humans in the fed and fasted states are very limited [48]. Echo-planar MRI was used in humans to monitor the changes in a viscous meals viscosity by Marciani et al. [49] and they found significant reduction in the meals viscosity with time due to dilution by the gastric juice [49]. Viscosity is also affected by pH in addition to soluble meal content and concentration [4]. Test meals containing dietary fibres are administered that have viscosities ranging from 10 to > 10,000 cP [4,48,49]. Authors like Mudie et al., Malkki and Abrahamsson et al. have characterised typical meals to have viscosities ranging from 10 to 2000 cP [4,50,51].

The volume of liquid in the stomach depends greatly on the amount of liquid ingested, the rate and amount of secretions and the rate at which it empties into the small intestine [4]. This has been extensively reviewed by Mudie et al. [4]. The volume of liquid in the GI tract can affect the amount and potentially the concentration of the dissolved drug. Kwiatek et al. [52] attributed a progressive decrease in initial gastric volume as a function of meal volume to a larger portion of liquid nutrient passing through the small intestine during a rapid early emptying phase. They also found a further increase in the gastric volumes due to gastric

secretions before the volumes started to decline. They found that this increase was independent of caloric load and greater for smaller rather than the larger infused meals [52].

The hydrodynamics of the GI are partially dependent on the contractions of the stomach and small intestine as well as the amounts of liquids and solids present [4]. These contractions cause motility that propel food through the GI tract in a peristaltic motion, mixes chime within the GI lumen and juxtaposes chime with the brush border of the enterocytes [53]. The autonomic nervous system and various digestive system hormones control the contractions [4,53]. These contractions in the fasted state are characterised by cyclic fluctuations. This cyclic contractility is called the migrating motility complex (MMC). The MMC in the fed state is replaced by regular, tonic contractions that propel food towards the antrum and mix it with gastric secretions [54,55]. The GI motility can thus affect or influence gastric-emptying rates, mixing patterns of solids and liquids in the stomach and intestine and intestinal transit times. The issue of the GI hydrodynamics is quite complex and is not fully covered in this review and as such interested readers are referred to a review by Mudie et al. and all the references therein [4].

Other physiological factors include the surface tension which can affect dissolution by influencing the wetting of dos- age forms, bile salts and phospholipid compositions [4,12,56]. Surface tension values range from 31 to 45 mN/m with a median value of 36.8 in the fasted gastric juice, whereas similar values of ~ 30 mN/m have been reported or observed in all GI compartments in the fed state [17,20,22,46]. Duodenal surface tension in the fasted state is reported to be in the same range as that in the gastric juice. Due to secretion of bile salts from the gall bladder, surface tension in the jejunum tends to be lower as to that of the stomach and duodenum [12,20]. Higher surface tensions means decreased wetting of dosage forms [56]. For interested readers, the influence of bile salts, phospholipids and their compositions in the fed and fasted states are detailed in Bergstrom et al. [12] and all the references therein.

Dissolution and absorption is also affected by the temperature of the GI fluids. The average GI temperature is generally considered to be 37 °C. Temperature can affect the diffusion coefficients of the drug and buffer species, the drug solubility and also the bulk drug concentration [4,57].

The transit or residence time of a drug in the intestinal tract is a strong determinant of dissolution and absorption [4]. This does affect the amount of time a drug substance has to dissolve and absorb in the GI tract. Factors such as gastric- emptying rate and flow rate can affect the transit time of a dosage form in different segments of the GI tract and this can vary significantly for just one individual as was found by Weitschies et al. [58]. McConnell et al. [59] also found variability in the transit time (1.5 - 5.4 h with a mean value of 3.2 h) for a single individual on eight separate occasions after 1 -1.4 mm ethylcellulose-coated pellets were administered. Coupe et al. [60] reported transit times of 2.2 - 5.9 h for pellets and 0.9 - 6.2 h for 11.5 mm tablets in the small intestine. Intestinal transit time is greatly important for dosage forms that are not fully absorbed as a change in the contact time with the absorption area can result in a change of the fraction or amount of the drug absorbed. DeSesso and Jacobson [53] showed that although generally speaking, an increase in transit time will lead to an increase in the absorption of poorly or incompletely absorbed drugs, absorption can be decreased in cases where the transit time is prolonged owing to an inhibition of the smooth muscle motility due to a decrease in the agitation of the unstirred layer. Small intestinal transit time is more reproducible and has a range of about 3 - 4 h [1,61]. Colonic transit time, on the other hand, is highly variable and is typically 10 - 20 h [62-64].

3. Dissolution media

An understanding of all these physiological parameters can serve as a basis for designing dissolution testing methods and systems that can more fully represent the GI tract in humans

and allow more IVIVC to be obtained, thus improving the oral bioperformance of dosage forms [65]. Currently, none of the guidance or international pharmacopoeias describes media to simulate food effects. Thus, water, simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) are still the most commonly used dissolution media. These have been described as early as 1955 [4]. Compendial dissolution media usually used are SGF, SIF, and water. SGF of the United States Pharmacopeia (USP) is the traditional medium to simulate gastric conditions in the fasted state. This medium has a pH of 1.2 and contains hydrochloric acid, sodium chloride, pepsin and water [66]. The SIF, a medium that was first described as a standard test solution in the USP > 50 years ago is the medium frequently used for the simulation of the small intestinal conditions in the fasted state [66]. The only parameter that has been changed is the pH of the medium. As it was assumed that the pH in the small intestine was very close to blood plasma, the pH of SIF was initially set at 7.5. This, however, was revised to pH 6.8, to match the typical measured pH values in the mid-jejunum [67]. This was important as the use of an in vitro medium with an unsuitably high pH would probably lead to false-positive results as in the cases for poorly soluble, weakly acidic drugs and enteric-coated dosage forms.

For the sole purpose of simplicity, water is a medium that is widely used for QC purposes. Due to many formulations being intended to be ingested with a glass of water, water could be argued as being physiologically relevant. As the pH of water can vary at its source and as water has no buffering capacity, a more biorelevant media could be appropriate [66]. It is important to bear in mind that all these compendial media do not take into account key parameters of the changing GI environment after food intake and are, therefore, not very useful in helping to predict food effects. It is, therefore, crucial to run dissolution tests under conditions that closely resemble the key parameters of human GI physiology. The addition of physiologically relevant dissolution media to the choice of adequate equipment and

appropriate instrument parameters are of great importance since our knowledge of the GI physiology has increased over the years. This led to the development of biorelevant dissolution media (BDM) to simulate conditions in the stomach and small intestine before and after meals over the past 10 - 15 years [66]. This BDM often includes different additives which allow the fasted and fed states in humans to be mimicked and can range from being very simple to very complex [47,68]. The fasted state SGF (Table 1) containing pepsin and low amounts of bile salt and lecithin was developed by Vertzoni et al. [69]. This was later updated to better comply with physiologically measured values of osmolarity (Table 1) [70,71]. The fasted state simulating intestinal fluid (FaSSIF) was developed to simulate fasting conditions in the proximal small intestine (Table 1) [66,68]. This medium contains bile salts and phospholipids (lecithin) in addition to a stable phosphate buffer system that results in a pH representative to values measured from the mid-duodenum to the proximal ileum. The bile salts and lecithin facilitate the wetting of solids and solubilisation of lipophilic drugs into mixed micelles, thereby considerably enhancing the dissolution of poorly soluble lipophilic drugs. Sodium taurocholate is a representative of bile salt in the media because cholic acid is one of the more prevalent bile salts in human bile [72-74]. FaSSIF was updated in 2008 by changing the buffer to maleic acid to comply with the pH of the fasted and fed state (Table 1) [13,47,68]. As the ideal, medium representing initial gastric conditions in the fed state should have similar nutritional and physicochemical properties to that of a meal, for example, the standard breakfast recommended by the US FDA (1 English muffin with butter, 1 fried egg, 1 slice of cheese, 1 slice Canadian bacon, 1 serving of hash browned (fried shredded) potatoes, 6 ounces of orange juice, 8 ounces of whole milk, carbohy- drate 73 g, 292 kcal, 1222 kJ, 45% of calories, protein 29 g, 116 kcal, 485 kJ, 18% of calories, fat 27 g, 240 kcal, 1004 kJ, 37% of calories) [75] to study the effects of food in BA and bioequivalence studies and both standardised homogenised cows' milk with a fat

content of 3.5% (whole milk) and Ensure® Plus have a similar composition to a breakfast meal with respect to the ratio of carbohydrate:fat:protein, they are used to simulate fed state gastric conditions. Drug release or dissolution in the proximal part of the small intestine is highly dependent on the drug being dosed in either in the fed or fasted state [66]. After ingesting a meal, there are changes that occur in both the hydrodynamics and the intraluminal volume. The pH of the chyme after a solid meal is lower than the intestinal fluid pH in the fasted state, whereas buffer capacity and osmolality show sharp increases [66,76]. The secretion of bile is also a factor as well as interactions with the drug and ingested components [66]. The fed state simulating intestinal fluid (Table 1) is used to help reflect conditions after food ingestion in the upper small intestine [66,68]. This BDM often has a substantial impact on the apparent solubility of molecules with solvation limited solubility. That is to say, the poor water interactions of some molecules are improved through wetting and solubilisation by additives such as surfactants and/or lipids [77]. Other media developed and used include the Copenhagen fasted and fed media in which the pH is kept constant and the male- ate is used as a buffering component (Table 1) [78-80]. Studying the dissolution rate in different BDM and using the different experimental results obtained to select compounds to advance further development is one way to speed up the assessment of in vivo performance. The use of a 'snapshot medium' as pro- posed by Jantratid et al. to simulate both gastric and intestinal fluids during different stages after a meal consumption has some potential drawbacks, including several 'snapshot' dissolution media being needed to reflect changes in the aspirate compositions during digestion in the small intestine [47]. Despite these drawbacks, they make dissolution testing more physiologically relevant and can be used in predicting formulation performance and food effects in vivo [47,81,82].

4. Effect of food on drug relelase

The various types of available oral extended-release (ER) dosage forms pose a challenge in being able to accurately predict their *in-vivo* behaviour. An ideal oral ER dosage form should be one that provides a consistent drug release over the entire dosing interval, regardless of administration in relation to food intake. It is widely known that substituting one ER formulation for another or administering the same formulation under varying dosing conditions (e.g., fasted vs fed state) can have unexpected results. Resultant effects from this range from 'dose-dumping' to sub-therapeutic plasma levels [83-85].

Most oral controlled-release formulations are designed to release all drugs within 12 - 18 h, because oral dosage forms are removed from the GI tract usually after a day. The presence of food in the stomach tends to delay gastric emptying. In the fasted state, MMC greatly regulates gastric-emptying rate, whereas in the fed state, gastric emptying is influenced by low-amplitude contractions as well as pyloric resistance and duodenal feedback mechanisms [4]. There is a variation in the volume of liquid in various compartments of the GI tract and between individuals. This variation also occurs with time, prandial state, the amount of liquid ingested, the volume of gastric and pancreatic secretions, gastric-emptying rate, intestinal transit time and uptake and efflux of liquids along the GI membrane [4]. Postprandially speaking, gastric emptying is largely dependent on meal size and composition [54]. MMC can be interrupted when nutrient liquids or solid meals are ingested due to a feedback mechanism in the duodenum. A study by Dressman showed a 25% glucose solution to empty in 75 min [54]. An examination of the ratio of the initial postprandial liquid volume in the stomach to the volume of the infused meal (nutrient drink) by Kwiatek et al. [52] found a decrease in the postprandial liquid volume in the stomach to occur as a function of the infused meal volumes (ratios of 1.25, 0.95, 0.92, and 0.83 for 200, 400, 600 and 800 ml meal volumes, respectively). The same authors also showed that in the later postprandial period,

when gastric emptying was at a steady rate, both meal volume and calorie load affected the rate of gastric emptying, with the rising or increasing the meal volume producing a significant increase in gastric emptying ($p < 0.001$) and rising or increasing calorie load being associated with a significant decline in gastric emptying ($p < 0.001$) [52]. A summarisation by Dressman [54] of the typical solid-meal half time in humans found them to range from 70 to 130 min [54]. Among different foods also, carbohydrates and proteins tend to be emptied from the stomach in < 1 h [11].

As food intake triggers several secretions in the small intestine, the composition of the fed and fasted state intestinal fluids can vary greatly. The differences in bioavailability when drug is administered in fed state versus the fasted state could be partly attributed to this compositional difference of the fed and fasted intestinal fluids [4]. This is as a result of interactions which may occur between the oral formulation of the drug and the food administered [86-90].

After a meal, the gastric-emptying rates for liquids and sol- ids are much slower in comparison to fasting conditions [91]. This is true also when drug is taken after food consumption. This is evident by the reduction in plasma peak concentration which now tends to occur at later times and also an increment in lag times in plasma concentration-time profiles. In cases where a rapid onset is required or high peaks are needed to reach a therapeutic effect, this reduction in the absorption of drug could be critical or fatal [92]. Abrahamsson et al. showed nifedipine's dosage form to erode faster in the GI tract postprandially when compared under fasting conditions. Felodipine's dosage form, on the other hand, was hardly affected [93,94]. The physical and physiochemical factors tested with values obtained were pH (2.3 - 6.8), ionic strength (0.08 - 0.2 M), surface tension (41 - 72 mN/m), osmolarity (190 - 600 mOsM) and viscosity (1 - 280 mPas). It was observed that these values were within the limits or ranges of previous work done [23,95]. The different

variations produced by the factorial design used in this study affected the erosion rates of the dosage forms of the two drugs. However, it was nifedipine that was greatly affected. It was also noted that an increase in urea and hydroxypropyl methylcellulose (HPMC) had no effect on felodipine but had substantial effect on nifedipine. Other factors such as pH, salt concentration and the use of surfactant, although causing erosion to a minor degree was disregarded together with the use of urea (as the osmolarity controlling agent) and HPMC (as the hydrophilic matrix former) as the explanation for prandial effects. This was because the administration of nifedipine after a meal enhanced the erosion of the drug's dosage form [87].

Another potential reason for a slower absorption with food could be the effects on the drug dissolution from a solid dosage form. This was, for example, suggested as the cause of a food effect obtained for a tablet formulation, whereas no food effect was obtained for an oral solution in a paracetamol bioavailability study [96]. As these unwanted side effects may result in severe risks for the patients, it is thus highly important to be able to forecast the in vivo release rates under various dosing conditions using in vitro data. However, for some lipophilic drugs, co-administration with a meal has been shown to increase bioavailability as compared to the fasted state. Work done by Sunesen et al. [97] showed that the bioavailability of the poorly soluble drug danazol was threefold higher when taken with a meal high in lipid content as compared with 200 ml of water. Leyden [98] showed the oral bioavailability of tetracycline hydrochloride to be negatively affected due to the chelation of the drug with food components. The enhanced solubilising capacity of the intestinal fluids due to bile and pancreatic secretions and the presence of exogenous lipid products are attributed to the increased bioavailability for some drugs in the fed sate [45]. Food intake can influence the following: rate of drug release from the dosage forms, the rate of drug absorption, the amount of drug absorbed or all of these three simultaneously [99]. The intraluminal content, which itself is at least partly determined by the size and the composition

of the co-administered meal, can also affect the rate of drug release from various ER formulations. 'Positive' and 'negative' food effects can result depending on the type of dosage form and the intraluminal conditions.

A loss of the integrity of matrices or coatings (i.e., devices that control drug release of ER dosage forms) results from positive food effects. This can represent a great risk for the patient, especially in cases when a large amount of the dose is dumped within a short period of time [100,101]. Fats, high concentrations of bile components and pH changes [101,102] are typical triggers for increased drug-release rates. These same factors can cause negative food effects for reasons such as adsorption of food contents, a decrease in luminal diffusivity due to an increase in viscosity in the upper GI tract and changes in the absorption rate due to food-induced changes in GI motility and passage time along the GI tract [103,104].

Abrahamsson et al. [92] investigated if food components, as represented by a multicomponent nutritional drink for tube feeding, could affect tablet disintegration of standard tablets in vitro as well as in vivo. They found that tablet disintegration was delayed between 5 min and > 1 h in the simulated gastric fed medium as compared to a simple buffer. They found this effect was dependent on the tablet composition [66]. On administering nutritional drinks to three Labradors, a similar delay in tablet disintegration was also found in vivo as observed by removing the tablet from the stomach at different times through a gastric fistula. This delay in tablet disintegration appeared to be caused by a precipitation of a film, mainly consisting of protein, on the tablet surface as indicated by disintegration studies with pure nutrients. The drug dissolution of a soluble compound, metoprolol tartrate, from a standard tablet was also strongly delayed in the simulated fed medium. Lentz [90] has also reviewed some of the current methods for predicting human food effect.

Other factors which may also affect the rate at which a drug is released from its hydrophilic gel matrix may include the formulation composition [105-108], the physiochemical properties of the drug and polymer [109-114] and the processing and compaction conditions [115-117]. All these factors can influence the choice of the polymer viscosity and chemistry used.

An ideal ER product should demonstrate complete bioavailability, minimal fluctuations in drug concentration at steady state, reproducibility of release characteristics independent of food and minimal diurnal variation. In vitro dissolution studies under simulated fasting and fed conditions is one approach to get better understanding of the potential for food interactions on dissolution of immediate release formulations. In addition, establishment of in vivo predictive in vitro methods is importance in developing new products as well as in evaluating changes of compositions and manufacturing procedures.

5. Dissolution apparatuses

Drug molecules are required to be present in a dissolved form in order for them to be transported across biological membranes. The process by which this happens is known as dissolution. Dissolution can, thus, be defined as process enabling drug molecules to leave its solid phase to enter into solution [118]. The first proposed basic transport-controlled model for solid dissolution was made by Noyes and Whitney in 1897 in which they suggested that when surface area is constant, the dissolution rate is proportional to the difference between solubility and the bulk solution concentration [119]. This is depicted as Equation 1.

solubility and the bulk solution concentration [119]. This is depicted as Equation 1.

$$\frac{dM}{dt} = \frac{DA}{h} \times (C_s - C_b) \qquad \text{Equation 1}$$

Where;

dM/dt = rate of dissolution (mg/s)

D = diffusion coefficient (cm^2/s)

h = thickness of the diffusion layer (cm)

A= surface layer of drug particles (cm^2)

C_s = Saturated concentration of drug in the diffusion layer (mg/ml)

C_b = concentration of drug in the bulk fluid at time t (mg/ml)

The above equation can be affected by properties of the drug substance, drug product and GI tract, as discussed previously. Dissolution testing is a QC procedure employed in pharmaceutical product development to assist in the selection of a candidate formulation. In research, the dissolution testing method helps detect the influence of critical manufacturing variables such as the effect of binders, mixing, granulation, coating, excipients, comparative studies of different formulations, IVIVC and possibly as an in vivo surrogate under strictly defined conditions. It is, therefore, apparent that sensitive and reproducible dissolution data derived from physicochemically and hydrodynamically defined conditions are necessary in order to compare various in vitro dissolution data and to be able to use such results as a surrogate for possible in vivo bioavailability, bioequivalence testing and IVIVC [1,2,120-130].

The four types of compendial dissolution apparatuses used for testing the oral dosage forms include the USP I (basket) and the USP II (paddle) apparatuses which can be successfully used for QC purposes, such as lot-to-lot quality testing [65]. These methods, however, are not

physiologically relevant as they use large volume of media (500 - 1000 ml), enable the use of one dissolution medium at a time and have hydrodynamics that do not resemble the GI tract [51,65]. Several studies have investigated the flow pattern of the dissolution apparatuses USP I (basket) and USP II (paddle) at various speeds by using computational fluid dynamics [131]. However, the hydrodynamics of these systems are far from that calculated for the human stomach [132]. In fact, the drug dissolution from a solid formulation is greatly influenced by fluid flow and mechanical forces, and this must be taken into account when designing an in vitro method which aims to predict the in vivo behaviour of a formulation [133]. It has been shown in some studies that the complex hydrodynamics and three-dimensional fluid flow pattern produced by the USP paddle apparatus within different regions of the dissolution vessel varies significantly with a relatively more stagnant region at the bottom portion of the vessel [134,135].

Strides have been made in making dissolution testing methods more biologically based. This shows the significant progress that has been made since the first compendial dissolution test (USP I apparatus) was introduced in 1970 Consequently, to mimic and more closely reflect the possible in vivo dosage form surface exposure, have reliable dissolution data and be able to discriminate between release behaviour of various modified release formulations, it is therefore important that we gain a better understanding of the role of hydrodynamics in relation to delivery system and release mechanisms necessary for the development of alternative dissolution methods [136, 137]. The other two compendial dissolution apparatuses are the USP III (reciprocating cylinder, Bio-Dis) and IV (flow-through cell) which offer the advantages of determining release from the dosage form under various, consecutive conditions simulating the GI physiology. The release experiments performed with Bio-Dis and flow-through cell can be set up with a series of dissolution media in one single run, thus making it possible to mimic the “history” of the dosage form as it passes through the GI tract

and to generate an IVIVC on an a priori basis [65, 82, 138, 139]. The USP III apparatus provides a means of stepping through different buffers and has been reported to be a very useful technique for extended release dosage forms [138-140]. The Reynolds number is a non-dimensional parameter in fluid dynamics which provides an estimate of the ratio of fluid inertia (or flow acceleration) to frictional force in the flow around a dosage form [51,140]. The hydrodynamic conditions generated in a USP II apparatus can be compared to the expected in vivo hydrodynamics by using the Reynolds number and the Reynolds numbers for bulk flow in the USP II apparatus are around 2000 [141] which is significantly greater than the physiological range (0.1 - 30) as suggested by Abrahamsson et al. [51,140]. Although, there are no reported values describing the Reynolds numbers for bulk flow in the USP III apparatus, Jantratid et al. [47] reported the hydrodynamics produced by the USP III to be more favourable than those produced by the USP II apparatus when correlating the performance of lipid-based dosage forms in the fed-state stomach. The USP IV apparatus is reported to provide hydrodynamic conditions with a Reynolds number < 30 close to those suggested for the in vivo range and can be used in assessing the performance of ER dosage forms in response to changing pH or different biorelevant media [140,142].

Numerous other *in-vitro* test methodologies have been developed by scientists in an attempt to understand and replicate the complicated processes of in vivo drug dissolution. Authors such as Carino et al. [143], Gao et al. [144] and Gu et al. [145] have developed dissolution apparatuses that better capture aspects of the physiological environment as compared to the USP tests. For example, Gu et al. modified the conventional six-vessel USP dissolution system to a multi- compartment dissolution system to include a ‘gastric’ compartment, an ‘intestinal’ compartment, an ‘absorption’ compartment and a reservoir to simulate the dissolution and absorption in the GI tract [145]. Carino et al. developed an automated artificial stomach-duodenum model to simulate dog physiology in the fasted state [143]. By

doing so, they obtained excellent estimations of the relative bioavailability of carbamazepine crystal forms. Gao et al. also developed a fast, easy to use and material sparing in vitro dual pH-dilution method aimed at mimicking the physiologically relevant pH, dilution volumes and residence times experienced by a drug formulation during GI transit in rats [144]. This dynamic process provides a better representation of the transit of the drug formulation through the GI tract, which more closely captures the kinetic aspects of the actual in vivo drug release process. Garbacz et al. have also showed diclofenac and nifedipine drug dissolution profiles to be predicted using a dissolution apparatus that mimics in vivo physical stresses [146,147]. Kostewicz et al. [148] also developed a two-compartmental apparatus using a peristaltic pump using fasted and fed state-simulated media. Their sampling was performed manually with a syringe filtration step and a high- performance liquid chromatography analysis. Dilution of the duodenal medium by the inflowing gastric medium was, however, left unaddressed. Also, pH was also not raised back to the original value as it was maintained only by the action of the contained buffer. In the second apparatus, however, pH, volume and the composition of the duodenal fluid were all left without intervention [65,148]. Psachoulias et al. [149] presented an improved method, where although a gastric and a duodenal compartment were used, the dilution of the duodenal fluid which was the FaSSIF V2 plus was compensated by an inflow of a concentrated medium from a third vessel. The dynamic gastric model as developed by the Institute of Food Research in Norwich, UK, which consists of two sections simulating the fundus and antrum, has been used by Vardakou et al. [150,151] and Mercuri et al. [152] in comparison to the compendial methods of dissolution to try and predict in vivo performance of oral formulations. This machine is also capable of processing homogenised meals and a duodenal compartment can also be added to the experimental process allowing this model to be a so far, unsurpassed artificial model of the stomach [65,153-155]. Several authors have also used a multi-compartmental

artificial GI system known as the TIM-1 which was developed by the TNO Nutrition and Food Research Centre in Zeist, The Netherlands, to try and establish a more accurate prediction of in vivo performance [156-159]. The TIM-1 consists of four interconnected compartments of the stomach, duodenum, jejunum and ileum that allow the simulation of the GI tract [65]. This apparatus maintains successive transport of chyme through its different compartments and ensures peristaltic movement, thus allowing the simulation of the physical forces applied in GI track [65,160]. Despite the TIM-1 model being full representative of the dynamic dissolution approach, its complexity means that there are laborious preparations and manipulations during experimentation, higher demands on maintenance than in the case of simpler instruments and long time is needed for one experiment (~ 1 whole day) and experiments can be quite costly [65]. These different dissolution models and several others, as reviewed by McAllister [140,] as such provide skilful approaches with the aim of reducing the number of experiments conducted *in-vivo*.

Drug release from oral ER hydrophilic tablet matrix formulations are governed by drug diffusion and/or erosion depending on the drug's solubility through the gel layer [161-164]. Factors that can affect the properties of the gel layer include the physiochemical properties of the drug and polymer, formulation composition, processing conditions and the environmental variables such as the characteristics of the GI fluids [106-110,114,115,165,166]. Two major properties of the GI fluids are ionic strength and pH [91,95,166]. These two proper- ties vary greatly along the GI tract under fasted and fed conditions [91,95,166]. These factors may affect the rate at which a drug is released from its hydrophilic gel matrix [6-10,165,167,168]. Mu et al. [166] investigated the influence of physiological variables, such as pH and ionic strength, on drug release from a polysaccharide matrix for controlled release and found pH to influence drug release from both extragranular and intra- granular heterodisperse polysaccharide-based controlled release system. This was especially the case for drug release

in the acidic media of pH ranging between 1.2 and 2.5 [166]. They also found that there were no significant differences in drug release in pH between 4.5 and 7.5 [166]. By using MRI to understand swelling dynamics of hydrophilic polymers that affect drug release at different pH and ionic strength, Mikac et al. [169] found the position of the swelling front of the matrix tablet to be the same, independent of the different xanthan gel structures formed under different conditions of pH and ionic strength. The position of the erosion front, however, was strongly dependent on pH and ionic strength, as reflected in different thicknesses of the gel layers that were obtained [169]. Kavanagh and Corrigan [170] observed the wet weight (reflecting swelling with time) versus time profiles of K100LV HPMC polymer to have large differences due to the media of various ionic strengths used (buffer, saline, acid and deionised water). The time to attain maximum wet weight tended to increase (from ~ 2 to 6 h) with increasing ionic strength of the medium and the erosion rate also decreased [170]. There was much of a less effect on HPMC K15M which is a higher molecular weight polymer. As a result of the polymer being non-ionic, it was concluded that the pH of the media used did not correspond or correlate with the observed effects. It was also observed that the dissolution medium uptake decreased linearly as ionic strength for all the HPMC polymers (K100LV, K4M and K15M) were increased. They also observed that at the same ionic strength and agitation (rpm), the erosion of the wet weight of the HPMC polymer K100LV in phosphate buffer was slightly lower than its erosion in saline. The reasoning behind this was attributed to the presence of both sodium and phosphate ions and their ability to greatly dehydrate more than if it was sodium ions present only [171]. It can, thus, be concluded that the ionic composition of the medium used can have an effect on the swelling and erosion behaviour of HPMC matrices, despite them being non-ionic polymers [172].

Asare-Addo et al. [6] introduced a simple method to differentiate between robust and non-robust or poor formulations. They evaluated the influence of agitation in *ascending and

**descending sequences as a systematic method of development process to potentially discriminate between fed and fasted states (*ascending order of agitation: agitation was increased by 5 dips/min [dpm] every time the cylinder containing the dosage form moved from one vial to the other. Thus, in pH 1.2 the agitation was 5 dpm, in pH 2.2 it was10 dpm, in pH 5.8 it was 15 dpm, in pH 6.8 it was 20 dpm, in pH 7.2 it was 25 dpm and in pH 7.5 it was 30 dpm. **Descending order of agitation: agitation was decreased by 5 dpm every time the cylinder containing the dosage form moved from one vial to the other. Thus, in pH 1.2 the agitation was 30 dpm, in pH 2.2 it was 25 dpm, in pH 5.8 it was 20 dpm, in pH 6.8 it was 15 dpm, in pH 7.2 it was 10 dpm and in pH 7.5 it was 5 dpm). Theophylline ER matrices containing hypromellose (HPMC K chemistry) were evaluated in media with a pH range of 1.2 -- 7.5, using an automated USP III apparatus (Table 2).

The results showed K15M and K100M HPMC tablet matrices withstood the extremities of agitation with similarity values ranging from 51 to 82 (Table 3). The uses of diltiazem hydrochloride and hydrochlorothiazide also showed agitation in ascending and descending forms for the K100M tablet matrices again to be resilient to such extreme agitations (f2 = 51 - 93, unpublished data) (Table 3). The authors then likened the various levels of agitations to the effects of different food components exerting its effects [6]. Abrahamsson et al. [92] showed the disintegration of a tablet with strong food effects to happen in the presence of single components of food in the following order: fat emulsion (F) > carbohydrate (C) > protein (P). A combination of all three components of food delayed the disintegration time by 33 min showing that the type and com- position of a meal to have critical effects on tablet disintegration as a result of food interactions [92]. Asare-Addo et al. [6] likened these different food components to the differing agitation rates applied to the HPMC matrices tested, suggesting that the fastest drug release profiles be attributed to the fat emulsion diet and the slowest to the combination of the three components of food. The same authors

developed the methodology further to include the effects of ionic strength. Ionic strength was studied over the range of 0 -- 0.4 M [166]. Theophylline blended with HPMC K4M, K15M and K100M all proved resilient at all the ionic strengths tested (f2 = 56 - 80) [8]. The poor solubility of the hydrochlorothiazide meant even the low viscosity HPMC K100LV tablet matrices also exhibited resilience against the varying ionic strengths [9]. The incorporation of diltiazem hydrochloride meant dissimilarity occurred even with the highest viscous HPMC K100M matrix tablets (Figure 2D) [9]. This was due to the cationic nature of the drug. As the tablet matrix moves from vial to vial a change in the hydration properties of the gel and thus a difference in the total solubility of the ionised and the non-ionised forms of the drug occurs. With a drug pKa of 7.7, it is important to note that the additional salt to increase ionic strength and those in the buffers potentially affects the ionisation constant thereby exerting a strong ionic effect on the diltiazem HCl dissolution as seen in Figure 2. For example, at an ionic strength of 0.001 M, morphine's pKa values were determined to be 8.13 ± 0.01 and 9.46 ± 0.01, whereas at ionic strengths of 0.15 M morphine pKa values were determined to be 8.17 ± 0.01 and 9.26 ± 0.01 at 25 C [173,174]. The varying ionic strengths were likened to low salt content and high salt content of food. K100M HPMC tablet matrices had the lowest drug release rate for all three model drugs and produced a strong gel layer suggesting high viscosity grades to perhaps be the best candidates for producing controlled release profiles that are less affected by food [7].

6. Conclusion

An understanding of all the physiological parameters can serve as a basis for designing dissolution testing methods and systems that can more fully represent the GI tract in humans and allow more IVIVC to be obtained, thus improving the oral bioperformance of dosage forms. Simulation of GI conditions is essential to adequately predict the in vivo behaviour of drug formulations. To reduce the size and number of human studies required to identify a

drug product with appropriate performance in both the fed and fasted states, it is advantageous to be able to pre-screen formulations in vitro. The choice of appropriate media for such in vitro tests is crucial for their ability to correctly forecast the food effect in pharmacokinetic studies. Several methods of dissolution testing have been conducted and are still ongoing that seek to further understand and develop media and dissolution methods to better represent the in vivo conditions and to aid in the better prediction of in vivo drug release.

The rationale behind the developed methodology of varying agitation in ascending and descending sequences using the USP III apparatus as a systematic process for potentially discriminating fasted and fed states was to represent the various levels of agitation to mimic the fed and fasted states in humans. Where the effect of ionic strength and pH of dissolution media on the model drugs' release from hypromellose matrix tablets were investigated, the evaluation of ionic strength showed that though this method could be an additional tool in allowing for foods with differing salt contents to be screened, considerations should also be given to the nature of the drug used. This was the case with the cationic drug diltiazem HCl. It was noticed that an increase in the ionic strength of the media used brought about a decrease in the drugs release. This, however, was not the case for the theophylline and hydrochlorothiazide tablet matrices. The resilient nature of the produced gel layer around the higher molecular HPMC tablet matrices indicates that these polymers might be the best candidates for producing release profiles less affected by potential food effects. Systematic change of agitation method and ionic strength evaluation may be used as additional tools in allowing for the identification of potential fed and fasted effects on drug release from hydrophilic matrices in the drive for developing dissolution methodologies that are more relevant in helping to achieve more IVIVC.

7. Expert opinion

To reduce the size and number of human studies required for identifying a drug product with appropriate performance in both the fed and fasted states, it is advantageous to be able to pre-screen formulations in vitro. The choice of appropriate media for such in vitro tests is, therefore, crucial in their ability to correctly forecast the food effect in pharmacokinetic studies. With the improved understanding of all the physiological parameters that can affect the oral bioperformance of dosage forms, strides have, therefore, been made in making dissolution testing methods more biologically based with the view of obtaining more IVIVC. These dynamic dissolution systems are often expensive and can be time-consuming. The rationale behind the developed methodology of varying agitation in *ascending and **descending sequences using the USP apparatus III as a systematic process for potentially discriminating fasted and fed states to represent the various levels of agitation to mimic the fed and fasted states in humans presents a cost-effective way of conducting these tests. However, the biggest challenge is that further work is needed to understand which food components represent which levels of agitation. With the several dissolution testing methods being conducted and are still ongoing, it is hoped that a further understanding and development of media and dissolution methods that better allows to represent the in vivo conditions and to aid in the better prediction of in vivo drug release can be developed.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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Figures and Tables

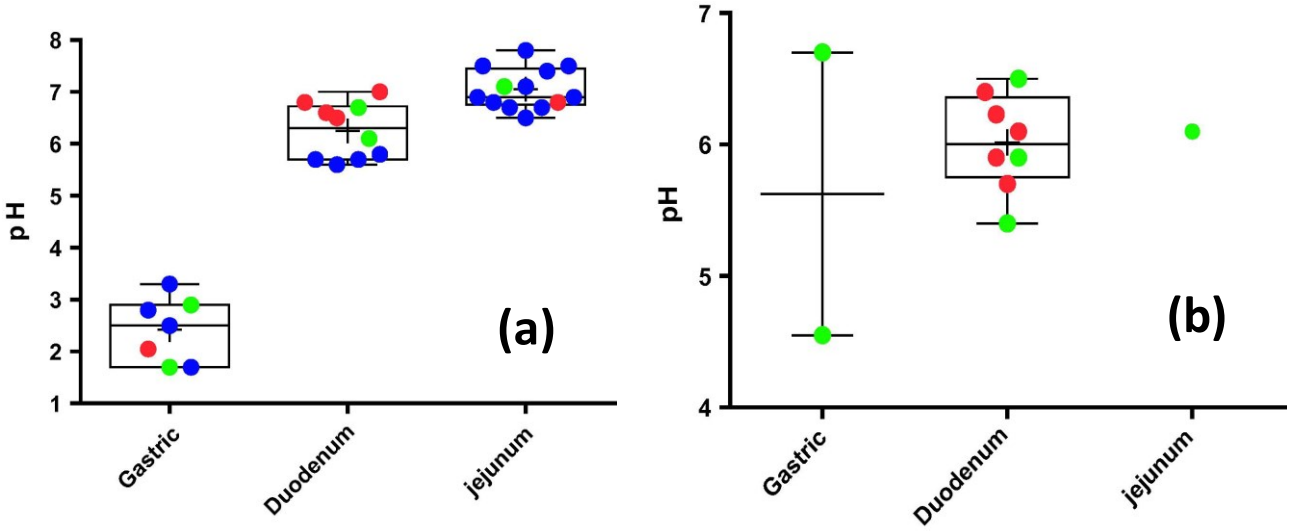

Figure 1. (a) pH measured in fasted gastric, duodenal and jejunal fluids. (b) pH in fed gastric, duodenal and jejunal fluids. Box-whisker plots show minimum and maximum values, as well as 25, 50 and 75 percentile. The cross indicates the mean value. Each data point represents a group of participants ($n = 1\text{-}10$ coloured red, $n = 11\text{-}20$ coloured blue, and $n > 20$ coloured green) as reported in one publication (Figure adapted from ref [12])

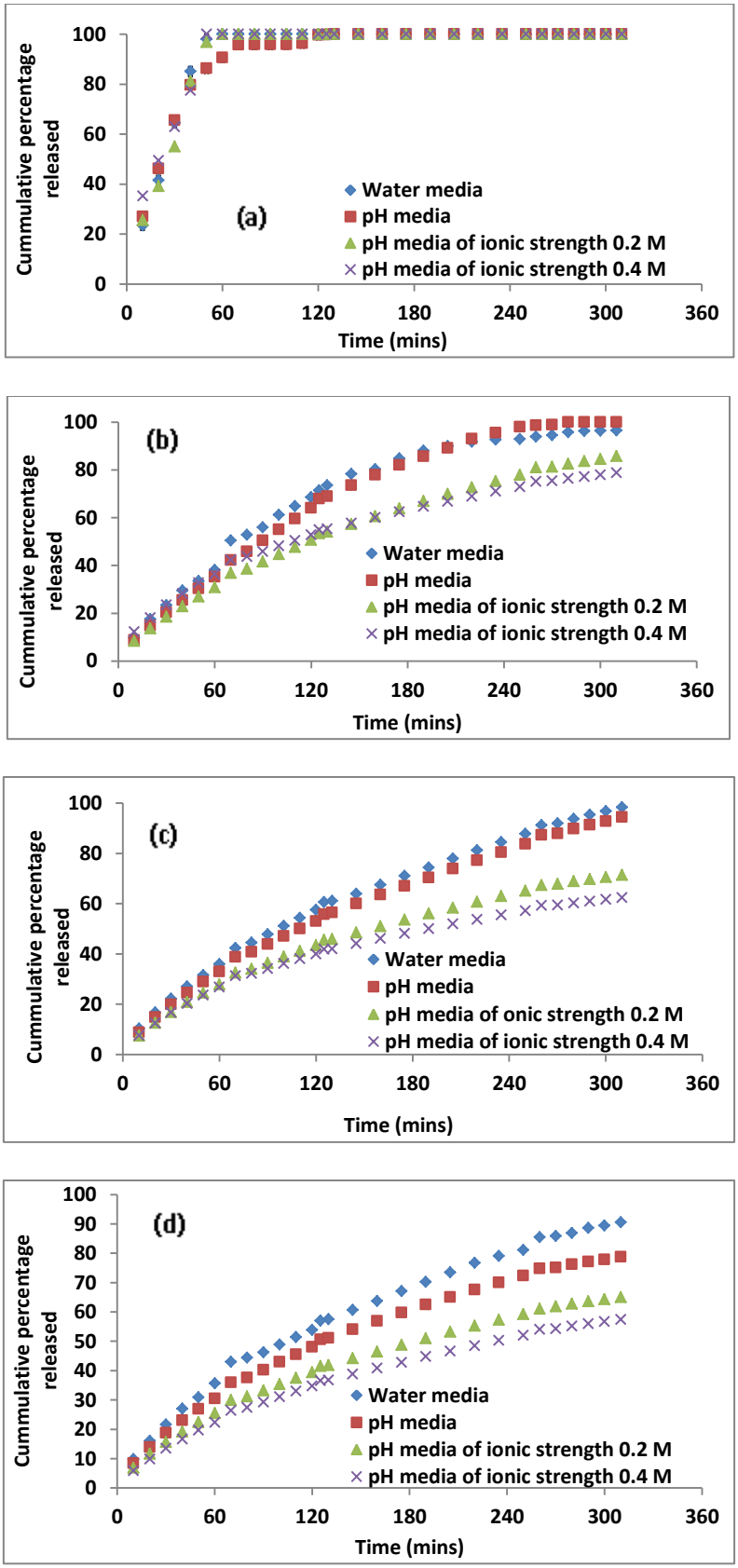

Figure 2. The influence of media ionic strength on diltiazem HCl release in pH 1.2 – 7.5 (please refer to table 1 for actual pH values) from HPMC matrices a. K100LV b. K4M c.

K15M d. K100M. Standard deviations smaller than the symbol size were not shown on the graphs (Adapted from ref [36]). The original buffers used in the experimentation of "pH media" have different ionic concentration strength levels. These ranged from 0.05 to 0.14 M. The use of sodium chloride at the 0.2 and 0.4 M ionic concentration strength levels in addition to the "pH media" meant that the actual ionic concentration strength at the 0.2 M level ranged between 0.25 and 0.34 M and for the 0.4 M ranged between 0.45 and 0.54 M [ref 7].

Adapted from [36]

HCl:Hydrochloric acid

Table 1. Biorelevant simulation of conditions in the fasted and fed stomachs (Table modified from ref **[12]**)

	FaSSGF[a]	FaSSGF-V2[b]	FeSSGF[c]	FaSSIF[d]	FaSSIF-V2[b]	Copenhagen Fasted[e]	FeSSIF[d]	FaSSIF-V2[b]	Copenhagen Fed[e]
pH	1.6	1.6	5	6.5	6.5	6.5	5	5.8	6.5
Buffer Capacity (mM/pH)	–	–	25	10	10	–	75	25	–
Buffer type	HCl	HCl	Acetate	KH_2PO_4	Maleic Acid	Trizma Maleate	Acetate	Maleic Acid	Trizma Maleate
Osmolarity (mOsm)	120.7	186.9	400	270	180	270	635	390	Varies
Surface tension (mN/m)	42.6	42.6		45.5	–	–	46.3	40.45	
Particle size	–			–	–	–	–	–	–
BS (mM)	80μM	80 μM	–	3	3	2.5	15	10	5–20
PL (mM)	20 μM	20 μM	–	0.75	0.2	0.625	3.75	2	1.25–5
BS/PL	4	4		4	15	4	4	5	4
MO (mM)	–	–		–	–	–	–	5	0–10
OA (mM)	–	–		–	–	–	–	0.8	0–45
Pepsin (mg/mL)	0.1	0.1	–	–	–	–	–	–	–
Long life milk buffer ratio	–	–	1:1	–	–	–	–	–	–

FaSSGF - Fasted state simulated gastric fluid; FaSSGF-V2 - Fasted state simulated gastric fluid version 2; FeSSGF - Fed state simulated gastric fluid; BS - Bile salt; PL - phospholipid; HCl - hydrochloric acid. FaSSIF - fasted state simulated intestinal fluid; FeSSIF - fed state simulated intestinal fluid; BS - bile salt; PL - phospholipid; MO - mono-olein; OA - oleic acid.

a Vertzoni et al. ref [69]; b Vertzoni et al. ref [70]; c Jantratid et al. ref [47]; d Galia et al., [68]; e Kleberg et al. ref [80]

Table modified from [12]

Table 2 Agitations applied during dissolution testing of theophylline K100LV, K4M, K15M and K100M formulations using an automated USP Apparatus III (Table adapted from ref [6]).

Media pH	Agitation (dpm)						
1.2	5	10	15	20	30	5*	30**
2.2	5	10	15	20	30	10	25
5.8	5	10	15	20	30	15	20
6.8	5	10	15	20	30	20	15
7.2	5	10	15	20	30	25	10
7.5	5	10	15	20	30	30	5

*Ascending order of agitation; agitation was increased by 5 dpm every time the cylinder containing the drug moved from one vial to the other. Thus, in pH 1.2 agitation was 5 dpm, in pH 2.2 - 10 dpm, in pH 5.8 - 15 dpm, in pH 6.8 - 20 dpm, in pH 7.2 - 25 dpm and in pH 7.5 - 30 dpm. **Descending order of agitation; agitation was decreased by 5 dpm every time the cylinder containing the drug moved from one vial to the other. Thus, in pH 1.2 agitation was 30 dpm, in pH 2.2 - 25 dpm, in pH 5.8 - 20 dpm, in pH 6.8 - 15 dpm, in pH 7.2 - 10 dpm and in pH 7.5 - 5 dpm.

Table adapted from [6]

Dpm: dips per minute

USP: United States Pharmacopeia

Table 3. The amount of the drug released (%) where, at what time and similarity when increasing or decreasing the agitations during the dissolution test. Similarity factor was calculated using the drug release profile obtained at 10 dpm as the reference standard.

Theophylline formulation

Formulation		**K100LV**		**K4M**		**K15M**		**K100M**	
Agitation (dpm)		**5-30**	**30-5**	**5-30**	**30-5**	**5-30**	**30-5**	**5-30**	**30-5**
Drug released	**Amount (%)**	100	100	64	84	46	51	38	49
	Medium pH	7.2	2.2	7.5	7.5	7.5	7.5	7.5	7.5
	Time (min)	280	120	310	310	310	310	310	310
Similarity factor	**(f2)**	51	-	55	42	63	76	82	51

Diltiazem hydrochloride formulation

Formulation		**K100LV**		**K4M**		**K15M**		**K100M**	
Agitation (dpm)		**5-30**	**30-5**	**5-30**	**30-5**	**5-30**	**30-5**	**5-30**	**30-5**
Drug released	**Amount (%)**	100	100	100	100	86	91	74	76
	Medium pH	2.2	2.2	7.5	7.2	7.5	7.5	7.5	7.5
	Time (min)	120	120	310	280	310	310	310	310
Similarity factor	**(f2)**	-	-	76	41	89	47	93	60

Hydrochlorothiazide formulation

Formulation		**K100LV**		**K4M**		**K15M**		**K100M**	
Agitation (dpm)		**5-30**	**30-5**	**5-30**	**30-5**	**5-30**	**30-5**	**5-30**	**30-5**
Drug released	**Amount (%)**	86	83	55	64	44	54	27	36
	Medium pH	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
	Time (min)	310	310	310	310	310	310	310	310
Similarity factor	**(f2)**	61	43	69	44	74	43	81	51

A depiction of (-) means it was not possible to calculate similarity value. 5-30 depicts the ascending order of agitation where agitation was increased by 5 dpm every time the cylinder

containing the drug moved from one vial to the other. Thus, in pH 1.2 agitation was 5 dpm, in pH 2.2 - 10 dpm, in pH 5.8 - 15 dpm, in pH 6.8 - 20 dpm, in pH 7.2 - 25 dpm and in pH 7.5 - 30 dpm. 30-5 depicts the descending order of agitation where agitation was decreased by 5 dpm every time the cylinder containing the drug moved from one vial to the other. Thus, in pH 1.2 agitation was 30 dpm, in pH 2.2 - 25 dpm, in pH 5.8 - 20 dpm, in pH 6.8 - 15 dpm, in pH 7.2 - 10 dpm and in pH 7.5 - 5 dpm. The time and medium pH show the time in min at which the drug release was completed for each matrix formulation.

Dpm: dips per minute