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Research Article

A Novel Approach in Distinguishing Between Role of Hydrodynamics and Mechanical Stresses Similar to Contraction Forces of GI Tract on Drug Release from Modified Release Dosage Forms

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Abstract. The objective of this study was to determine the influence of mechanical stresses simulating gastrointestinal contraction forces of 2.0 N (stomach) and 1.2 N (intestine) on the gel properties and drug release characteristics from sustained release swelling and eroding hydrophilic matrices during dissolution studies. Two batches of tetracycline-sustained release tablets containing hydroxypropyl methyl cellulose (HPMC) were manufactured and subjected to USP apparatus II (pH 2.2 buffer) dissolution studies. Hydrated tablets were periodically removed, placed in a petri dish, and multiple times (six cycle) compressed with a flat-ended probe (diameter 1.3 cm) on a texture analyzer at preprogrammed force of either 2.0 or 1.2 N to determine force-distance profiles and changes in drug release rate. The calculated similarity factor values showed dissimilar dissolution profiles using standard dissolution profile as a reference. The similarity factor (f_2) values were especially lower than 50 at 2.0 N and, when profiles between the two batches compressed at 1.2 and 2.0 N, were compared with each other. The changes in dissolution pattern and release rate were significantly different after 4 h of dissolution. At 8 h, tablets were fully hydrated and no force could be detected by the probe, indicating a very soft gel matrix. It appears that the contraction forces in the stomach and intestine are capable of altering drug release from modified release hydrophilic matrices during transit in the human GI tract. Accounting for these forces during dissolution can enhance predictions of *in vivo* drug release, achieve better *in vitro* and *in vivo* correlation, introduce improvement in dissolution methods, and better understand the critical quality attributes (CQAs) and factors in quality by design (QbD) during the product development process.

KEY WORDS: drug release rate; hydrophilic matrix systems; mechanical stress and dissolution; modified release drug product; texture analysis.

INTRODUCTION

Many new chemical entities (NCEs) fail during early drug development phases because of undesirable toxicity and/or lack of efficacy instigated by poor solubility, permeability, and bioavailability (1). It is indispensable to have a strategy by which properties of such drug candidates can be accurately and predictively identified in the early stages of drug development phases. In 1995, the biopharmaceutics classification system (BCS) was implemented as a new approach to better predict oral drug absorption and was adopted by the U.S. Food and Drug Administration (FDA) (2). The BCS classifies compounds into four groups based on their aqueous solubility and intestinal permeability: class I (high solubility, high permeability), class II (low solubility, high permeability), class III (high solubility, low permeability), and class IV (low solubility, low permeability). Since the introduction of BCS, a number of mechanistic models for the prediction of drug bioavailability after oral administration of drugs have been published including software such as GastroPlus™, which is based on the modification of the original compartmental absorption and transit (CAT) model, referred to as advanced CAT model; Simcyp, which is based on the advanced dissolution absorption and metabolism (ADAM) model; PK-SIM; and GI-Sim model based also on CAT model with greater consideration of events in the GI lumen with respect to dose, particle size and dissolution limited absorption situations (3,4). These models have been shown to be useful with relative accuracy in the *in silico* predictions of fraction absorbed and plasma exposure of drugs (3,5,6). Furthermore, BCS has been used as a tool to predict *in vitro* dissolution of drug substances, to potentially optimize dissolution conditions by using appropriate apparatus, to develop biorelevant media, and to introduce new

Dedication This work is dedicated to Professor M.R. Hojat, Department of Psychiatry and Human Behavior, and the Director of Jefferson Longitudinal Study, on the occasion of his 66th birthday. He is one of the pioneers in the development of the scales that measure aspects of professionalism in medicine including collaborations between physician, nurse, and pharmacist.

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parameters to closely simulate GI conditions and to transit time within different parts of the GI tract (7). For example, introduction of multiple biorelevant media representing fasted and fed conditions reflecting changes in physiological and the digestion processes has been recently introduced (8).

With respect to the development of modified release drug delivery systems (MR) including enteric-coated dosage forms, an understanding of their *in vivo* behavior is critical and is generally based on *in vitro* tests (mainly dissolution testing in a series of biorelevant media or simulated GI conditions) used as a gadget to predict drug product performance *in vivo*, especially when combined with human bioavailability data and deconvolution of such data.

For example, in the case of enteric-coated products, the dissolution rate of various enteric-coated diclofenac sodium tablets was studied under USP-recommended dissolution method and a suggested modified version. In the first study, conditions were at 100 rpm paddle speed in pH 6 and 7, maintaining sink condition. In the second study, the effect of mechanical stress other than purely hydrodynamics was tested on tablets by placing 5 g of 3-mm-diameter glass beads in a pear-shaped 1000-mL flask, rotating at 100 rpm at an angle of 30° in a water bath at 37 C, pH 6 and 7 (see Fig. 1) (9). Dissolution rate at both pH conditions was significantly higher when glass beads were used. Based on the results of dissolution and human bioavailability study, authors concluded that a more accurate and predictable *in vivo* pharmacokinetics was achieved when dissolution in the presence of mechanical stress associated with the use of glass beads was involved. Study clearly shows that although compendial dissolution methods are valuable in assuring batch-to-batch uniformity, for *in vitro* and *in vivo* correlation (IVIVC) and biowaiver purposes, standard dissolution methods require explicit modification related either to the selection of appropriate apparatus, type of dosage forms, release mechanism, or the target area for drug release in the GI tract. In the case of enteric-coated tablets, it appears that inclusion of *in vitro* mechanical stresses simulating the GI contraction forces and motility during dissolution testing allows for better *in vivo* prediction of absorption.

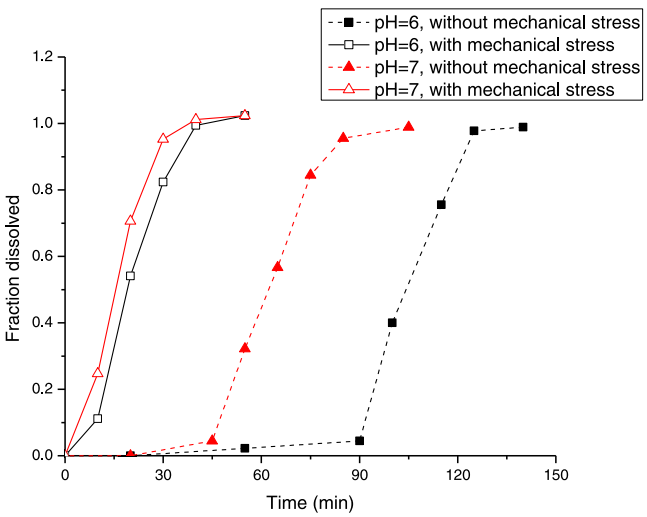

Fig. 1. Release profiles for enteric-coated tablets with and without mechanical stress at two different pH conditions (data redrawn from (9))

Modified release, sustained release hydrophilic matrices or drug products that are administered orally have to pass through a series of GI compartments and environments while releasing drug slowly for absorption into the systemic circulation. Transit times average around 2 h in the stomach and 3–4 h in the small intestine (10). During this time, controlled release formulations are subjected to the mechanical forces meant to digest and tumble the food. These mechanical forces were measured by Kamba *et al.* (11,12) and found to be around 1.9 N (~2.0 N) in the stomach of fed subjects and 1.2 N in the intestines of fasting subjects. The stomach and intestines go through cycles of varied contraction forces, with the highest forces and frequency of occurrences recorded during phase III of the cycle. These are characterized by strong sustained contractions with frequency of 2.5–3.5 per min for 5–15 min (13). It is reasonable to assume that the drug release from swelling and eroding hydrophilic matrices will be affected by the gastrointestinal contraction forces due to deformation and changes in gel structure and surface area as a result of these stresses. Such effects may cause unexpected burst of drug release with implications similar to dose dumping and associated toxicities. The objectives of our study was to draw attention to this aspect of drug release on hydrophilic matrix-type modified release systems by measuring the effects of these forces in an *in vitro* setting, paving the way for future improvements in drug dissolution systems and methods that are more representative of *in vivo* conditions.

MATERIALS AND METHODS

Materials and Equipment

Tetracycline hydrochloride (Sichuan Pharmaceutical Co. Ltd., Sichuan, China), Methocel K4M (hydroxypropyl methyl cellulose (HPMC); Dow Chemicals Co., MI, USA), dibasic calcium phosphate dihydrate (Amend Drug & Chemical Co., NJ, USA), lactose fast flow (lactose monohydrate; Foremost, Baraboo, WI), Polyox WSR-301 NF Grade (polyethylene oxide (PEO); Union Carbide Corporation, CT, USA), fumed silica micron sized (Grace Davison, Columbia, MD, USA), magnesium stearate (Amend Drug & Chemical Co., NJ, USA), texture analyzer TAXT2i (Stable Microsystems Ltd., Surrey, UK), Stokes single punch tablet press (Stokes-Merrill Corp., Bristol, PA, USA), VanKel 7000 dissolution apparatus (VanKel Technology Group, NC, USA), and Agilent 8453 Diode Array UV-Vis spectrophotometer (Agilent Technologies, CA, USA) were used.

Tablet Manufacturing

Tablets were manufactured by direct compression of the powder mix. For batch number ME-1, model drug tetracycline hydrochloride (24%), PEO (15%), HPMC (36%), and dibasic calcium phosphate (24%) were sifted through a 600-μm sieve and were mixed for 10 min in a V blender. Fumed silica (0.5%) and magnesium stearate (1%) were sifted through a 250-μm sieve and blended with the previous mix in a V blender for 5 min. The final blend was compressed on a Stokes single punch tablet press equipped with a 10-mm flat-faced punch and die set. The batch size was 200 tablets in each case. The second batch designated as ML-1 was prepared using the

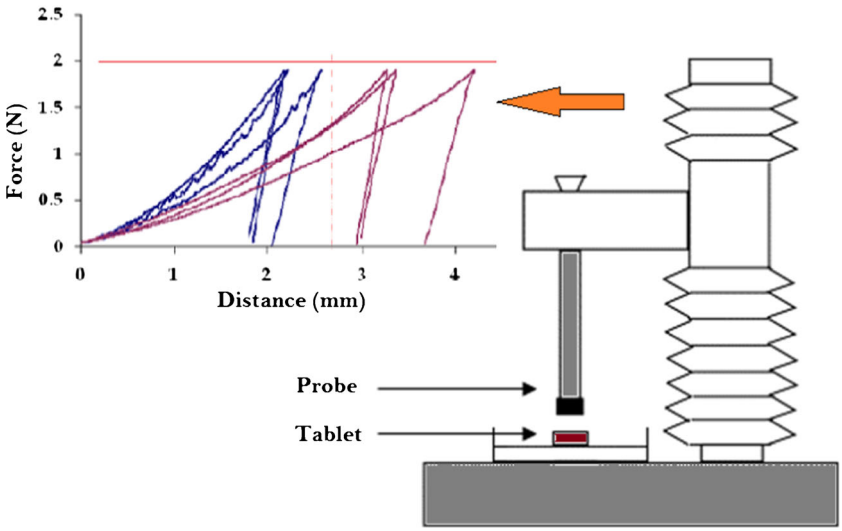

Fig. 2. A texture analyzer was used to exert multiple predetermined fixed forces (2.0 or 1.2 N) on each tablet measuring the force-distance relationship (*F-D*) during dissolution study. A typical *F-D* profile is shown (see *inset*)

same procedure and composition as for the first batch, except for replacement of dibasic calcium phosphate with lactose monohydrate, a more soluble tablet filler.

Analytical Method

Analysis of tetracycline release in the dissolution medium was done by UV spectrometry at 277 nm. The absorptivity factor ($A_{1\%}$) was calculated from the standard calibration curve. The calibration curve was linear within the range used in analysis (R^2=0.9999). Stability of tetracycline in solution was assessed, and it was found that tetracycline concentration does not change significantly throughout the duration of the experiment, which did not exceed 10 h.

Dissolution

Dissolution study was performed on each of the two batches to determine their dissolution profiles under standard conditions (without the application of any mechanical forces). The dissolution apparatus used was a modified USP 26 dissolution apparatus II (14). The modification involved the addition of a single mesh and ring assembly in the dissolution vessel below the paddle, and the tablet was placed on top of the mesh. This prevents the tablet from adhering to the bottom of the vessel to ensure a more homogeneous matrix swelling and drug release from the entire tablet surface area (15). Paddle rotation speed was set at 75 rpm. The dissolution medium used was 900 mL of hydrochloric acid buffer at pH 2.2 in each vessel at 37°C. Six-milliliter samples were drawn at 1, 2, 3, 4, 6, 8, and 10 h from each dissolution vessel and were substituted with 6 mL of fresh medium.

In the non-control dissolution experiments, six tablets of either batch of tetracycline tablets (ME-1 and ML-1) were placed in the dissolution apparatus under the same mentioned conditioned for control tablets. After 1 h, each tablet was carefully taken out from its vessel and placed on a small petri dish and was then subjected to axial mechanical force using a texture analyzer equipped with a 13-mm flat-ended cylindrical probe as shown in Figs. 2 and 3.

Description of steps 1 to 5 for Fig. 3 is as follows:

1. A tablet was placed in a dissolution vessel with 900 mL medium on the inserted mesh.
2. After 1 h, dissolution medium was sampled (6 mL) and measured for tetracycline release at 277 nm.
3. The tablet was gently taken out from the vessel and placed in a petri dish.
4. The tablet was placed under the texture analyzer equipped with a cylindrical probe with a diameter of 1.3 cm and subjected to compression forces as stated above.

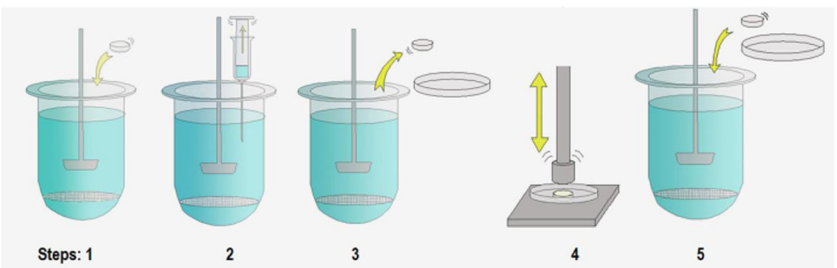

Fig. 3. Steps taken in removing tablets from the vessel, recording force-displacement (*F-D*) profiles, and returning the tablet back into the vessel at different time points

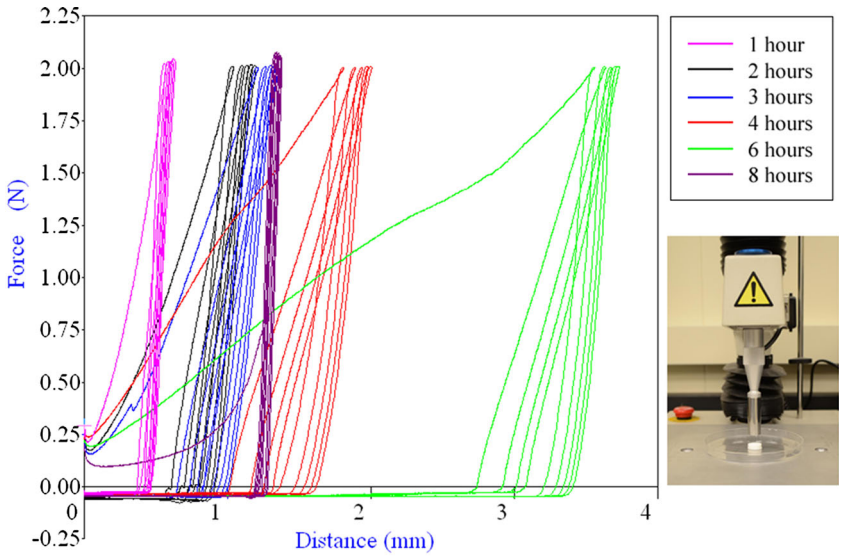

Fig. 4. Typical force-displacement profiles at each sampling point (2, 3, 4, 6, and 8 h); six tablets were used in each run. Note that the profile at 8 h shows no resistance to probe (distance travelled by the probe is about 1.3 mm without sensing any force until it reaches the base plate of the machine) due to very soft nature of the gel matrix

5. Tablet was carefully placed back into the vessel. Residuals in the petri dish were rinsed with 6 mL of medium.

Texture Analysis

The texture analyzer was programmed to apply five consecutive axial compressions on the tablet, each reaching a maximum force of 1.2 or 2.0 N, to resemble the contraction forces in the human intestine or human stomach, respectively. This amount of force is much less than that needed to break the tablet (16,17) but was enough to cause some deformation in the hydrated gel surface of the tablet, especially in the late time period. After each tablet was subjected to the compressional mechanical force, it was carefully placed back in the dissolution medium; the probe tip and petri dish were rinsed with 6 mL of fresh medium to ensure no drug loss. The same procedure was repeated at 2, 3, 4, 6, 8, and 10 h for each of the six tablets. Six-milliliter samples were also drawn at each of the sampling points for absorbance measurements. The time that each tablet was kept outside its dissolution medium at every compression cycle was about 3 min. This time was taken into account by adding 3 min to the time of sampling at each compression cycle. Figure 4 shows a typical observation in force-displacement profiles up to 8 h after multiple application of force at each time point. It is assumed that drug release from hydrated and swollen matrices is not affected by exposure to air outside the dissolution vessel based on controlled experiments conducted prior to texture analysis. In controlled experiments, three tablets were removed from the dissolution vessels periodically and kept in a petri dish for 3 min and were returned into the dissolution bath and drug release measured against the three control tablets in the same dissolution bath.

RESULTS AND DISCUSSION

Drug release from the two formulations under different conditions is shown in Figs. 5 and 6. Both formulations showed a typical sustained drug release under control conditions with no significant burst. Formulation with batch number ME-1 showed slower release due to the effect of the insoluble filler dibasic calcium phosphate as one of the excipients relative to formulation with batch number ML-1, containing soluble excipient lactose showing higher release.

Under simulated intestinal and stomach contractual forces, the formulations started losing mechanical consistency after 3 and 6 h for formulations ML-1 and ME-1, respectively, leading to a significant increase in drug release as compared to the control. Batch number ME-1 released 52% drug during the first 10 h when no force was applied, which increased to 72% drug release with a 1.2 N force and 100% drug release

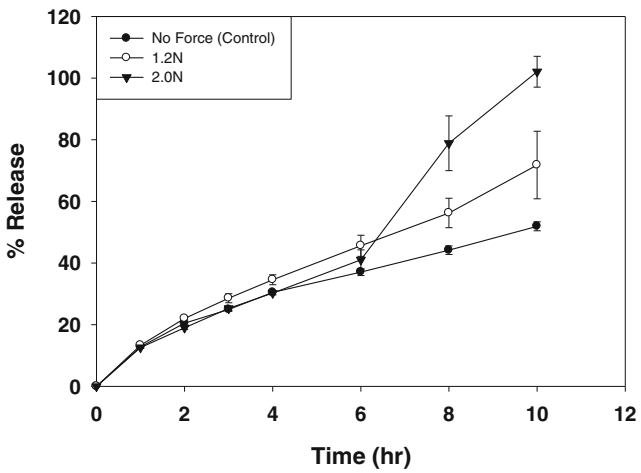

Fig. 5. Effect of mechanical forces on the release profile of tetracycline from hydrophilic matrices containing insoluble excipient (batch no. ME-1)

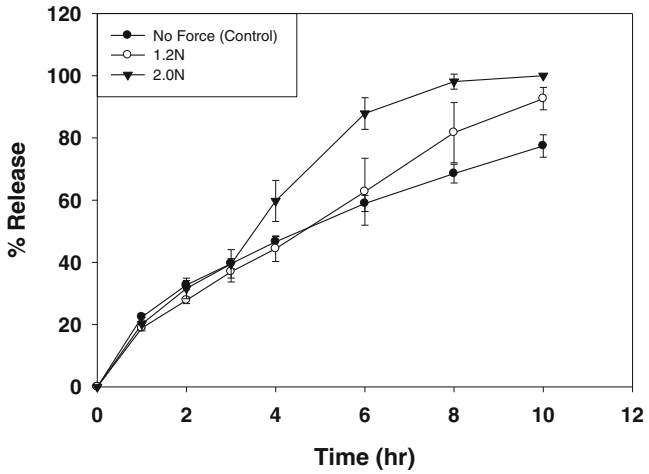

Fig. 6. Effect of mechanical force on the release profile of tetracycline from hydrophilic matrices containing soluble excipient (batch no. ML-1)

with a 2.0 N force. Batch number ML-1 released 77% of the drug during the first 10 h under control conditions, increasing to 93% with a 1.2 N force and 100% with a 2.0 N force.

The FDA uses the similarity factor f_2 as an indicator of dissolution profiles' sameness (18)

$$f_2 = 50\mathrm{Log}\left\{\left[1 + 1/n\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right\}$$

where R_t and T_t are the percent drug dissolved at each time point for the reference and the test formulation, respectively.

When the f_2 values were calculated for the dissolution profiles of the two designed tetracycline tablets against control (reference) tablets, the profiles were either not similar or very weakly similar (see Table I), indicating that mechanical stress equivalent to contractile forces can cause a significant acceleration of drug release from a swellable matrices designed to release drug over an extended duration of more than 4 h.

The calculated similarity factor values showed dissimilar dissolution profiles under control and non-control conditions, especially at 2.0 N, and when profiles between the two batches at 1.2 and 2.0 N were compared with each other (see Table I for similarity factors (f_2)). This shows that the potential effect of contractual forces in the stomach and intestine on drug release should be expected, and these forces are capable of altering drug release from modified release hydrophilic matrices during transit in the human GI tract.

Table I. Similarity (f_2) Between Dissolution Profiles of Formulations ME-1 and ML-1

Batch no.	1st profile	2nd profile (N)	f_2 value
ME-1	Control	1.2	50.8
	Control	2.0	30.1
	1.2 N	2.0	40.1
ML-1	Control	1.2	54.2
	Control	2.0	37.5
	1.2 N	2.0	42.8

CONCLUSION

The main goal of our study was to evaluate any effects that the contractile forces in the stomach and intestine in the range of 2.0 or 1.2 N may have on the drug release pattern of controlled release hydrophilic matrices made of swellable polymers. The reported force values or mechanical forces vary widely, but Kamba *et al.* (11,12) used a tablet-shaped device physically similar to controlled release tablets and measured the contraction force values after administration to human subjects, and therefore, their results (2.0 and 1.2 N for stomach and intestine, respectively) appear more relevant to the current study. As an initial observation, differences in the amount of drug released between the two formulations (ME-1 and ML-1) were expected, due to the solubility of lactose in one batch *versus* insoluble dicalcium phosphate in the other.

The first set of dissolution studies on batch number ME-1 showed no significant effect of the mechanical force applied for the first 3 to 4 h, indicating that the matrix structure and the underlying dry core could stand mechanical forces of the stomach and intestine for the initial few hours. However, the mechanical force applied at 6 h and beyond (force of either 2.0 or 1.2 N) was able to cause enough deformation and disruption to the polymeric gel structure, which showed a significant increase in the release of tetracycline for both batches when compared to the control as demonstrated by the similarity factor values. Accounting for these forces during dissolution can enhance predictions of *in vivo* drug release and can therefore help achieve better IVIVC or *in vitro* and *in vivo* relationship (IVIVR) for drug release from similar dosage forms or of different strengths. A more in-depth understanding of matrix dynamics and drug release via simulations may pave the way for improved dissolution methods, better understanding of the critical quality attributes (CQAs), and factors in quality by design (QbD) during the product development process (ICH guidelines) (19). Additionally, information may be useful in the context of biowaivers and drug approval process, especially for matrix-type modified release systems and dissolution rate-limited cases within the BCS and developability classification system (DCS) (20) framework.

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