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Research paper

In vitro and in vivo erosion of two different hydrophilic gel matrix tablets

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Abstract

The aim of the present work was to establish in vivo predictive in vitro tests for the tablet erosion of two different compositions (A and B) of hydrophilic matrix tablets based on hydroxypropyl methylcellulose. The tablet erosion was studied in a modified USP II apparatus at different agitation intensities and ionic strengths according to 2^2 factorial design. The in vivo tablet erosion was studied in 8 healthy human volunteers by gamma scintigraphy after administration of the tablets together with breakfast. In vitro agitation intensity increased the erosion rate for both tablets whereas increased ionic strength caused a slower rate for tablet A and a faster rate for tablet B. The choice of in vitro testing conditions proved to be critical for the attainment of in vivo predictive results. The best in vitro/in vivo correlation for the two formulations was obtained at a paddle stirring rate of 140 rpm and a ionic strength of 0.14 obtained by addition of sodium chloride. © 1998 Elsevier Science B.V. All rights reserved

Keywords: Hydrophilic matrix tablets; Tablet erosion; Gamma scintigraphy; In vitro/in vivo correlation

1. Introduction

Hydrophilic gel matrix tablets are a well known type of extended release (ER) formulation for oral administration [1,2]. This principle has also been successfully applied for several drugs as exemplified by the marketed ER tablets of felodipine (Plendil®, Astra), nifedipine (Nifelan®, Elan) and alprazolam (Xanax® XR, Pharmacia/Upjohn).

The main constituents for this kind of tablets are hydrophilic polymers, e.g. hydroxypropyl methylcellulose (HPMC), which in contact with an aqueous environment forms a gel matrix. The drug release proceeds by diffusion through the gel layer and/or erosion of the tablet matrix. The release of poorly soluble compounds is controlled by erosion [3–5]. The tablet erosion is thus the most critical property for such drugs in order to obtain the desired target plasma concentration profiles and clinical benefits of ER administration.

The varying conditions along the gastro-intestinal (GI) tract can potentially affect the tablet erosion for a gel matrix tablet and thereby alter the drug release rate. In vitro studies have shown clear effects of agitation intensity and ionic composition of test media while changes in pH have little effect, at least for non-ionic polymers such as HPMC [3,6–8]. The in vivo relevance of such effects is, however, less clear since interpretation of drug release in this respect is rare and almost solely made from plasma concentration data, which can be confounded by other pharmacokinetic factors. Furthermore, the in vivo milieu is complex and variable. In particular, knowledge regarding the mechanical stress exerted by the different motility patterns and hydrodynamic conditions in the GI tract is limited. In vivo studies of tablet erosion of hydrophilic matrix tablets could provide improved understanding of the relevance of such factors. This is of importance both for choice of in vitro dissolution test methods and for formulation design.

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Gamma scintigraphy provides an opportunity for non-invasive studies of tablet erosion in man. By using a non-diffusible radionuclide which is dispersed in the gel matrix, the tablet erosion can be monitored by measuring radioactivity remaining in the tablet at different times [9]. The tablet position in the GI tract can also be monitored by gamma scintigraphy which allows for elucidations of site-specific properties of the tested formulations.

In the present study, the tablet erosion was investigated in vitro and in vivo for two different hydrophilic gel matrix tablets. Different in vitro test conditions were used with the main aim to establish a test which could predict in vivo performance.

2. Materials and methods

2.1. Study formulations

Two different hydrophilic gel matrix tablets (A and B) were included in the study. Both tablets included approximately 50% HPMC. A and B contained HPMC 2910 50 cps and 10 000 cps, respectively. Tablet A also included 1% carboxypolymethylene and 6% ethylcellulose as release rate controlling agents. Tablet A contained 30 mg nifedipine, a non-ionic drug, whereas tablet B was a placebo. Both tablets were circular, biconvex with a diameter of 10 mm and they were manufactured by standard procedures including wet granulation.

The tablets included in the in vivo study where labelled with 4 MBq Cr-51 in an inert, non-diffusible form [9]. The radionuclide was homogeneously dispersed in the tablet matrix as a marker for the erosion and the GI location of the tablet.

2.2. In vitro testing

The tablet erosion was studied in 900 ml 0.005 M phosphate buffer, pH 6.5, thermostatted to 37°C in a USP apparatus II (paddle). The dissolution equipment was modified with a stationary basket in order to avoid random sticking of the tablets to the beaker wall [10]. The tablet erosion was determined by weighing the tablets after drying to constant weight and expressed as percentage of the initial weight. The effects of paddle stirring rate between 50 and 150 rpm and ionic strength between 0.1 and 0.3 by addition of sodium chloride were evaluated by a 2^2-factorial design with a centre point (100 rpm/μ = 0.2). Single measurements of the tablet erosion were made for each time point except for triplicates in the centre point experiment. The tablet erosion rate was characterised by the mean erosion time (METvitro), corresponding to moment analysis determination of mean dissolution time [11]. Since the tablet erosion was linear up to 90% erosion, the mean erosion time was determined by linear regression as the time when 50% of the tablet had eroded. The effect of the paddle stirring rate and the ionic strength on METvitro were calculated by multiple linear regression after log transformation, the statistical significance of the effects was determined and a model established for predictions of METvitro at different test conditions.

The radiolabelling of the tablets was validated by investigating the amount of radioactive marker remaining in the tablet at different times by use of an ion-chamber detector. Tablet erosion was concomitantly determined by weighing as described above. The same equipment as described above and 0.1 M phosphate buffer including 1% sodium lauryl sulfate was used. The paddle stirring rate was 100 rpm.

2.3. In vivo study

The study was approved by the Swedish Medical Product Agency, the Ethics Committee of the Medical Faculty of the University of Gothenburg, and the Isotope Committee of Sahlgren's University Hospital, Gothenburg.

The study was a two-way, randomised cross-over study with a wash-out period of at least 5 days. The study included 8 healthy male volunteers aged 20–36 years, weighing 72–85 kg and with a height of 172–192 cm. The subjects abstained from food and fluids after 2200 h on the day before drug intake. The use of tobacco, alcohol, prescription and over-the-counter drugs were not permitted prior to or during the study. The tablets were swallowed together with 200 ml of tap water immediately after ingestion of a breakfast containing two slices of white bread, 40 g cheese, 300 ml milk and 20 g cereals (2000 kJ). The osmolarity of the breakfast after homogenisation was about 600 mosmol as determined by freeze-point reduction. Standardised meals were served 4, 7, 10, 13 and 24 h after intake. The gammascintigraphic images were collected frequently over the first 16 h, at 20 h and at several times between 24 h and 36 h. The gamma-camera equipment and the measuring procedures were applied as described earlier [9].

The time for the gastric emptying and the arrival to the ileo-caecal region was determined as the midpoint of the time interval between the last image of the tablet in the preceding region and the time for the first detection in the new region. The tablet erosion was determined as the percentage of the initial radioactivity in the tablet defined as a region of interest of 10×10 pixels positioned around the pixel with maximum intensity. Data points were omitted from further analysis in case of (a) tablet movements during sampling, defined as images with anomalous spreading of the radiation in relation to the preceding and the subsequent images, (b) location close to the field of vision of the gamma cameras, or (c) lack of congruity of the positioning of the tablet between the anterior and the posterior camera. The individual erosion–time curves were fitted to the Weibull function, which has been suggested as a model of wide applicability to in vitro dissolution data [12]. The Weibull function was expressed as

$$M = M_o[1 - e^{-((t-T_o)/a)^b}]$$

where M is the fractional tablet erosion at time t, M_o is the final asymptotic plateau level in the erosion–time curve, T_o is the lag-time of no erosion, a is a measure of the rate and b is parametric description of the shape of the curve form. M_o, T_o, a and b was determined by non-linear regression by using WinNonLin (Scientific Consulting, USA). The mean erosion time in vivo (METvivo) was determined from the Weibull model by use of the area between curve method [13].

3. Results

3.1. In vitro studies

Tablet erosion, determined from the amount of Cr-51 remaining in the tablets and from the dry weight of the tablets, is given in Fig. 1. The METvitro obtained by the two methods differed by less than 1 h for both tablets. This similarity indicated that the disappearance of Cr-51 from the tablet reflected the tablet erosion with a precision sufficient for the present purposes. The variation between the individual measurements of the tablet erosion by weighing was not larger than 2% at any time point. The corresponding variation for the six individual measurements of the amount Cr-51 remaining in the tablets was typically about 8% and not larger than 12% in any case. This low variability further confirmed the suitability of the radiolabelling procedure for studies of tablet erosion in vivo.

The METvitro for the different experiments in the factorial design are given in Table 1. Both tablets eroded by an approximately constant rate up to 90% erosion and the coefficient of determination (r^2) was above 0.97 in all cases. The different test conditions clearly affected the tablet erosion rate for both tablets but not the shape of the erosion–time profiles. The two tablets had approximately the same erosion rate at a paddle stirring rate of 100 rpm and an ionic strength of 0.2, but their sensitivity to the changes of the test

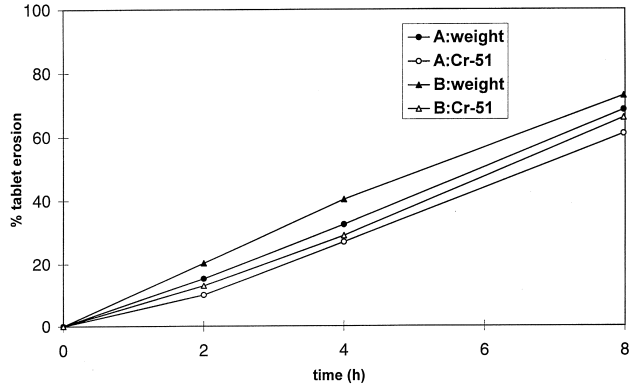

Fig. 1. Mean in vitro tablet erosion for tablets A and B determined by weighing of tablets (n = 2) and remaining amount of Cr-51 (n = 6) in the tablets.

Table 1

METvitro for tablets A and B obtained under different test conditions

Experiment no.	Test conditions		METvitro (h)	
	Ionic strength	Paddle stirring rate (rpm)	Tablet A	Tablet B
1	0.1	50	15	17.2
2	0.3	50	25	8.9
3	0.1	150	4.7	8.3
4	0.3	150	6.2	4.6
5	0.2	100	9.1	8.5
6	0.2	100	8.7	8.8
7	0.2	100	8.5	8.7

conditions was very different. The multiple linear regression model describing the effect of paddle stirring rate and ionic strength on the erosion rate, expressed as METvitro, provided good fits to the data as indicated by r^2 values of 0.98 and 0.99 for tablets A and B, respectively. The influence of the paddle stirring rate and the ionic strength and the interaction term between these two factors are shown in Fig. 2. The paddle stirring speed significantly increased the erosion rate for both tablets. The ionic strength also affected the erosion rate significantly but the magnitude was of opposite direction for the two tablets. For tablet A the METvitro increased by 50% at an increase of the ionic strength from 0.1 to 0.3, whereas for tablet B it decreased by 50%. The interaction term was not significant in any case, implying that the two tested factors did not interact regarding the influence on the erosion.

3.2. In vivo tablet erosion and GI transit

The median (range) gastric emptying time of tablets A and B was 4.0 h (2.6–14 h) and 3.7 h (2.1–10 h), respectively. The time after intake to reach the ileo-caecal region was 6.2 h (4.8–9.2 h) and 5.5 h (3.9–14 h) for tablets A (n = 7) and B (n = 8), respectively. In one subject, the erosion–time curve had reached its final asymptotic plateau level for tablet A before the ileo caecal region was reached. No tablet was expelled from the GI tract before total disintegration.

The individual erosion–time curves are given in Fig. 3 together with depictions of GI localisation. The individual and mean (SD) variables from the Weibull algorithm representing the lag-time and final plateau level are given together with METvivo in Table 2. One subject on tablet B was excluded from the evaluation of tablet erosion because too many data points had to be omitted according to preset definitions. In most subjects, the erosion rate was approximately constant during the major the part of the process. The mean (SD) METvivo was 5.0 (1.8) h and 8.1 (2.5) h for tablets A and B, respectively. The erosion–time curves reached a plateau when 5–20% of the radioactivity remained in the region of interest defined as the tablet. The final level most probably reflected gathering of released

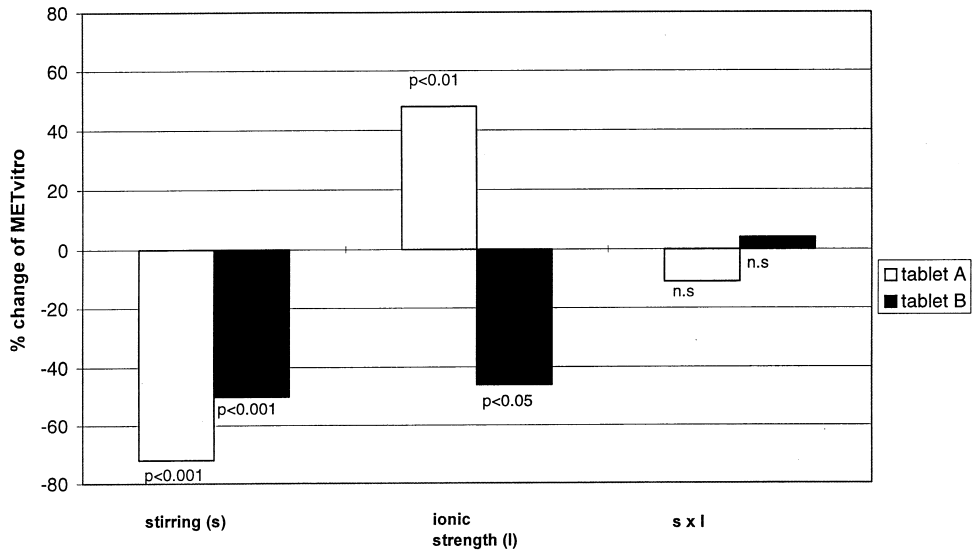

Fig. 2. The effect of paddle stirring rate and ionic strength on METvitro for tablets A and B expressed as percent change from low to high levels in experimental design.

material rather than incomplete erosion of the tablets. The erosion rate for both tablets varied substantially between the individual subjects. No clear tendencies towards shifts of the erosion rate could be detected at the time of entry into a new region in the GI tract.

3.3. In vitro/in vivo correlation of tablet erosion

A prediction model for the relationship between METvitro and the in vitro test variables was established for each tablet. The best predictability of the models was obtained by excluding the cross-term. Thereby, coefficients of prediction (q^2) of 0.85 and 0.99 were achieved for tablets A and B, respectively. These models are illustrated in Fig. 4 by contour plots for tablets A and B which are superimposed in one graph together with depictions of METvivo. As can be seen in Fig. 4, identical METvitro and METvivo can be obtained for a range of in vitro test conditions for each tablet. For example, METvitro of 8.1 h for tablet B could be obtained by using a paddle stirring rate between 70 and 150 rpm at varying ionic strengths between 0.12 and 0.30. Correspondingly, METvitro equal to METvivo could be obtained for tablet A between 130 and 150 rpm at ionic strengths between 0.10 and 0.22. However, it was only at 140 rpm and ionic strength 0.14 that a good correlation could be obtained for both tablets.

4. Discussion

The erosion for each tablet varied between the individuals beyond what could be attributed to variations in the experimental methodology and between tablets in each batch. This variability has thus to be attributed to physiological effects on the tablets in the GI tract. Both tablets in the present study were sensitive for the degree of agitation and variations in this respect are probably the main source of the in vivo variability. A similar conclusion was made in another human study on eroding HPMC matrix tablets [14]. The destructive action of the GI motility on tablets has also been well illustrated in a study where the integrity of hydrophobic matrix tablets of different crushing strength was examined after faecal recovery [15]. The intensity of mechanical stress exerted by the GI motility seems thus to be a significant factor with respect to mechanical impact on matrix tablets. Consequently, in order to minimise the variability of erosion controlled drug release from hydrophilic matrices, the effect of agitation intensity should be minimised.

Increased concentrations of sodium chloride in the dissolution medium affected the drug release in opposite direction for the two tested tablets. This could be attributed to the different gel matrix compositions since the other excipients were partly the same for the two tablets and inert with respect to control of drug release. Solutes such as sodium chloride compete for the available water in the gel layer and thereby reduce the hydration of the polymer. Increased salt concentrations can thereby lead to a stronger gel due to increased extent of hydrophobic HPMC–HPMC interactions primarily between methoxy-substituents [3]. At further increased solute concentrations the integrity of the hydrophilic matrix can be rapidly lost due to failing of gel formation or precipitation of the polymer which may cause ‘dose-dumping’ [3,7]. The decreasing erosion rate of tablet A at increasing salt concentrations thus reflects an improved gel strength provided by more intense polymer–polymer interactions. Ionic effects on the two other matrix constituents of tablet A, carboxypolymethylene and ethylcellulose, is very unlikely for the latter hydrophobic polymer whereas carboxypolyethylene may be influenced. Tablet B contained a higher molecular weight HPMC than tablet A. Polymer precipitation and faster disintegration could therefore be

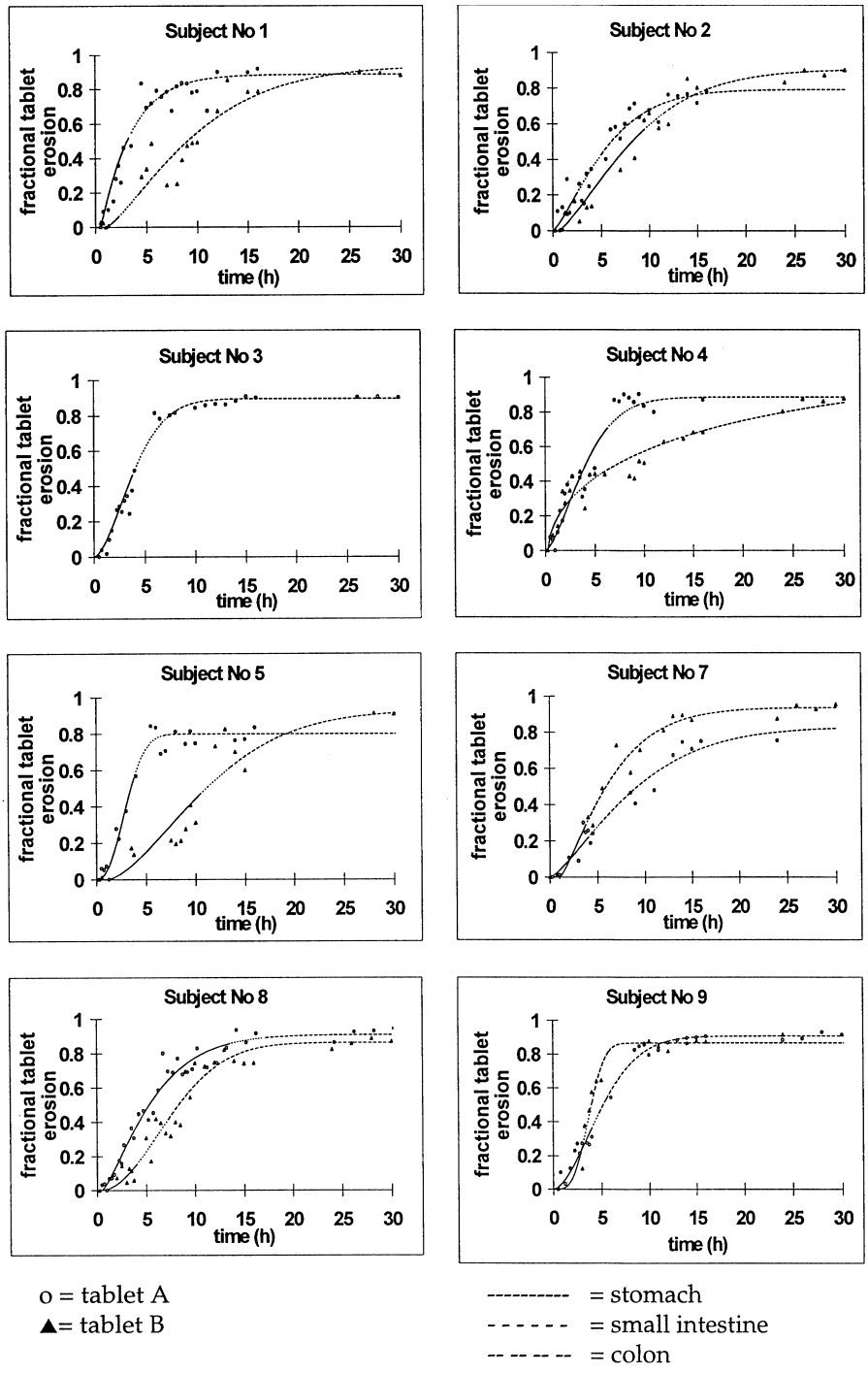

Fig. 3. Individual observed and fitted (Weibull function) in vivo erosion–time data for tablets A and B also including depictions of GI localisation of tablets.

expected at lower ionic strengths for this composition than for tablet A [16]. The polydispersity of HPMC may explain why the gel formation did not fail completely for tablet B at increasing ionic strengths based on the assumption that it was only a higher molecule fraction of the polymer in the tablet that was not properly hydrated.

In the in vivo study, a transient increase of the solute concentration in the liquid phase in the upper GI tract can be expected after the hyperosmotic meal. If this affected the HPMC hydration an initial phase of more rapid erosion should occurred for tablet B in accordance with the in vitro solute effect. However, no such trend was detected. Similarly, administration of a 0.5 M phosphate buffer solution together with a HPMC matrix tablet to humans did not affect the release rate whereas differences were obtained in vitro compared to lower buffer concentrations [17]. The solute sensitivity of the gel matrix formulations seems therefore to be of limited importance for the variability of matrix erosion in vivo probably due to the transient character of elevated solute concentrations in the GI tract.

Table 2

Individual and mean (SD) lag-time (T_o), final plateau level (M_o) and METvivo determined from in vivo erosion–time data fitted to the Weibull algorithm

Subject no.	Tablet A			Tablet B		
	M_o	T_o	METvivo	M_o	T_o	METvivo
1	0.89	0.5	3.5	0.93	1.0	9.6
2	0.79	0	5.3	0.91	0.5	8.1
3	0.90	0	4.1	–	–	–
4	0.89	0	4.2	0.89	0	9.4
5	0.80	0	3.1	0.93	1	12
7	0.83	0	8.9	0.94	1	6.5
8	0.91	0.5	5.8	0.86	0.4	8.0
9	0.90	0	5.2	0.87	0.5	3.8
Mean	0.86	0.1	5.0	0.90	0.6	8.1
SD	0.05	0.2	1.8	0.03	0.4	2.5

To establish an in vitro test method that provides in vivo predictive results is crucial for the usefulness of the method in product development and documentation. The present results illustrate the importance of choosing proper test conditions in order to obtain a good in vitro/in vivo correlation. For example, under certain test conditions the in vivo predictability were so poor that the ranking between the tablets with regard to erosion rate was opposite to the in vivo results. However, at one point (140 rpm/ionic strength = 0.14) within the tested domain of different in vitro conditions, the same METvitro and METvivo was obtained for both tablets, and this test condition could thus be viewed as optimal for in vivo predictions after administration together with food. Encouragingly, the ionic strength of 0.14 is well within the normal physiological range [18].

The paddle stirring rate of 140 rpm which provided similar in vitro and in vivo tablet erosion rates may also give some indication of the agitation intensity in the stomach and intestine after intake together with food, since it was found to be valid for two different gel formulations. There was a large variability between individuals as indicated by the wide range of METvivo. The slowest erosion obtained in vivo corresponded to a paddle stirring rate just below 100 rpm whereas the fastest reflected a value above 150 rpm at the physiologically relevant ionic strength. The use of a stationary basket slightly increased the tablet erosion rate compared to use of the standard apparatus [19] and in vivo relevant paddle stirring rates would consequently be somewhat higher compared to present results. Shameem et al. found that in vitro dissolution at paddle stirring rates between 10 and 100 rpm reflected the in vivo situation for an eroding HPMC matrix tablet after intake with food. They used a more water-soluble drug, which implies that diffusion and not tablet erosion was controlling the drug release. The drug release could be expected to be less sensitive to agitation intensity under such circumstances compared to pure erosion controlled drug release [8]. This may explain the differences between the studies regarding the levels of in vivo relevant paddle stirring rates.

In conclusion, the choice of agitation intensity and dissolution medium composition is critical for the attainment of in vivo predictive results when testing erosion controlled drug release from hydrophilic matrix tablets. A test medium with an ionic strength of 0.14 obtained by sodium chloride seems to provide physiologically relevant conditions, the mechanical stress exerted by the GI motility on the hydrophilic tablets can correspond to paddle stirring rates as high as around 150 rpm in the USP II apparatus. Minimal impact on the tablet erosion of variations in agitation seems therefore to be a desirable goal in the design of tablets with erosion controlled drug release in order to reduce the variability of the in vivo performance.

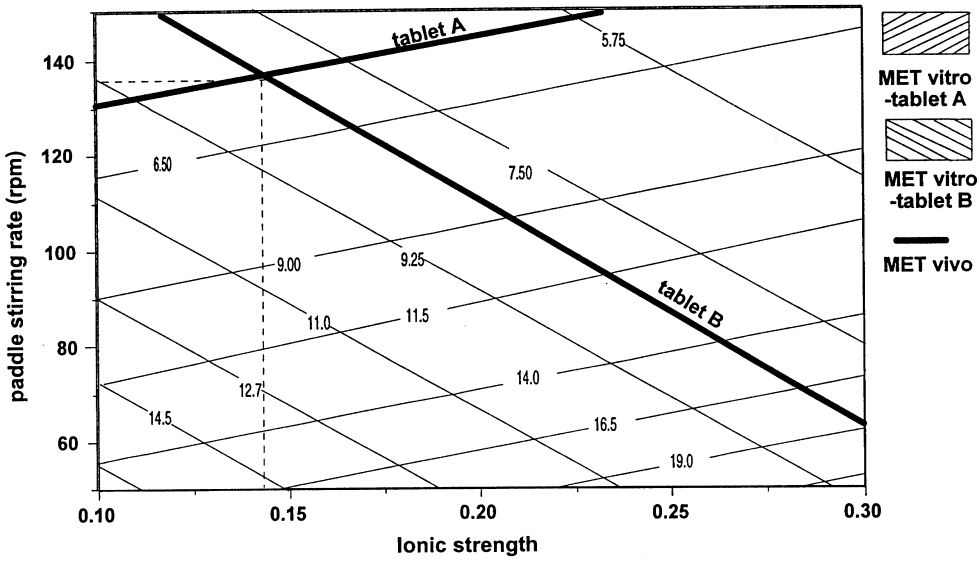

Fig. 4. Contour plot of METvitro (h) for different paddle stirring rates and ionic strengths for tablets A and B also including depictions of METvitro (h).

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