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Study of dissolution hydrodynamic conditions versus drug release from hypromellose matrices: The influence of agitation sequence

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ABSTRACT

In this article, the influence of agitation in descending and ascending sequences as a systematic method development process for potentially discriminating fed and fasted states and evaluation of its effects on the drug release from swelling gel-forming hydrophilic matrix tablets were investigated. Theophylline extended release (ER) matrices containing hypromellose (hydroxypropyl methylcellulose (HPMC)) were evaluated in media with a pH range of 1.2–7.5, using an automated USP type III, Bio-Dis dissolution apparatus at 5, 10, 15, 20, 25 and 30 dips per minute (dpm). Agitation had a profound effect on the drug release from the HPMC K100LV matrices. Drug release in pH 1.2 changed from about 40% at 5 dpm to about 80% at 30 dpm over a 60 min period alone. The matrices containing HPMC K4M, K15M and K100M however were not significantly affected by the agitation rate. The similarity factor f_2 was calculated using drug release at 10 dpm as a reference. The ascending agitations of 5–30 dpm and the descending order of agitation 30–5 dpm were also evaluated. Anomalous transport was the only kinetic of release for the K4M, K15M and K100M tablet matrices. The lower viscous polymer of K100LV had some matrices exhibiting Fickian diffusion as its kinetics of release. The use of systematic change of agitation method may indicate potential fed and fasted effects on drug release from hydrophilic matrices.

1. Introduction

Hydroxypropyl methylcellulose (HPMC) or hypromellose polymers are commonly known for their binding, water retention, thickening and film forming properties. HPMC is used in cosmetics [1], topical formulations and ophthalmic surgery [2,3], film-coating [4] and as an alternative to gelatin for two-piece hard capsules [5]. Reilly [6] considers the use of hypromellose in the drug industry as a pharmaceutical necessity. HPMC is also the most commonly used hydrophilic polymer carrier in extended release matrices because of its ability to provide robust formulations and obtain desired release profiles for a wide range of drugs [7,8] due to its stability, global regulatory acceptance, cost effectiveness and non-ionic nature [9–11].

It is well known that food administration can affect the bioavailability of oral dosage forms as a result of interactions which may occur between the formulation and the food [12,13]. Researchers have demonstrated that the gel layer formed around hydrophilic matrices, upon its contact with gastro-intestinal (GI) fluids, is eroded allowing drug release. This erosion is the dominant release mechanism for poorly soluble drugs. The other mechanistic approach is that the soluble portion of drug is released through the process of diffusion through the gel layer [14–17]. After a meal, the gastric emptying rates for liquids and solids are much slower in comparison to fasting conditions [18]. This is true also for when drug is taken after food consumption. This is demonstrated by the reduction in blood plasma peak concentration which tends to occur at later times and also by an increment in lag-times in plasma concentration–time profiles. In cases where a rapid onset is required or high peaks needed to reach a therapeutic effect, this reduction in the absorption of drug could be critical or fatal [19].

Two major properties of the GI fluids that should be considered when evaluating ER matrix performance are ionic strength and pH. These properties vary greatly along the GI tract under fasting and fed conditions [18,20] and may affect the rate at which a drug is released from its hydrophilic gel matrix [15,21,22]. Other factors which may also affect the drug release rate are the physiochemical properties of the drug and polymer [23–25], formulation composition [26–28] and tablet manufacturing process parameters [29–31].

The dissolution testing procedure is a quality control during product development and in pharmaceutical production and is of great importance in the selection and facilitation of candidate formulations for in vitro in vivo correlations (IVIVC) [32–34]. This is

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Table 1
Agitations applied during dissolution testing of theophylline ER matrix tablets.

Media pH	Applied agitation (dpm)						
	Constant					Ascending	Descending
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

achievable by the use of data from in vitro dissolution from certain defined physiological and hydrodynamic conditions to help facilitate possible bioequivalence testing, in vivo bioavailability and IVIVC [34]. Various researchers have used different dips per minute (dpm) with physiological and biorelevant dissolution media in their work in evaluating fasted and fed states with the most commonly dpm used agitation rate of 10 [35–39].

To the best of our knowledge, there was no systematic study conducted that showed the influence of order (ascending or descending) of agitation during in vitro dissolution testing on drug release in the media with varying pH. Therefore, the aims of this investigation were to develop a methodology that allows the study and evaluation of the effects of agitation (dip rate) and different pH ranges on the release of theophylline from HPMC ER matrix tablets using an automated USP type III, Bio-Dis dissolution apparatus and using this methodology of systematic change of agitation to possibly indicate potential fed and fasted effects on drug release from hydrophilic matrices.

2. Materials and methods

2.1. Materials

Hydrophilic matrix tablets were prepared using anhydrous theophylline (Sigma, UK) as the model drug and HPMC (METHOCEL™ K100LV, K4M, K15M and K100M; Colorcon, UK) polymers as the hydrophilic matrix former.

Dissolution buffers were prepared according to the USP using the following materials: potassium chloride (Acros Organics, UK) and hydrochloric acid (Fisher Scientific, UK) for pH 1.2 and pH 2.2 and potassium phosphate monobasic-white crystals (Fisher BioReagents, UK) and sodium hydroxide (Fisher Scientific, UK) for pH 5.8, 6.8, 7.2 and 7.5 media.

2.2. Tablet preparation

Round cylindrical tablets with a diameter of 9.56 mm and the target weight of 250 mg were prepared by blending theophylline with HPMC in the ratio of 4:1 for 10 min in a Turbula® (Type T2 C, Switzerland) blender. The tablets were compressed using a single punch tableting machine (Model MTCM-1, Globe Pharma, US) at 1500 psi (5.55 kN). The die wall was lubricated each time before tablet compression with a 1% (w/v) suspension of magnesium stearate in acetone.

Tablet dimensions were obtained using the electronic digital calliper (Fisher Scientific, UK). The ultrapycnometer 100 (Quantachrome Instruments, UK) was used in the determination of the true density of the powder mixtures. Tablet porosity was then calculated according to Eq. (1).

$$\text{Tablet porosity} = 1 - \left[\frac{\text{tablet weight/tablet volume}}{\text{true density of powder}}\right] \times 100 \qquad (1)$$

2.3. Drug dissolution testing

The automated USP type III Bio-Dis (Varian, US) was used to carry out the dissolution tests with dip rates ranging from 5 to 30 dpm. The vessels contained 250 mL of the appropriate medium (pH 1.2–7.5) and the mesh on the top and bottom screens of the cylindrical tablet holders was fixed at 864 μm. The temperatures were kept constant at 37 °C. The absorption of the released theophylline was measured at 271 nm using an UV/visible spectrophotometer (Varian, Cary 50).

2.4. Effect of pH and agitation

Drug release behaviour of the above formulations was investigated in six dissolution media to determine the sensitivity of different grades of HPMC to the pH. A series of buffer solutions that simulated the stomach and intestinal conditions in fasted and fed states with the pH values of 1.2, 2.2, 5.8, 6.8, 7.2 and 7.5 were used. The dissolution testing was conducted for 310 min for all formulations [36].

The influence of agitation on drug release was studied according to Table 1. Firstly, agitation was kept constant at 5, 10, 15, 20 or 30 dpm in all the vials at the varying pH. Then in the second part of the study 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. The reverse was done as well when the 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.

All four theophylline and HPMC (K100LV, K4M, K15M and K100M) formulations were tested against this developed methodology. This allowed discriminating the effect of the agitation on the formulations where different grades of the HPMC were used. The transit times in the different pH used to simulate the digestive tract are depicted in Table 2. All these experiments were carried out in triplicate.

Table 2
Transit times and pH values used in the study for mimicking the GI segment (adapted from [36]).

GI tract segment	pH value	Transit time (min)
Stomach	1.2	60
Stomach	2.2	60
Duodenum	5.8	10
Jejunum	6.8	120
Proximal ileum	7.2	30
Distal ileum	7.5	30

Table 3
Physical characterisation of the tablets used in the study.

Tablet parameter	Formulation			
	K100LV	K4M	K15M	K100M
Weight (mg)	250.47 ± 0.84	250.30 ± 0.54	251.30 ± 3.89	251.03 ± 0.88
Volume (cm^3)	0.26742	0.26975	0.26541	0.27041
Porosity (%)	36.91	36.77	33.57	37.18

2.5. Similarity factor

To determine the similarity between the obtained drug release profiles f_2 factor [40,41] was calculated according to Eq. (2).

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} w_t (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\} \quad (2)$$

This being a mathematical treatment of the dissolution data where;

n = number of pull points for tested samples.

w_t = optional weight factor.

R_t = reference assay at time point t.

T_t = test assay at time point t.

Similarity factor was calculated using the drug release profile obtained at 10 dpm as the reference standard. An f_2 value ranging from 50 to 100 suggests a similarity in the test and the reference drug release profiles. The closer the f_2 value is to 100, the more similar or identical the release profiles are. Also dissimilarity occurs with a decrease of the f_2 value [34]. With regard to the pull points used, due to the fast drug release from the K100LV tablet matrices, one value greater than 85% (87.56%) was used. These values were used to avoid bias in the similarity factor, f_2 [42].

2.6. Mechanism of drug release

The Power law as in Eq. (3) was introduced by Peppas and his fellow workers [43,44]. It is a simple yet more comprehensive way of describing drug release.

$$\frac{M_t}{M_\infty} = kt^n \quad (3)$$

where;

M_t = cumulative absolute drug amount at time t.

M_∞ = cumulative absolute drug amount at infinite time.

k = constant (incorporates the structure and geometrical characteristics of the device).

n = release exponent which determines the mechanism of drug release.

In general, n values close to 0.5 are indicative of the drug release primarily by diffusion. Values of 1 for n means drug is released by the process of swelling. Anomalous transport is the term given to values which occur between n values of 0.5 and 1. This is an indicator of the superposition of both processes [45]. However for cylinders, which were the shape of the tablet matrices made in this experimentation, the n values are slightly different as derived by [45,46]. Values of n up to 0.45 suggest Fickian diffusion, and values above 0.89 suggest Case-II transport. Values between these two suggests anomalous transport occurring.

3. Results and discussion

Physical characterisation of the produced compacts is presented in Table 3. Figs. 1–4 show the influence of agitation on drug release from tablets made using different HPMC polymer grades, i.e., K100LV, K4M, K15M and K100M respectively. It was observed that for the matrices that contained lower viscosity polymer K100LV, once in water with the applied agitation, fragments of the tablet were coming off from the matrix surface into the solution before a full gelatinous layer was formed. This was very evident with the increased agitation of 30 dpm. It is important that the formation of a gel layer occurs quickly enough to prevent fast water penetration inside the tablet core and potential matrix disintegration [45,47]. None of the tablets produced that underwent the various levels of agitations disintegrated.

Table 3 also shows the porosity of all tablets made of different HPMC polymers. It is clear from the table that all tablets showed similar porosities. The authors do not believe that in the present study porosity of tablets played a major role in the drug release behaviour from HPMC matrices. Therefore, no further discussion was made on the effect of porosity of tablets on drug release.

Drug release rate was in the order of K100LV > K4M > K15M > K100M. This showed that the erosion occurring as a result of the increased agitation was more rapid for the HPMC with the lower molecular weight, which in this case was the K100LV. This was consistent with the work carried out by Tahara et al. [48] and Kavanagh and Corrigan [49] that showed that erosion was quicker for lower viscosity polymers. They also showed that matrices made of HPMC polymers with higher molecular weight were less susceptible to erosion as a result of them having a higher intrinsic water holding capacity.

The type of food ingested could greatly affect the amount of drug released. Lipids are a major component of food and influence drug absorption. Ingested lipid decreases gastric motility [50–52]. Also the presence of lipid digestion products within the upper small intestine induces the secretion of biliary and pancreatic fluids that dramatically alter the luminal environment [52–55]. Abrahamsson et al. showed the disintegration of a tablet with strong food effects happening in the presence of single components of food in the order; fat emulsion (F) > carbohydrate (C) > protein (P). In other words protein had the least effect on the disintegration of tablets. A combination of all three components of food delayed the disintegration time to 33 min [19]. Abrahamson's results thus show that the type and composition of a meal had vital or critical effect on tablet disintegration as a result of food interactions. These different food components could thus be related to the differing agitation rates applied with perhaps the fastest drug release profiles being attributed to the fat emulsion diet and the slowest to the combination of the three components of food.

Fig. 5 where the dip rate was plotted against the drug release in its respective medium show that with an increase in the agitation an increase in the theophylline release rate from HPMC matrices occurred. The positive slope in Fig. 5a at pH 1.2 indicates that there was a rapid tablet erosion taking place as the dip rate was increased. Also evident here is the proof that erosion was higher for the polymers with lower molecular weight. It can be seen at pH 1.2 that about 80% of the drug was released from the K100LV formulation as compared to about 40%, 32% and 25% in the case of K4M, K15M and K100M matrices respectively at 30 dpm. This was in sharp contrast to the release of 37%, 18%, 17% and 12% for the formulations of K100LV, K4M, K15M and K100M respectively at a lower dpm of 5 in the same medium. The relatively higher amount of drug in the initial medium of pH 1.2 could be due to some portion of the drug near the surface dissolving into the medium before the gel

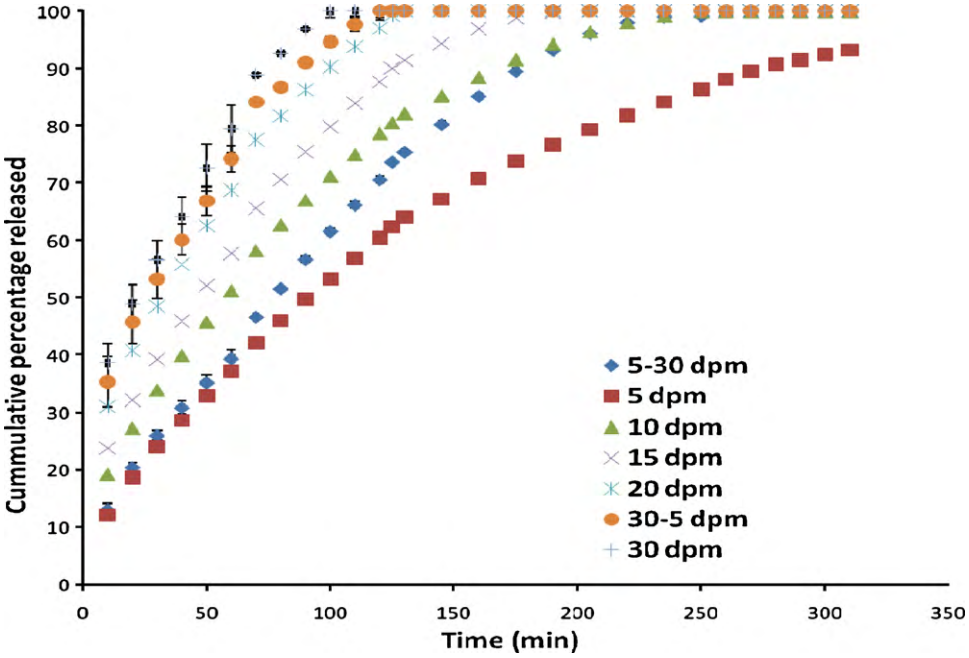

Fig. 1. The effect of rate and order of agitation on drug release from HPMC K100LV matrices.

layer was formed. The decrease in the drug release from K100LV formulations and thus the decline in the positive slope in the drug release-dip rate profiles in pH 2.2–7.2 in Fig. 5(b–f) are a result of the decreasing amount of the theophylline left as it had gone into solution at higher dip rates. K4M, K15M and K100M matrices were more resilient to the effects of agitation in comparison to the K100LV formulations. K4M had a higher release rate as compared to the K15M and K100M. This was expected as K100M has the highest viscosity. Again the drug release-dip rate graphs showed the linearity of the increased drug release as agitation was increased till pH 7.2 when it was evident that at 30 dpm, most of the drug had gone into solution discontinuing the linearity of the K4M. If there was a higher drug loading, this linearity would have continued. This linearity however was always present in the case of K100M, and even in pH 7.2 only about 52% of the drug was released at a constant agitation of 30 dpm. This depicts how the development of this methodology in the manipulation of dip rates could potentially be used in the discrimination between fed and fasted effects on HPMC polymer matrices.

A comparison of the ascending and descending agitations rates used showed that a lot more of the drug was released from the tablet matrices when agitation started at high 30 dpm (Table 4).

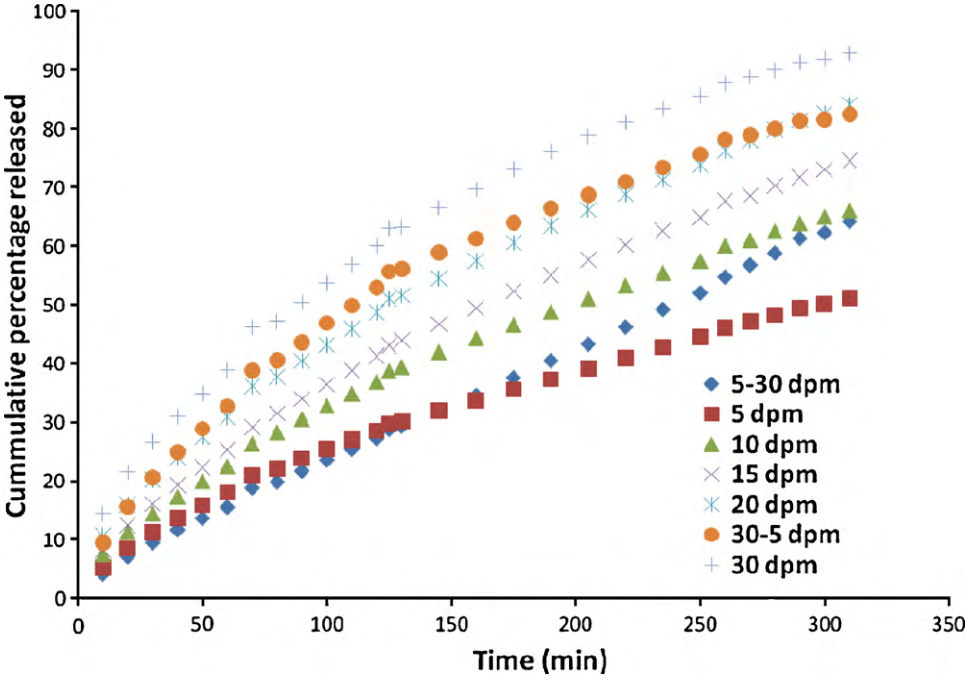

Fig. 2. The effect of rate and order of agitation on drug release from HPMC K4M matrices. Standard deviations were smaller than the symbol size and as such were not shown here.

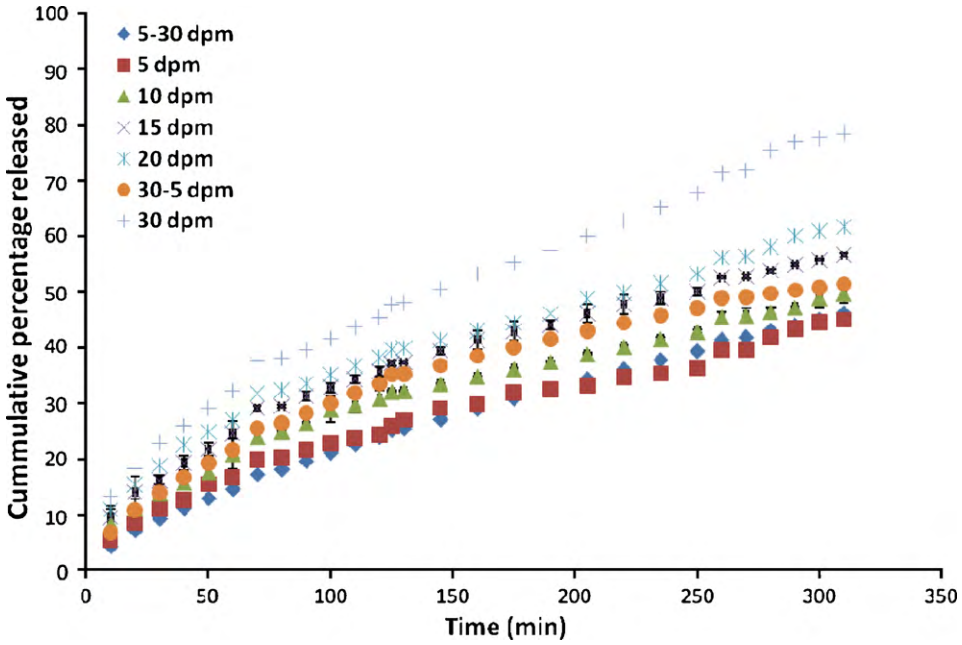

Fig. 3. The effect of rate and order of agitation on drug release from HPMC K15M matrices.

Table 4
The amount of the drug released (%) when increasing or decreasing the agitations during the dissolution test.

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	82	46	51	38	49
	Medium pH	7.2	2.2	7.5	7.5	7.5	7.5	7.5	7.5
	Time (min)	260	120	310	310	310	310	310	310

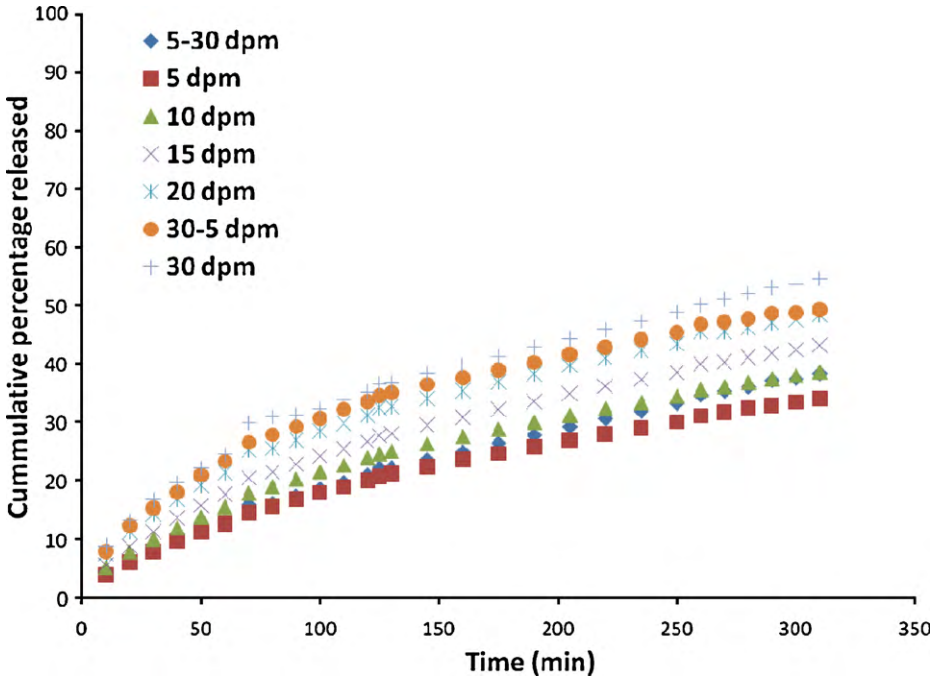

Fig. 4. The effect of rate and order of agitation on drug release from HPMC K100M matrices. Standard deviations were smaller than the symbol size and as such were not shown here.

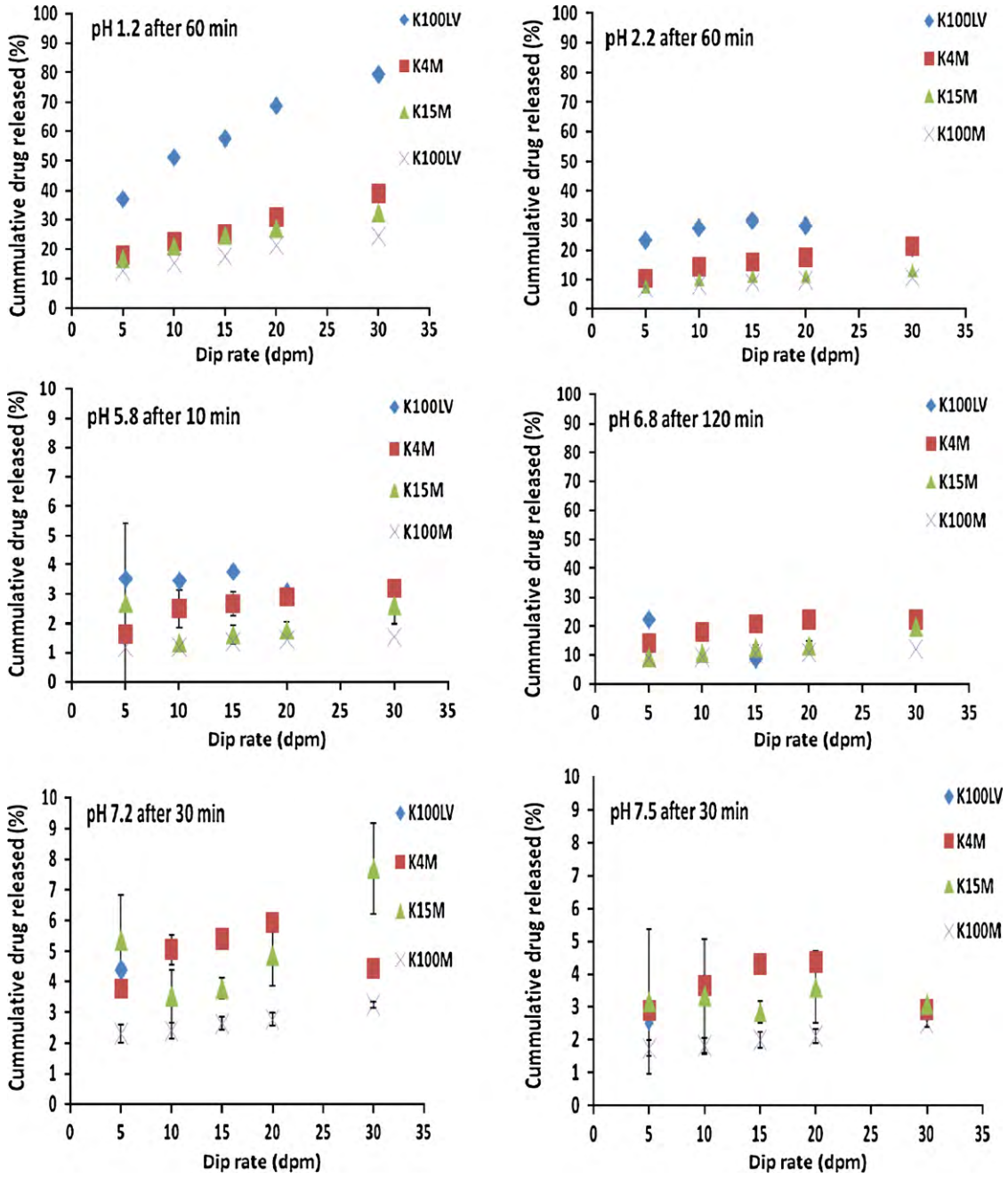

Fig. 5. (a–f) The cummulative drug release from matrices made from different HPMC grades at the varying agitation rates in a particular medium after their respective times. Standard deviations smaller than the symbol size were not shown on the graphs.

In the case of the K100LV tablets all drug was released in pH 2.2 after 120 min with starting agitation of 30 dpm with 75% of the drug being released in pH 1.2 alone. When agitation was started at 5 dpm, the entire drug was released much later in the pH 7.2 after 260 min with 40% of the drug being released this time in pH 1.2 only. This stark difference could be attributed to the increased agitation not allowing the gel layer formation properly. This difference may also be due to increased rate of erosion of the gel layer following an increase in agitation. This big difference was less apparent with the higher molecular weight K15M and K100M HPMC polymers. The small intestine is usually the primary site of drug absorption because of its greater mucosal surface area and a range of transport mechanisms [56]. Because food inhibits the rate of gastric emptying, increased or prolonged retention of dosage form in the stomach may cause an increase in the proportion of the drug that dissolves prior to passage into the small intestine. Again the development of this methodology allows for the possible evaluation of this phenomenon.

A distinctive but brief elevation of gastric pH occurs after the ingestion of food despite an increased gastric acid secretion due to the diluting and buffering effect of the food components [54,56]. After gastric emptying, there is a gradual decline in the gastric pH until the fasted-state pH environment has been re-established. The influence of pH on drug release is evident in Fig. 5(a–f). When the slope values of the dip rate vs. cumulative drug release (Fig. 5) for tablet matrices were calculated, it was observed that there was a general decrease in the slopes of the release profiles in the varying pH of the medium. A closer look at the slope values (these slope values were obtained from % release vs. square root of time) for different agitations obtained from Fig. 6 and tabulated in Table 5

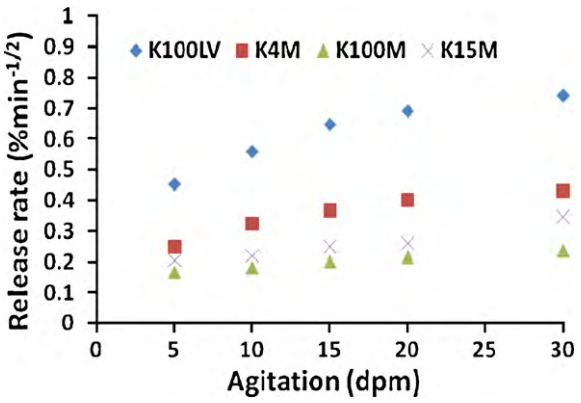

Fig. 6. Drug release rate changes from HPMC K100LV, K4M, K15M and K100M tablets with respect to the differing agitations used.

showed that for the K chemistry polymers, slope values were in the order of K100LV > K4M > K15M > K100M. This could be attributed to a number of reasons, i.e. the gel being formed on the surface of the tablet upon its introduction into media limiting the amount of drug being transported into the solution as drug moved from one medium condition to another. The change in the tablets geometry as a result of agitations in previous medium/media meant the remaining tablet matrix had a decreased surface area. The little drug remaining in the gel layer thus has a relatively lower slope upon its introduction into the ensuing fresh volume of dissolution medium. The K100M tablets however had lower slope values as compared to the K4M and K15M tablet matrices. This can be attributed to the more resilient nature of the K100M polymer as it was less prone to the effects of agitation. This meant little drug diffused across the layer into the medium.

Fig. 7 shows the effects of agitations in the ascending order of 5–30 dpm and the descending order of 30–5 dpm on the release of theophylline. The effects of agitations in these cases were very evident for the K100LV tablets. The susceptibility of the K100LV tablet matrices to the effects of erosion was very evident as agitation started in the descending order of 30–5 dpm. This shows that the effects of food (agitation) should be evaluated in order to predict the amount of drug released in the stomach, duodenum, jejunum, proximal and distal illeums and prevent a potential dose dumping. Additionally it has to be taken into account that the increase in stomach pH in response to food ingestion makes it difficult in the prediction of the likely overall effect on bioavailability [20]. The K15M and K100M tablet matrices were however less affected. Agitations where not needed in a formulation could cause relatively fast drug release resulting in a possible toxicity or making drug not available in the required medium or site. This thus shows the importance of formulating robust formulations as drug release in the desired medium is important.

The similarity factor, f_2, was used to give an in-depth analysis of the overall drug release dissolution profile. The drug release profile at 10 dpm was used as the reference profile due to the reasons given in the introduction section. With f_2 values of 57.5 at 15 dpm and 51.4 at 5–30 dpm, there was similarity occurring between the release profiles for those K100LV tablet matrices. A value of 42.0 suggested there was no similarity at 5 dpm. Due to the fast drug release from the K100LV tablet matrices, it was not possible to ascertain f_2 values at some of the faster agitation rates of 20 , 30 and 30–5 dpm. f_2 Values of 46.8, 32.9 and 42.2 for agitations 20 , 30 and 30–5 dpm for the K4M matrices suggested that the drug release profiles were dissimilar. The higher viscous polymers of K15M and K100M showed similarity at all levels of agitations with the exception at the highest rate of agitation of 30 dpm with values of 35.8 and 45.5 respectively (Table 6).

Table 7 shows that with regard to the K4M, K15M and K100M formulations, anomalous transport was the only kinetics of theophylline release as their n values were above 0.45 [45,46]. In the case of matrices containing HPMC K100LV subjected to 30 dpm and also where agitation was changing in ascending order 5–30 dpm and in the descending order 30–5 dpm n values were 0.4334, 0.2002 and 0.441 respectively which is an indication of Fickian diffusion [45,46]. However, in the case of low agitation rates 5, 10, 15 and 20 dpm for the K100LV tablet matrices, the drug release mechanism followed anomalous transport as their n values are above 0.45 but less than 0.89.

Table 5
Drug release rates from tablet matrices made from K100LV, K4M, K15M and K100M polymers.

Agitation	Drug release rates (%min$^{-1/2}$)			
	K100LV	K4M	K15M	K100M
5	0.451807	0.248484	0.205145	0.164537
10	0.558163	0.324214	0.218922	0.180361
15	0.64667	0.36641	0.249184	0.2006
20	0.689852	0.401154	0.260834	0.215215
30	0.739959	0.430674	0.346819	0.235803

Table 6
Similarity factor values obtained for the theophylline dissolution profiles from the HPMC matrices using release at 10 dpm as a reference.

Agitation (dpm)	Formulation			
	K100LV	K4M	K15M	K100M
5	42.0	53.2	65.0	70.7
15	57.5	66.5	61.7	73.0
20	–	46.8	53.1	55.3
30	–	32.9	35.8	45.5
5–30	51.4	55.1	63.3	81.9
30–5	–	42.2	76.3	50.9

Table 7
The effect of agitation rate on mechanism of drug release for formulated tablet matrices.

Formulation	Agitation (dpm)	RSQ (r^2)	n
K100LV	5	0.9918	0.5957
	10	0.9914	0.5471
	15	0.9935	0.5346
	20	0.9920	0.4744
	30	0.9819	0.4334
	5–30	0.9834	0.2002
	30–5	0.9902	0.4410
K4M	5	0.9962	0.6460
	10	0.9978	0.6416
	15	0.9980	0.6467
	20	0.9977	0.6013
	30	0.9951	0.5425
	5–30	0.9959	0.7964
	30–5	0.9884	0.6132
K15M	5	0.9928	0.5862
	10	0.9952	0.5250
	15	0.9951	0.5117
	20	0.9942	0.4867
	30	0.9954	0.5141
	5–30	0.9980	0.6793
	30–5	0.9885	0.5724
K100M	5	0.9947	0.6299
	10	0.9940	0.5826
	15	0.9922	0.5792
	20	0.9916	0.5264
	30	0.9887	0.5067
	5–30	0.9965	0.6616
	30–5	0.9854	0.5116

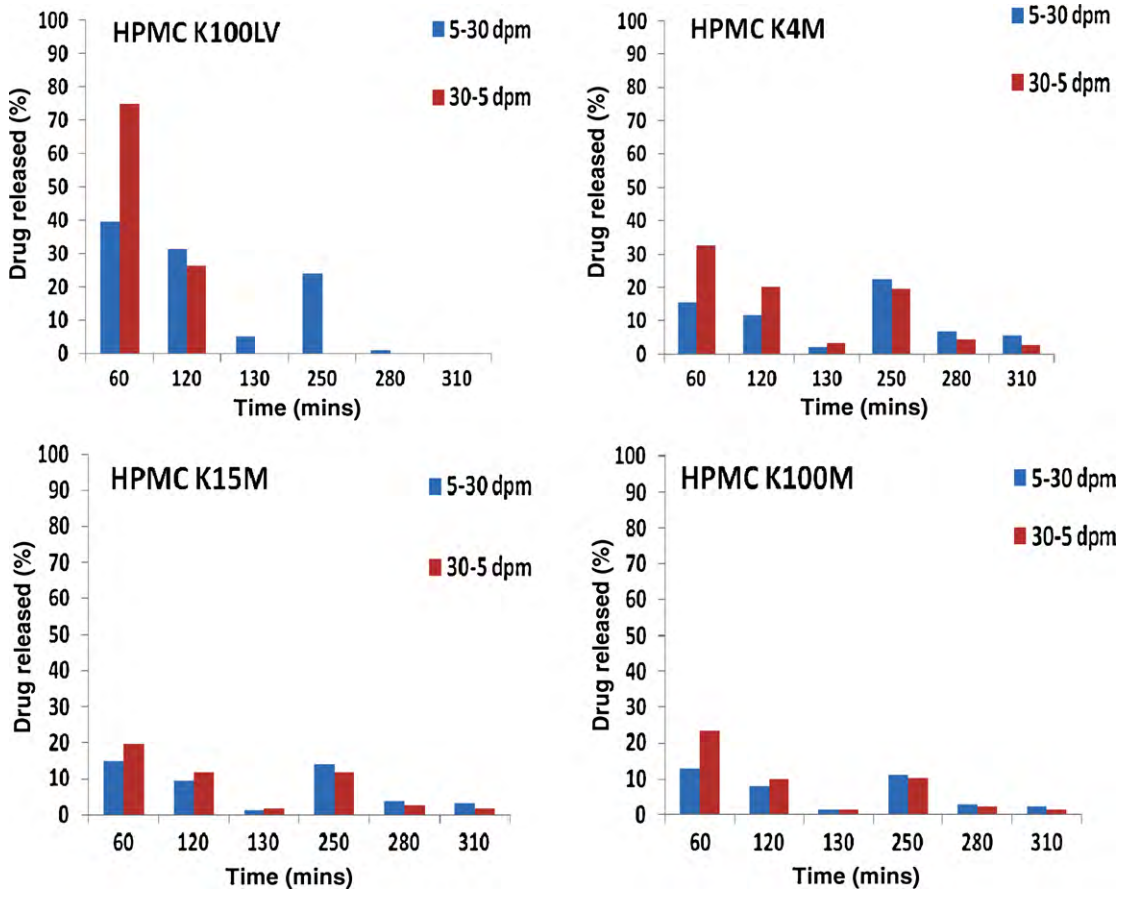

Fig. 7. The theophylline release from matrices made with different HPMC grades at ascending and descending agitations.

4. Conclusion

The drug release rate increased as agitation was increased for all matrices investigated in the study. Ascending and descending agitation in the dissolution vials containing media with varying pH resulted in significant differences in theophylline release rates for the K100LV and K4M tablets. This investigation highlights the importance of controlling drug release in the desired dissolution medium as agitation could cause a fast drug release that could potentially cause toxicity in vivo or make drug not available at the required site. The resilient nature of the produced gel layer around K4M, K15M and K100M matrices indicates that these polymers might be the best candidates for producing release profiles less affected by potential food effects compared to other polymers used in the study. The systematic change of agitation method may thus be used to indicate potential fed and fasted effects on drug release from hydrophilic matrices.

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