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Dynamic Dissolution: A Step Closer to Predictive Dissolution Testing?

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Abstract: The use of compendial dissolution techniques to characterize the performance of oral drug delivery systems is an established area of pharmaceutical science. However, compendial equipment is recognized as being limited in its ability to replicate the dynamic aspects of *in vivo* dissolution that are associated with dosage form transit through a rapidly changing and complex gastrointestinal lumenal environment. This review provides an overview of noncompendial dissolution models which have been developed to address the deficiencies of the traditional dissolution bath and provide scientists with a way of assessing product performance under physiologically relevant conditions.

Keywords: Oral drug delivery; dissolution testing; dynamic dissolution; biorelevant dissolution

Introduction

Dissolution testing of drug products is often viewed as one of the cornerstones of pharmaceutical research. Given the historical weight of research which can be traced back to Noyes and Whitney in 1897,[1] it is not unsurprising that this subject is often taught in undergraduate courses with an emphasis on the physicochemical properties of drug substances and product/formulation attributes rather than the relationship between formulation performance and the complex gastrointestinal physiological factors which ultimately determine absorption and exposure. The origins of the concept of dissolution impacting the absorption of a drug substance from the GI tract were attributed to a publication by Edwards in 1951[2] in an excellent historical perspective on dissolution by Dokoumetzidis and Macheras.[3] From then, decades of research in this area have provided pharmaceutical scientists with an increased understanding of the many factors impacting oral exposure following dosage form administration. However, the working apparatus and underlying concepts used by scientists to routinely assess the dissolution characteristics of drug substance and dosage forms have not evolved significantly over the same period. Indeed, the USP I/II apparatus typically used around the globe to measure product performance can trace its origins back to the 1960s with formal adoption of the basket stirred flask test by the USP and NF in 1970.[3]

So while formulation science has delivered many diverse ways to overcome the traditional obstacles of solubility and dissolution rate which compromise drug absorption,[4−11] our

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ability to discriminate between formulations is often hampered by the basic nature of the dissolution tools available. The simple basket or paddle stirred USP I/II systems provide a well-stirred, medium-rich environment in which dosage form disintegration and dissolution can be evaluated. Such a static, closed environment is limited by the absence of an absorptive sink and the relevance of the resulting hydrodynamics is also questionable given the continuous stirring and large volumes of media often deployed.[3,12,13] The comparison to human physiology is stark: the *in vivo* gut lumen is a rapidly changing dynamic environment with fluctuating fluid volumes and chaotic mixing provided by peristaltic contractions of varying intensity.[14−18] *In vivo* solubility and dissolution rates are affected by the unique physicochemical properties of the drug and dosage form and by physiological factors such as pH, fluid composition and hydrodynamics.[19] The composition of intestinal fluids is likely to vary considerably due to meal ingestion, diet, gastric emptying, secretion, intestinal transit and motility. all of which can impact both saturation solubility and dissolution rate.[16,20−26]

While it is difficult to fully predict the *in vivo* dissolution rate due to the many factors involved, the increased use of *in vivo* techniques such as the Loc-I-Gut and lumenal sampling techniques to directly monitor drug solubility or dissolution has helped underpin the development of improved predictive models.[21,23,27−31] Direct measurement using fasted and fed state human intestinal fluids has shown that both solubility and dissolution can be significantly higher than FaSSIF or FeSSIF media, an effect attributed to the presence of dietary lipids in real intestinal fluids which help solubilize hydrophobic compounds.[25] Since the widespread adoption of biorelevant SGF, FaSSIF and FeSSIF media as described

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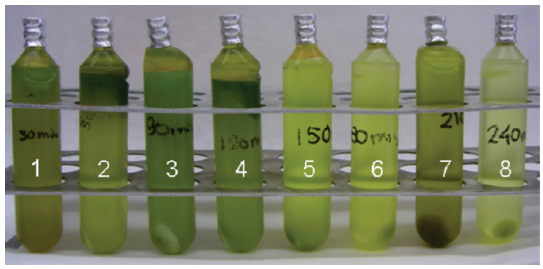

Figure 1. Ultracentrifuged duodenal aspirates taken after administration of a glucose/olive oil/egg meal to a healthy volunteer. Numbers correspond to minutes after administration of the meal: 1 = 30 min, 2 = 60 min, 3 = 90 min, 4 = 120 min, 5 = 150 min, 6 = 180 min, 7 = 210 min, 8 = 240 min (picture supplied by Prof. Christos Reppas, National & Kapodistrian University of Athens, Greece).

by Galia et al.,[32] a number of authors have recognized the limitations of standard biorelevant media and have sought to refine the composition to more accurately mimic real intestinal fluids.[33−39] The challenge of defining a single medium capable of representing either the gastric or intestinal environment is considerable for all of the factors listed above which contribute to the inherent physiological variability in the luminal environment. This is demonstrated by Figure 1, which shows a series of duodenal aspirates taken after ingestion of a test meal.[23] The samples show visual changes in bulk fluid composition and chemical analysis of tonicity, pH, bile salt and lipid content confirms the effect of dynamic digestive processes occurring in the intestinal lumen on fluid composition.

Drug dissolution is also dependent on the available fluid volume that is a result of the net oral intake, secretion and water flux across the GI wall. Recently, intestinal fluid volumes and transit of dosage forms have been assessed by water-sensitive MRI.[40] It was found that small intestinal fluid volumes in the fasted state were highly variable with volumes ranging from 45 to 319 mL in the fasted state, with fluid clearly distributed along the length of the intestine as separated pockets. In the fed state, small intestinal fluid volumes decreased significantly and varied between 20 and 156 mL. It was concluded that conventional *in vitro* dissolution tests are not suitable to predict *in vivo* release because dosage forms are not in contact with fluid pockets for significant periods of transit through both the small and large intestine. Although the imaging technique used in this study has limitations which may limit the absolute accuracy of the volume determinations (as it measures only free water volume and not the volume available when water is mixed with various fluid components), it demonstrates that the free fluid is not homogeneously distributed along the gut and that the fluid volumes are considerably less than those typically used in compendial dissolution testing.

The use of dissolution data is also changing with an increasing emphasis on using it in conjunction with oral absorption simulation software to predict product performance. Biomodeling packages such as SimCyp, GastroPlus and TIMpk can accept dissolution data as an input, and several studies have shown the potential to improve the accuracy of predicted exposure by using a biorelevant solubility or dissolution data set.[41−45] Use of dissolution data

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in the traditional area of quality control is also evolving with a regulatory drive to develop quality by design dissolution methods which are truly reflective of product performance in patients.[12] When considered together, there is a substantial need to improve dissolution methodology to meet these requirements and provide a step-change in our ability to perform predictive dissolution. This paper seeks to review the key models which have been developed to address the deficiencies of the traditional dissolution bath and provide scientists with a way of assessing product performance under physiologically relevant conditions. A diversity of system designs are reviewed, but all share the common concept that a system which offers a dynamic environment with physiologically relevant conditions will provide an improved correlation with *in vivo* performance.

Multicompartment Dissolution Models

The standard USP I/II compendial dissolution approaches typically used to assess dosage form disintegration and dissolution and which use a single medium at a defined pH clearly do not mimic the change in lumenal conditions seen during transit from the stomach to the small intestinal compartment. Additionally, the hydrodynamics generated by the basket or paddle equipment have questionable relevance to the *in vivo* situation. The hydrodynamic conditions generated in a USP II apparatus can be compared to the expected *in vivo* hydrodynamics by using the Reynolds number. The Reynolds number is a nondimensional 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.[46] Reynolds numbers for bulk flow in the USP II apparatus are around 2000,[47] significantly greater than the physiological range (0.1 to 30) suggested by Abrahamsson et al.[46] In addition, the USP II apparatus can generate an uneven distribution of hydrodynamic forces which can be a significant source of variability.[48] To address these issues, Abrahamsson et al. describe a modified USP II apparatus that can simulate the range of *in vivo* shear stresses observed in the postprandial stomach.[46] This modified apparatus was used in conjunction with a reduced fluid volume (300 mL) to simulate the release of felodipine from a hydrophilic extended release matrix tablet in the fed stomach.[49] This study showed that it was necessary to simulate both intragastric digestion (lipase mediated lipolysis) and physiologically relevant hydrodynamics to accurately predict the release rate of felodipine in the fed state. The reciprocating basket or USP III apparatus, while providing a means of stepping through different buffer conditions, is not generally suitable for assessing the impact of pH change on immediate-release dosage forms but can be a useful technique for extended-release dosage forms.[50,51] While no literature data have been reported describing the Reynolds numbers for bulk flow in the USP III apparatus, a study by Jantratid et al.[52] suggests that the hydrodynamic conditions produced by the reciprocating basket apparatus are more favorable than those seen with the USP II apparatus when correlating the performance of lipid based dosage forms in the fed-state stomach. Over time, a variety of approaches to mimic the gastric emptying process have evolved. The USP describes two enteric methods (method A, which utilizes phosphate buffer addition to 0.1 N HCl to adjust pH to 6.8, and method B, which dictates that acidic medium is replaced by fresh pH 6.8 phosphate buffer) which are intended to reproduce the shift in pH when a tablet empties from the stomach to the duodenum.[53] However, while simple in concept and amenable to automation, this approach clearly does not accurately reproduce the physical aspects of emptying or the subsequent neutralization of acidic gastric fluid by intestinal bicarbonate and may itself be subject to equipment and methodology issues.[54] The flow-through USP IV apparatus is reported to provide hydrodynamic conditions (Reynolds number <30) close to those suggested for the *in vivo* range and can be used to assess the performance of extended-release dosage forms in response to changing pH or different biorelevant media.[55] It can also be a suitable technique for poorly soluble compounds as it offers the possibility of maintaining sink conditions when run in open-

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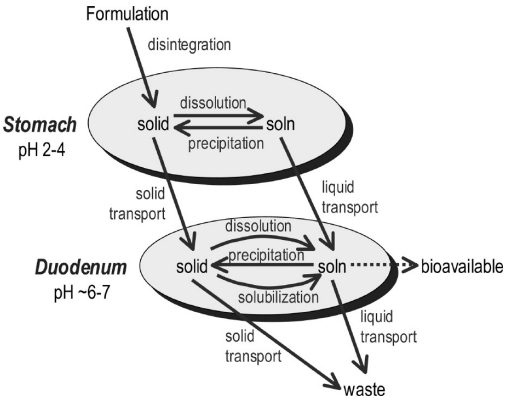

Figure 2. Dynamic processes present in the ASD.

loop mode[56] and is a useful tool to study the effect of the gastric to intestinal pH change on the dissolution of acidic drug substances.[57] However, it is limited in its ability to predict potential precipitation of basic drugs at intestinal pH due to the methodology constraints of the system. Given that weak bases with low intrinsic solubility can be >1000-fold more soluble at typical gastric pH (pH 1−2) than at typical intestinal pH (pH 5−7), the potential for precipitation is clear.[58] A number of noncompendial multicompartment dissolution models have been developed to more closely mimic the process of gastric emptying and potential precipitation in the intestinal compartment in a more biorelevant manner. These systems are typically configured to allow transport of buffer contents from a gastric compartment to a second intestinal compartment. A key exemplar of this class of system is the artificial stomach duodenal model (ASD) which has been used to evaluate the effect of gastric emptying on API dissolution, solubilization and precipitation in a separate duodenal compartment.[59−61] The schematic diagram in Figure 2 shows the various dynamic processes in the ASD model. After dispersion of API or formulated drug product in the stomach chamber (typical equipment configuration shown in Figure 3), contents are transferred at a controlled rate to the duodenum chamber, where it is mixed with simulated intestinal fluid (SIF) allowing the dynamic processes of dissolution, precipitation and recrystallization to be followed. In this configuration, fluid transport and infusion of fresh simulated GI fluids cause a continuous variation in the concentration of drug substance in both chambers. The *in vivo* relevance of ASD dissolution profiles is based on the assumption that the concentration of dissolved drug in the simulated duodenum is proportional to its bioavailability. This correlation was seen with PNU-140690, a sparingly soluble bivalent acid, when it was administered perorally to dogs with duodenal fistula as either the free acid or mono- or disodium salt.[62,63] Effluent fluid, drawn from the duodenal fistula, was analyzed for the fraction of drug present in solution or as the undissolved/precipitated solid form. It was found that the bioavailability of the three forms, measured in a different set of animals without fistula, agreed well with the measured fraction dissolved in duodenal fluids. Carino et al.[59] reported the successful use of the ASD model to simulate the fasted and fed state for dog physiology for carbamazepine crystal forms. In this model, the authors used the AUC of the concentration−time profile in the duodenum chamber as a relative indicator of bioavailability. This correlation is shown in Figure 4, which shows good agreement between the ASD "AUC" duodenal dissolution plot and the *in vivo* AUC for the three different carbamazepine crystal forms.

The design of the artificial stomach−duodenum model, while it has proven to provide a convenient method to assess the performance of immediate-release formulations, has some limitations. Results cannot be directly correlated to bioavailability for compounds which are bioavailability limited by permeability and/or metabolism. Additionally, its application to studies involving controlled-release formulations can be also considered limited since the model does not effectively simulate the lower gastrointestinal region thus possibly underestimating the efficacy of the formulation. The dissolution in the gastric compartment may be impacted by the effective volume available (typically between 20 and 70 mL) and the simple continuous method of stirring employed. However, the simplicity of this technique combined with biorelevant fluid transfer makes it a powerful tool to understand dynamic dissolution issues for compounds if they are subject to physical chemistry processes such as precipitation, dissolution or solubilization.

Another variant of a multicompartment/transport model has been described by Kostewicz et al.[64] As with the ASD

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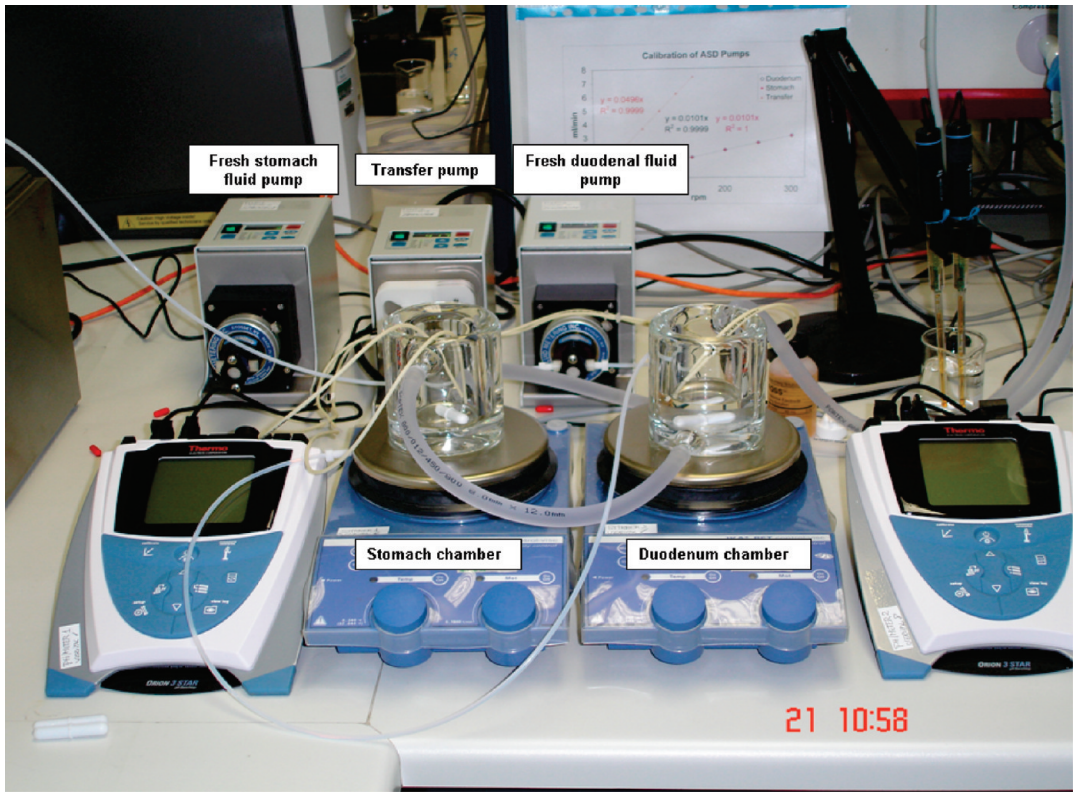

Figure 3. ASD equipment showing gastric and duodenal compartments and transfer pumps.

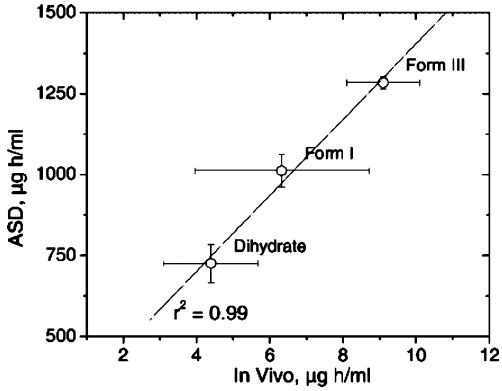

Figure 4. Correlation of area under the curve (AUC) obtained from ASD to that of *in vivo* results obtained in dogs for carbamazepine polymorphs.

model, transfer from the stomach to the intestine was simulated by pumping a solution of drug in simulated gastric fluid (SGF) into a second compartment containing FaSSIF or FeSSIF and examining drug precipitation in the receptor medium via concentration−time measurements. The *in vitro* precipitation of three poorly soluble weakly basic drugs (dipyridamole and two experimental compounds) was investigated with extensive supersaturation observed for all three. Under simulated fasted state conditions, precipitation occurred for all three compounds, whereas with simulated fed-state conditions, the higher concentrations of bile components and the lower pH of the fed-state media inhibited precipitation at concentrations corresponding to representative doses in all cases. Comparison with PK data[24] indicated that a combination of transfer model data with solubility and dissolution profiles should lead to better prediction of *in vivo* behavior of poorly soluble weak bases. The results of this study clearly demonstrated that poorly soluble weakly basic drugs have the potential to precipitate in the small intestine, even if they are fully dissolved in the stomach. While this is predictable on the basis of pH−solubility relationships, the phase of supersaturation which precedes precipitation cannot be predicted from physicochemical properties alone. Both the ASD and the Kostewicz transfer model appear to have utility in quantifying (or at least rank-ordering) the impact of supersaturation in the duodenal compartment for formulations or different solid forms on bioavailability.

Dissolution Models Which Simulate GI Physical Stress Forces

Data from *in vivo* imaging studies using magnetic moment imaging, gamma scintigraphy and telemetry capsules has helped underpin our understanding of the contractile forces applied to dosage forms during transit along the gastrointestinal tract.[65−67] An example of *in vivo* imaging data being

(65) Cassilly, D.; Kantor, S.; Knight, L. C.; Maurer, A. H.; Fisher, R. S.; Semler, J.; Parkman, H. P. Gastric emptying of a non-digestible solid: assessment with simultaneous SmartPill pH and pressure capsule, antroduodenal manometry, gastric emptying scintigraphy. *Neurogastroenterol. Motil.* **2008**, *20*, 311–319.
(66) Goodman, K.; Hodges, L. A.; Band, J.; Stevens, H.; Werner, W. Assessing gastrointestinal motility and disintegration profiles of magnetic tabelts by a novel magnetic imaging device and gamma scintigraphy. *Eur. J. Pharm. Biopharm.* **2010**, *74* (1), 82–92.

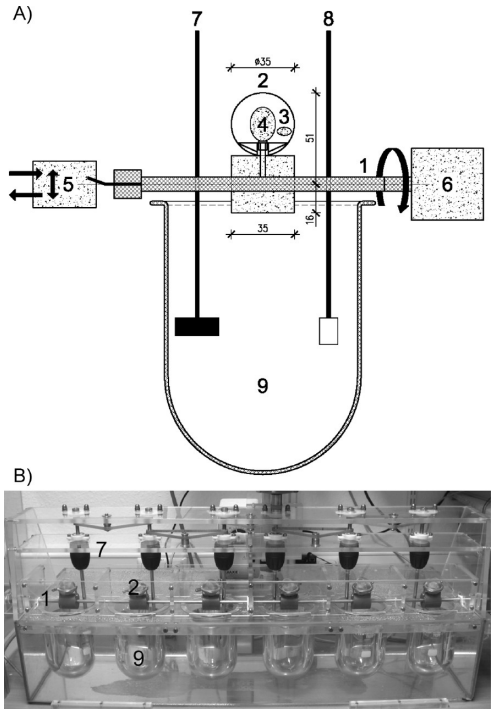

Figure 5. Schematic (A) and photographic (B) representation of the biorelevant dissolution stress-test device: (1) central axle (∅ 8 mm), (2) steel netting wire chamber (∅ 35 mm, mesh size 0.5 mm, wire 0.1 mm), (3) dosage form, (4) inflatable balloon, (5) solenoid valve system, (6) stepping motor, (7) stirrer (blade 35 × 15 mm), (8) sampling, (9) standard dissolution vessel (schematic and picture supplied by Prof. Werner Weitschies, University of Greifswald, Germany).

applied to dissolution design is provided by the novel stress test dissolution apparatus developed by Garbacz et al. and shown in Figure 5.[68] Real time imaging of the gastrointestinal transit of dosage forms has shown that movement is erratic with periods of rest and slow transit being punctuated with brief periods of high velocity movement.[69,70] The novel stress test apparatus is capable of mimicking this pattern of irregular movement and the physical forces applied on dosage forms

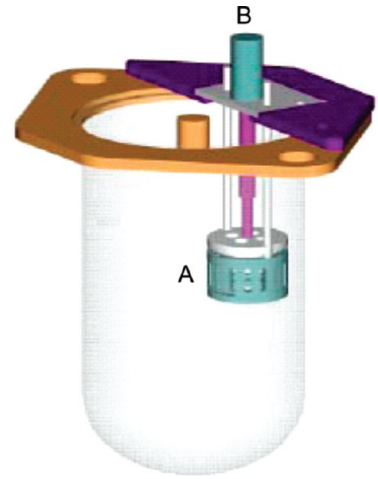

Figure 6. Schematic showing the modified USP II apparatus described by Burke et al.[71] The housing (A) depicted shows how the dosage form is held and compressed by the piston (B). Note that the standard USP II paddle is not depicted for reasons of clarity.

during gastric emptying and intestinal transit. Importantly, the dosage form is not in continuous contact with medium, reproducing the effect of transit through an intestinal compartment with segmented fluid distribution.[40] Using this equipment, it was possible to reproduce the multiple peaks seen in individual diclofenac plasma concentration profiles after dosing an extended release formulation. This was in contrast to the smooth continuous release profiles observed with a conventional USP II method. A less versatile, although simpler, means of replicating the physical forces applied to dosage forms is described by Burke et al.[71] This equipment, schematically shown in Figure 6, is a modification of the standard USP II apparatus and allows a dosage form to be held within a housing in which forces can be applied to the dosage form at intervals with varying levels of duration and intensity. Both types of apparatus would appear to have particular utility for assessing the mechanical robustness of extended-release formulations and their ability to withstand gastric forces and passage through the pylorus or ileocecal junction.

Combined Dissolution−Absorption Models

Drug dissolution in the GI tract *in vivo* occurs under sink conditions, and if the dissolution rate is slower than the permeation rate through the intestinal membrane, oral absorption may be dissolution rate limited.[72] Simple systems which provide an absorptive sink using a partitioning approach with octanol have shown some promise in improv-

(67) Weitschies, W.; Blume, H.; Monnikes, H. Magnetic marker monitoring: high resolution real-time tracking of oral solid dosage forms in the gastrointestinal tract. *Eur. J. Pharm. Biopharm.* **2010**, *74*, 93–101.
(68) Garbacz, G.; Wedemeyer, R.-S.; Nagel, S.; Giessmann, T.; Moennikes, H.; Wilson, C. G.; Siegmund, W.; Weitschies, W. Irregular absorption profiles observed from diclofenac extended release tablets can be predicted using a dissolution test apparatus that mimics in vivo physical stresses. *Eur. J. Pharm. Biopharm.* **2008**, *70* (2), 421–428.
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(71) Burke, M. Maheshwari, C. R. Zimmerman, B. O. *Pharmaceutical analysis apparatus and method*; USA Pat.
(72) Takano, R.; Furumoto, K.; Shiraki, K.; Takata, N.; Hayashi, Y.; Aso, Y.; Yamashita, S. Rate-Limiting Steps of Oral Absorption for Poorly Water-Soluble Drugs in Dogs; Prediction from a Miniscale Dissolution Test and a Physiologically-Based Computer Simulation. *Pharm. Res.* **2008**, *25* (10), 2334–2344.

ing the correlation to *in vivo* performance.[73,74] A novel extension of this concept has been reported by Vangani et al., who described a combined USP IV and USP II apparatus which incorporated an organic phase to mimic the absorption process.[75] This system utilized flow-through USP IV equipment as the primary dissolution apparatus from which dissolved eluent was transferred to a connected secondary USP II chamber containing a biphasic dissolution medium comprising an aqueous buffer (pH6.8 phosphate buffer) and organic solvent (either nonanol or a 1:1 mixture of cycloexhane and nonanol). The USP II paddle was modified with an additional small paddle to provide stirring in both aqueous and organic phases, and stirring was optimized to facilitate transfer of compound into the organic phase. The return line to the USP IV equipment was connected to the aqueous phase of the biphasic medium, completing the flow-through loop. This approach was used to characterize the dissolution profile of a poorly soluble experimental compound, AMG 517. It was reported that it had not been possible to generate meaningful data using USP IV apparatus for this compound due to the very low solubility across the physiological pH range. By using the combined system, it was found that *in vitro* release profiles for AMG 517 capsule formulations were superimposable with absorption−time profiles produced by deconvolution and allowed a rank-order correlation to be established.

A modification of the multicompartment/transfer model which incorporated a third module intended to simulate the absorption compartment was reported by Gu et al.[76] The system, based on a modified USP apparatus, comprised gastric and small intestinal compartments supplemented with a third compartment to simulate absorption. Hydrodynamics were controlled by paddles at 100 rpm, and a pH stat was used to maintain pH in the small intestinal chamber (pH 5.5 ± 0.2) which increased to pH 6.5 over a 1 h period. This was intended to simulate first the lower pH in the duodenum before exposing the compound to the higher pH in the jejunum.[77,78] Flow rate from the intestinal chamber to the absorption compartment could be adjusted based on the permeability of the compound. The amount of drug transferred to the absorption compartment after 3 h was determined as the *"in vitro"* absorbed amount which was correlated to *in vivo* bioavailability data for two weak bases with low intrinsic solubility (cinnarizine and dipyridamole). For these model compounds, it was possible to estimate the precipitation potential to diagnose whether precipitation is a contributory factor in the cause of poor oral bioavailability. This was clearly demonstrated with cinnarizine where the difference in the amount transferred to the *in vitro* absorption compartment was attributed to precipitation in the intestinal compartment despite complete prior dissolution. However, although dipyridamole and cinnarizine were shown to exhibit significant differences in precipitation *in vitro*, the correlation to *in vivo* data was hampered by the lack of information on the absolute oral bioavailability and first-pass metabolism of these compounds.

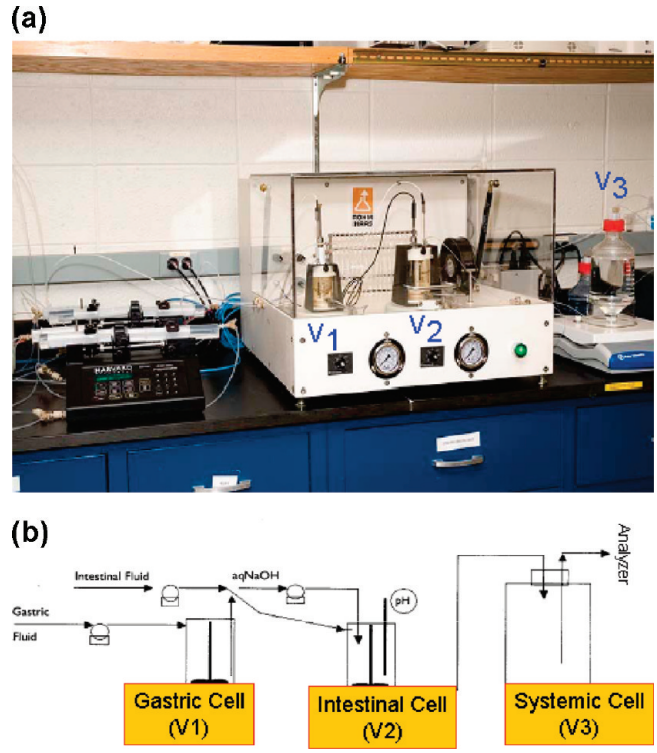

Figure 7. (a) FloVitro equipment showing gastric (V1), intestinal (V2) and absorptive compartments (V3). (b) FloVitro equipment schematic (schematic and picture reproduced with permission from Dow Chemical Company).

The FloVitro dissolution system provided by the Dow Chemical Company bears a number of similarities to the transfer model described Gu et al. The FloVitro system also comprises gastric and small intestinal chambers with an additional third compartment connected to the intestinal chamber which again is intended to function as an absorptive compartment.[79] The system is shown in Figure 7a with a

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(76) Gu, C.-H.; Rao, D.; Gandhi, R. B.; Hilden, J.; Raghavan, K. Using a novel multicompartment dissolution system to predict the effect of gastric pH on the oral absorption of weak bases with poor intrinsic solubility. *J. Pharm. Sci.* **2005**, *94* (1), 199–208.
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schematic description in Figure 7b. The utility of this model appears to stem from the use of a deconvoluted *in vivo* dissolution profile which is replicated *in vitro* through alteration of flow rates, volume and pH between the three compartments. Once matched, the *in vitro* release profile can be used to detect changes in product performance associated with batch variability or performance versus competitor products. As with the ASD and the transfer models described above, use of the FloVitro system as a prospective tool may be limited by the relevance of the hydrodynamics in the gastric compartment and its ability to deal with food effects other than those that are mediated by simple shifts in pH or bile salt solubilization.

The FloVitro approach, which integrates a tunable transfer system with deconvoluted *in vivo* dissolution data inputs, highlights the potential in combining a dynamic biorelevant dissolution test with biomodeling. This is clearly illustrated in a recent study which used a dynamic pH gradient dissolution method with flow-through hydrodynamics to generate a dissolution profile as a data input to the widely used GastroPlus software package.[45] In this study, the dissolution of montelukast sodium 10 mg tablets was investigated using a flow-through cell dissolution method following a dynamic pH change protocol to establish an *in vitro in vivo* relationship (IVIVR). USP IV apparatus was chosen because of its ability to simulate *in vivo* hydrodynamics better than USP I or II equipments and to allow a close simulation of the pH gradient in the gastrointestinal tract.[57,80,81] The dissolution profiles were entered as an input function for GastroPlus by using the tabulated *in vitro* dissolution and controlled-release dispersed data input function. The dissolution profile was then used by the software to calculate drug concentration in each compartment. The simulated plasma profile using the dynamic pH change method and flow-through cells appeared to match the *in vivo* profile well when the first-pass extraction effect was corrected. The simulated profile using USP II data and FaSSIF media did not predict the observed *in vivo* profile well. This study was one of the first to show the value in combining a pH change protocol, flow-through apparatus and computer simulation and illustrates the potential in combining dynamic dissolution methodologies and biomodeling software to significantly improve the accuracy of predictions of *in vivo* performance. In a subsequent study, dissolution profiles generated using USP II apparatus and the Kostewicz transfer model were used as data inputs to GastroPlus for etoricoxib, a poorly soluble weak base.[82] It was found that, unlike the previous findings using the transfer model with dipyridamole, intestinal precipitation of etoricoxib was not observed, and it was proposed that the degree of relative supersaturation was the differentiating factor between the two compounds. The combination of *in vitro* dissolution testing using biorelevant media and *in silico* physiologically based pharmacokinetic modeling was also successfully applied to predict the food effect seen with the poorly soluble drug celecoxib.[83] In this study it was shown that USP II testing with biorelevant media was not predictive when used alone to assess the extent of absorption as the extent of dissolution was limited by the closed volume setup. However, when the initial dissolution rates were used as inputs to the modeling software, *in silico* profiles were in good agreement with *in vivo* data.

More sophisticated approaches using a cell-based membrane have been developed to allow the impact of permeation on dissolution rate to be studied in a single assay.[84−87] Such dissolution−permeation (D−P) models have taken a number of different forms. A continuous dissolution−permeation system utilizing a Caco-2 cell membrane was first described by Ginski et al.[88] Yamashita et al.[89] have described the use of a two-compartment model consisting of two chambers, a dissolution and a receiver compartment separated by a Caco-2 monolayer. Similar systems focused on simulating

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the pH changes in the GI tract,[90−92] and Kataoka et al.[86] describe a D−P model in which a clinically relevant dose concentration could be applied. Buch et al.[84] used the D−P system to correlate the *in vitro* dissolution and permeation of fenofibrate, a BCS class II compound with *in vivo* data in rats. This comprehensive study assessed a number of bioenhanced formulations including solid dispersion, nanoparticulate and micronized approaches and showed that the D−P system, when used with biorelevant media, could predict formulation performance in rats. The D−P system has also proved to be a useful tool for probing the role of micellar solubilization on dissolution.[87] In addition to enhancing solubility and dissolution rate, the bile acid/lipid mixed micelles present in biorelevant media can also modulate permeability by restricting the amount of drug species present as the free form.[87,93,94] However, the myriad of colloidal substructures produced by lipid digestion suggest that the food effect correlation produced by this system using well-controlled biorelevant media may be overly simplistic. The concept of coupling a D−P system with a dynamic lipolysis model to recreate conditions closer to those seen *in vivo* would require a mechanism of protecting the cell membrane from digestive enzymes but would provide a very powerful tool for formulators, particularly when dealing with liquid SEDDS or SMEDDS formulations. Equally, combining a simple buffer transport model with an in-line permeation assay would be a powerful evolution of this class of dissolution test. However, like the simple buffer transport systems, the majority of D−P models reported in the literature are limited in their ability to reproduce *in vivo* relevant hydrodynamics and to deal with complex food materials. Additionally, despite their use of a biological membrane, D−P models do not reproduce the microenvironment of the gut epithelial layer due to the absence of an effective mucus layer. These constraints would appear to limit the use of D−P models to investigate very specific aspects of absorption such as the impact of micellar solubilization/binding on permeation rather than to holistically evaluate the net result of disintegration, dissolution and permeation on absorption.

Complex *in Vitro* Digestion Models

The simple multicompartment buffer transport models and dissolution−absorption models described above are useful tools to study in detail several aspects of the dissolution process. However, it should be recognized that the dissolution profile they provide can be limited not only by hydrodynamics and composition of media but also by the limited simulation of digestive processes.

A number of simple lipolysis models have been developed over recent years with an emphasis on understanding the performance of self-emulsifying drug delivery systems.[95] Dynamic *in vitro* digestion models such as those proposed by Zangeberg et al.[96,97] consist of a reaction vessel in which a pH stat maintains a constant pH in response to fatty acid production during lipolysis. The model allows samples to be taken and characterized following ultracentrifugation to determine drug distribution in three possible phases: (i) a pellet consisting of calcium soaps of fatty acids and precipitated drug, (ii) an aqueous phase containing micelles and vesicles and (iii) an upper oil phase. The presence of drug in the aqueous micellar/vesicular phase has been used to rank order formulations in terms of solubilizing capacity[98,99] and has been coupled with *ex vivo* intestinal permeability data to predict exposure in rats.[100] These simple models of lipolysis are useful to mechanistically understand the lipolytic digestion process and tailor a lipid-based formulation to produce the key intermediate colloidal species which will optimize exposure. However, they do not provide a means of allowing the interaction of formulations with whole food products and a wider range of digestive enzymes to be

(90) Kobayashi, M.; Sada, N.; Sugawara, M.; Iseki, K.; Miyazaki, K. Development of a new system for prediction of drug absorption that takes into account drug dissolution and pH change in the gastro-intestinal tract. *Int. J. Pharm.* **2001**, *221*, 87–94.

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(100) Dahan, A.; Hoffman, A. The effect of different lipid nased formulations on the oral absoprtion of lipophilic drugs: the ability of in vitro lipolysis and consecutive ex vivo intestinal permeability data to predict in vivo bioavailability in rats. *Eur. J. Pharm. Biopharm.* **2007**, *67* (1), 96–105.

assessed and they are limited in their ability to simulate gastric processing and gradual emptying to the intestine.

Two new systems, which have evolved from research in the nutritional area, offer the potential to simulate gastric processing and the effects of digestive processes on dosage form performance in a more complete way. The first of these systems is the Institute for Food Research (IFR, Norwich, U.K.) dynamic gastric model (DGM) which was developed from knowledge gained from echo-planar magnetic resonance imaging studies on the gastric processing of complex meals.[101−104] These studies showed that mixing in the stomach is inhomogeneous and hydrated regions of a meal bolus are selectively processed to the antral region of the stomach. The DGM is claimed to replicate these processes and provide an accurate *in vitro* simulation of gastric mixing, shear rates and forces, peristalsis and gastric emptying.[105] The equipment is composed of two main stages as shown in Figure 8. The first stage mimics the gastric mixing and dynamic secretrory profiles of the fundal regions of the stomach with the second stage replicating the shear forces and mixing observed in the antral region. It is possible to couple the output from the first two stages to a biorelevant simulation of the small intestine to generate a complete profile of digestion and dissolution. To date, the only pharmaceutical application of this system reported is a study which explored the ability of the DGM to replicate the dynamic digestion of a self-emulsifying drug delivery system (SEDDS) formulation.[106] It was suggested that the DGM provided a more accurate simulation of SEDDS digestion (at least in terms of droplet size) than conventional USP II apparatus. Clearly more studies are required to reach a judgment on the value of this system but its ability to reproduce gastric forces and meal processing should enable this system to have value in application areas such as the assessment of mechanical integrity of modified-release formulations and dose-dumping potential, alcohol interactions and quantifying the potential for food effects.

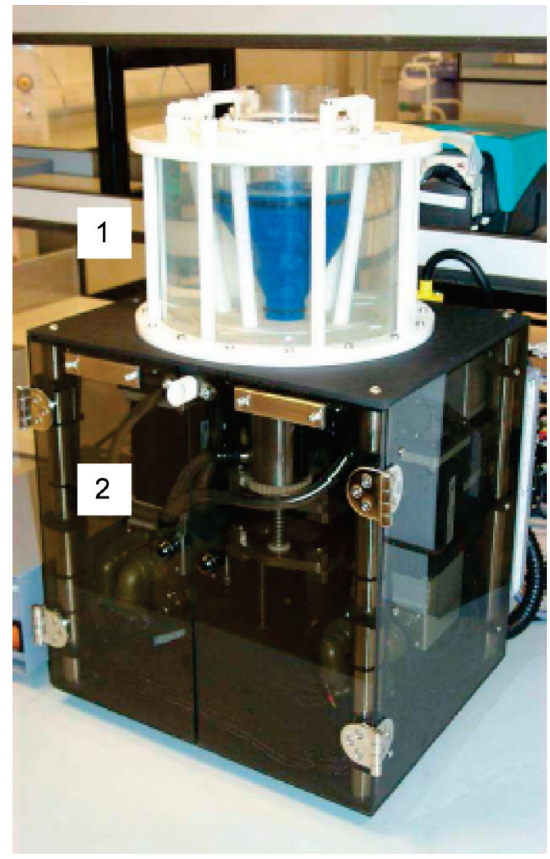

Figure 8. IFR dynamic gut model apparatus showing main body/fundal area (1) and antrum (2) (picture supplied by ModelGut, IFR, Norwich, U.K.).

The TNO TIM-1 system is a multicompartmental dynamic computer controlled system that simulates the human GI tract.[107] It was developed at the TNO Nutrition and Food Research center in Zeist, The Netherlands, and allows simulation of the *in vivo* dynamic digestive and physiological processes which occur in the human stomach and small intestine.[108] The parameters used in the TNO TIM-1 model design are based on data obtained from human volunteer studies, and the main parameters of digestion including temperature, pH, peristaltic mixing and transit, gastric secretion (lipase, pepsin, HCl), small intestinal secretion (pancreatic juice, bile and sodium bicarbonate) are control-

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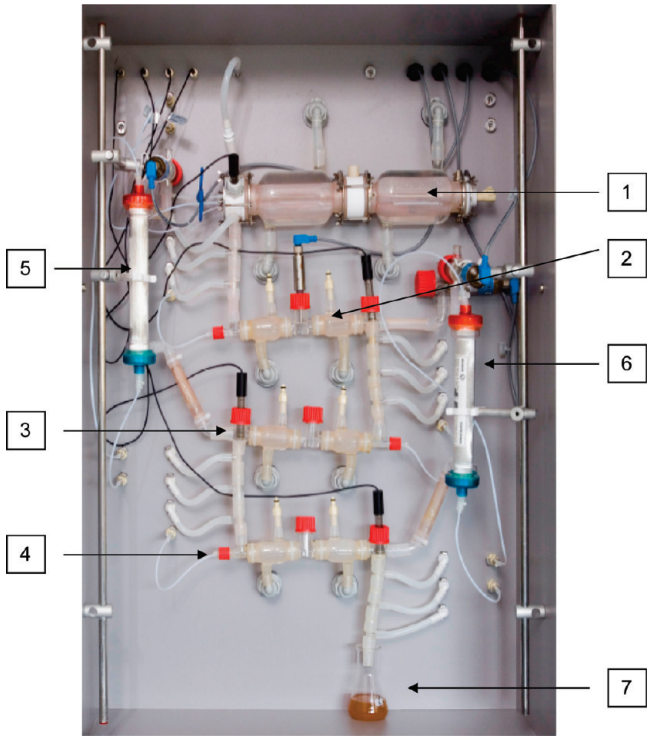

Figure 9. TNO TIM-1 apparatus: (1) gastric compartment; (2) duodenum; (3) jejunum; (4) ileum; (5) jejunal dialysis cartridge; (6) ileal dialysis cartridge; (7) ileal eluent (picture supplied by TNO, Quality of Life, Zeist).

lable. The equipment is shown in Figure 9 with a depiction of the layout of the four interconnecting components, the stomach, duodenum, jejunum and ileum. The absorption phase is simulated in the TIM-1 model by the use of a dialysis membrane which removes water and small molecules (including the products of digestion and dissolved drug substance). The jejunum and ileum compartments are each connected to semipermeable hollow-fiber membranes with a molecular weight cutoff of 5 kDa which allows the bioaccessibility (i.e., the amount of digested product or drug substance in solution and therefore available for absorption) to be quantified.[109] This passive absorptive surface means that *in vivo* processes such as active transport, efflux and intestinal wall metabolism are not modeled by the system. Nonbioaccessible fractions are collected at the end of the ileum compartment and represent unabsorbed material that will enter the large intestine. These sampling ports are shown in the schematic of the system depicted in Figure 10. Uniquely, hydrodynamics are controlled by changes in water pressure on flexible membranes which contain the lumenal contents. This enables mixing by alternate cycles of compression and relaxation, mimicking the mixing created *in vivo* by muscular peristaltic contractions. Additionally, transit is regulated by opening or closing peristaltic valves that connect each compartment. The TIM-1 system has been used to study the absorption of nutritional materials for a number of years,[109−112] but relatively few examples of its application to pharmaceutical dosage forms are available in the literature.

The first report to show utility of the TIM-1 system for studying the behavior of oral dosage forms under various physiological conditions was a study by Blanquet et al.[107] which evaluated the impact of transit time and food on the absorption of paracetamol in either free powder form or an a sustained release tablet. It was demonstrated that the profiles of jejunal absorption found *in vitro* were consistent with *in vivo* data and a good correlation was seen with T_{max} values for the immediate-release form. However, a direct quantitative correlation was not possible as first-pass extraction; volume of distribution and renal clearance were needed to calculate a predicted *in vivo* plasma profile. It was also shown that food intake (in the form of a standard breakfast) reduced the amount of paracetamol available for absorption. This was judged to be similar to clinical studies which showed a lower C_{max} and delayed T_{max} in the fed state compared to intake with water in the fasted state.[113−116] In a follow-up study, it was shown that the TIM-1 could be used to generate a level A IVIVC for paracetamol in both fasted and fed states.[117] A further study, originating from a product development group at GlaxoSmithKline (Harlow, U.K.), assessed the utility of the TIM-1 model to improve

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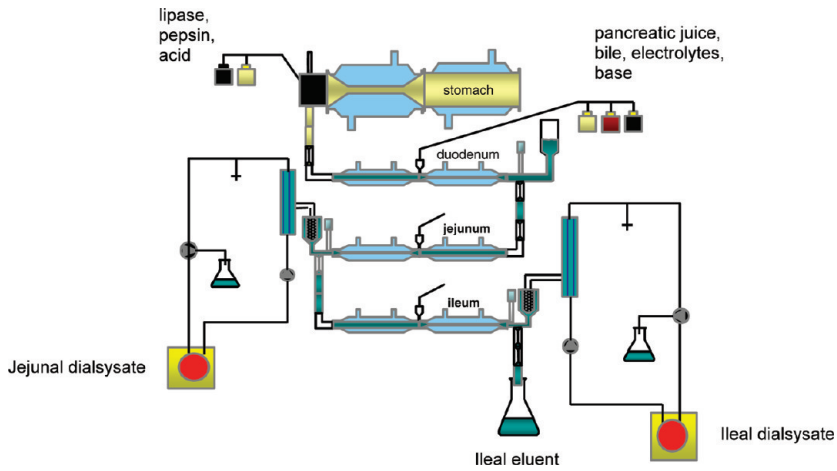

Figure 10. TNO TIM-1 schematic showing secretory and sampling ports (picture supplied by TNO, Quality of Life, Zeist).

the predictability of GastroPlus modeling of a paroxetine hydrochloride immediate-release tablet.[44] A deconvoluted dissolution profile from the TIM-1 model was used as the input rate of the drug for a GastroPlus model that had been built for paroxetine hydrochloride using known PK parameters. Despite recovery issues (possibly due to adsorption of the active to the flexible walls of the system or the dialysis membranes), it was shown that the TIM-1 dissolution profile provided an improved predicted plasma profile compared to the profile generated when a USP II dissolution profile was used. A further example of the application of the TIM-1 model to dosage form dissolution is provided by a study which assessed the release kinetics from a mesalamine tablet formulation.[118] This formulation utilized a pH-dependent enteric coating to delay the release of the active until the dosage form reaches the terminal ileum and targets release of mesalamine to the colonic area. During a 6 h transit through the gastric, duodenal, jejunal and ileal compartments of the TIM-1, less than 1% active was released. Visually, it was possible to examine the tablet at the end of transit to the terminal ileum and assess the integrity of the functional coating layer. Subsequent transfer of the dosage form to a TIM-2 model, a system which replicates the anaerobic conditions in the colonic region, showed successful release of active which correlated well with *in vivo* data.[119,120] The predictive ability of the TNO TIM-1 system was evaluated in a comparative study with compendial techniques using theophylline hydrophilic matrix sustained release tablets.[121] Dissolution profiles for the matrix tablets were obtained in the TIM-1 using a fasted state protocol and in both USP II and USP IV apparatuses using different paddle speeds and flow rates respectively. The profiles from the three systems were then compared to the plasma concentration profiles obtained by dosing the matrix tablets to healthy volunteers in the fasted state. It was seen that while both USP methods could provide a level A *in vitro in vivo* correlation, the predictability of the TIM-1 method was much better with a mean ratio between *in vivo* and *in vitro* data close to 1. It was suggested that the improved performance of the TIM-1 was due to its peristaltic mixing and fluid transfer method which more closely simulated the erosion of the hydrophilic gel layer of the matrix tablet than the paddles of the USP II or the laminar flow of the USP IV.

These examples suggest that the TIM-1 system, which provides an advanced level of control over a dynamic and complex lumenal environment, may have several advantages over conventional dissolution methodologies when assessing the performance of dosage forms in either the fasted or fed states. However, the complexity of the technique and lengthy equipment setup time is perceived as limiting the amount of data which can be generated in a reasonable time period. This particular limitation is exemplified by the examples described above, in which typically only two replicate runs are performed for each formulation tested and condition simulated. The use of dialysis at two sampling points in the TIM-1 small intestinal section contrasts with continuous diffusion across the small intestine *in vivo* and may limit the ability to assess the impact of formulation on compounds with a narrow absorption window in the upper small intestine. Furthermore, the use of a dialysis membrane to provide an absorptive surface may be limiting in terms of differentiating between components which have an active transport com-

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ponent. To compensate for this, one study, which assessed the bioavailability of lycopene and α-tocopherol from a whole food source, coupled the use of the TIM-1 model with a Caco-2 cell permeability assay.[122] TIM-1 intestinal fractions were added to Caco-2 cells after ultracentrifugation, filtration and dilution. It was observed that α-tocopherol absorption was limited by the presence of competiting digestion products whereas lycopene was unaffected. While this snapshot approach to sampling and permeability determination was shown to be useful, ideally a dynamic continuous profile is required to truly maximize the benefits of generating a biorelevant dissolution profile in the fed state and remains a challenge to be overcome. Moreover, public domain data on the use of the TIM-1 model is limited and more information from industrial users is required to accurately define the situations for which the TIM-1 model should be used in place of simpler alternative dynamic models.

Conclusions

In summary, this review of dynamic dissolution systems has demonstrated that the search for an accurate *in vitro* surrogate of the GI tract is still ongoing despite decades of research. In terms of application to drug development, the multicompartment and combined dissolution−absorption models offer a way to mechanistically study several of the key aspects of the dissolution process such as micellar solubilization/binding and the propensity for precipitation. As such, they can be viewed as useful additions to the dissolution toolkit and could potentially be used to refine data inputs to improve the predictive accuracy of biomodeling software. However, their control of hydrodynamics, an inability to deal with complex food matrices and overly simplified replication of the digestion process limit their potential to reduce and/or refine *in vivo* testing. The more complex systems such as the TNO TIM-1 and IFR DGM, while undoubtedly simulating the GI environment with a level of control and accuracy not previously achievable, have not yet conclusively proved that they represent a step-change rather than an incremental advance in dissolution science. The limited literature reports on the application of these emerging techniques certainly hints that such a prospect is within reach, particularly when coupled with biomodeling, but more studies are required to precisely define when these complex techniques uniquely add value. Given the limited access to these techniques it would appear that a cross-company, precompetitive, collaborative research partnership with the technology providers is needed to generate the data required to validate the widespread use of these techniques. Until such a systematic and comprehensive evaluation is completed, the search for a widely applicable predictive dissolution tool to enable the selection of the optimal oral delivery strategy will continue.

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