Available online at www.sciencedirect.com
ScienceDirect
International Journal of Pharmaceutics 355 (2008) 93–99
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Tablet disintegration and drug dissolution in viscous media: Paracetamol IR tablets

Jelena Parojčić *, Dragana Vasiljević, Svetlana Ibrić, Zorica Djurić

Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Belgrade, Vojvode Stepe 450, 11221 Belgrade, Serbia

Received 27 February 2007; received in revised form 8 October 2007; accepted 29 November 2007
Available online 5 December 2007

Abstract

An investigation into the influence of viscous media on tablet disintegration and drug dissolution was performed with the aim to simulate the potential formulation-specific food effect for a selected highly soluble model drug. Literature data on the in vivo drug absorption in fasted and fed state have been evaluated for in vitro–in vivo correlation (IVIVC) purposes. In vitro studies were conducted in simple buffer media with or without addition of HPMC K4M as a viscosity enhancing agent. Good IVIVC correlation ($r > 0.95$) was obtained for paracetamol dissolution in viscous media at 50 rpm and fed state absorption profiles, while in vitro dissolution in simple media at lower stirring speed was predictable of drug products in vivo behaviour in the fasted state. The data obtained support the existing idea that relatively simple dissolution media and/or set of experimental conditions may be used to differentiate formulation-specific food–drug interactions. Such tests would be a useful tool in the development of formulations that would not be susceptible to the influence of co-administered meal and, furthermore, facilitate regulatory decision on the necessity to conduct food effect studies in vivo.

Keywords: Food effect; In vitro–in vivo correlation; Paracetamol; Viscous media

1. Introduction

It is well recognized that co-administered meal may influence the process of oral drug absorption in the way that it is accelerated, delayed, decreased or increased. Although a number of factors with complex interrelationships may be responsible for the observed effect, food–drug interactions may be, generally, classified as physiologically and/or physicochemically based (Fleisher et al., 1999). Furthermore, they may be drug substance or dosage form (i.e. formulation) related. The most important interactions are those associated with a high risk of treatment failure arising from a significantly reduced bioavailability in the fed state. On the other side, food effect may be used as a strategy to improve oral absorption of co-administered poorly soluble drugs. Therefore, the effect of food is of great importance while evaluating drug efficacy and safety and should be recognized in the early phase of drug development (FDA/CDER, 2002; Li et al., 2002). There is a great interest for in vitro simulation of such interactions as the in vitro predictive methodology would considerably contribute drug development process and shorten the time and expenses for bringing drug products to the market. Although the in vitro models have been, so far, used with a moderate success, there is a potential for in vitro dissolution testing to aid the evaluation of physicochemical food–drug interactions, i.e. those associated with altered solubility and drug dissolution from the dosage form. In practice, it is difficult to determine the exact mechanism by which food changes the bioavailability of a drug product, however, identification and understanding of mechanisms governing food–drug as well as drug–drug interactions may contribute to the elucidation of drug absorption mechanisms. After the considerable efforts performed during the 1980s (Maturu et al., 1986; Macheras et al., 1987; Wearly et al., 1988; Junginger et al., 1990), the subject has recently regained increased interest in terms of both investigation of the underlying interaction mechanisms, as well as design of the in vitro models that would be predictive of a potential food effect after oral drug administration (Charman et al., 1997; Fleisher et al., 1999; Singh, 1999, 2005; Schmidt and Dalhoff, 2002;

* Corresponding author. Tel.: +381 11 3951363; fax: +381 11 3974349.
E-mail address: jelena.parojcic@pharmacy.bg.ac.yu (J. Parojčić).

0378-5173/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2007.11.058

Abrahamsson et al., 2004, 2005; Anwar et al., 2005; Persson et al., 2005). Meal-induced pH changes and resulting alterations of drug solubility, enhanced solubility of poorly soluble liphophylic drugs in the presence of lipid components of a high fat meal, as well as reduced dosage form disintegration time and drug diffusivity due to the increased intraluminal viscosity were recognized as the most important physicochemical factors generating food–drug interactions. Following the introduction of Biopharmaceutics Classification System (BCS), the attempts to employ it as a framework for predicting the occurrence of food effect have been made (Fleisher et al., 1999; FDA/CDER, 2002). Although it was postulated that BCS may be used as a basis for predicting potential food effect for a particular class of drugs, there are still major concerns whether food–drug interactions are predominantly drug substance- or drug product-related and this issue merits further considerations.

It has been stated that important food effects are least likely to occur with rapidly dissolving, immediate release drug products containing highly soluble and highly permeable drug substances (BCS Class I). However, reduced postprandial absorption rate and lowered peak concentrations were reported for this class of drugs (Jaffe et al., 1971; Koch et al., 1978; Walter-Sack et al., 1989; Stillings et al., 2000; Rostami-Hodjegan et al., 2002; Souliman et al., 2006). It was reported that in some volunteers maximum plasma concentrations of paracetamol following food did not reach levels required for effective analgesia (Stillings et al., 2000). It was, also, suggested that food effect was more pronounced in the case of high carbohydrate meals and/or meal enriched in dietary fiber (Jaffe et al., 1971; Walter-Sack et al., 1989). Such results are also supported by the canine studies showing that delayed gastric emptying and the effect of the elevated intraluminal viscosity was greatest for the highly soluble drugs (Reppas et al., 1998). There are also indications that the occurrence of such an effect may be formulation-specific. Lack of food effect observed in the case of drug administered in solution and/or in the form of soluble tablets supports such an assumption and oppose the generally accepted hypothesis that gastric emptying rate is the main factor responsible for the delay in postprandial drug absorption of highly soluble drugs. Kalantzi et al. (2005) investigated paracetamol tablet disintegration in canine stomach and reported that intragastric disintegration was slower in the fed than in fasted state for film-tablet formulation, while for the uncoated paracetamol tablets difference was minimal. Such reports indicate that question of drug products bioinequivalence in the fed state may become an issue. Although delayed postprandial paracetamol absorption was evident from a number of in vivo studies, this effect was not reflected in vitro using physiologically based dissolution media simulating fasted and fed state conditions (Galia et al., 1998; Souliman et al., 2006). Kalantzi et al. (2005) reported that dissolution of paracetamol from tablets (but not from suspension) was significantly slower in milk and it was concluded that employment of milk as drug release medium was predictable of drug products behaviour in the fed state. Similar findings were reported by Anwar et al. (2005) stating that viscosity was the key parameter responsible for the delayed tablet disintegration in milk.

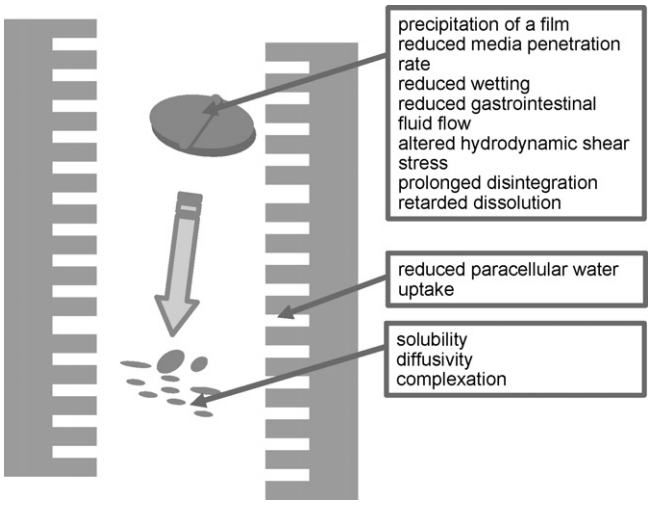

Fig. 1. Potential mechanisms of increased viscosity-induced food–drug interactions.

Increased media viscosity may affect dosage form disintegration and drug dissolution both in vitro and in vivo. A number of mechanisms responsible for this effect may be presumed: formation of the film layer on the tablet surface due to the precipitation of certain food components, decreased penetration rate of the media into the tablet, thus preventing wetting and tablet disintegration, which may be additionally delayed because of the reduced gastrointestinal fluid flow and reduced hydrodynamic shear stress encountered; further factors are related to altered drug solubility, potential complexation and decreased diffusivity of the dissolved drug, as well as the reduced water uptake by the intestinal epithelia (as dietary fibers absorb water and hydrate) which may decrease the contribution of the paracellular transport to the total absorption of small hydrophilic molecules (Fig. 1). The role of delayed tablet disintegration as the prevailing mechanism contributing food–drug interactions was emphasized more recently by Abrahamsson et al. (2004) and Anwar et al. (2005).

The aim of this work was to evaluate the impact of increased media viscosity on tablet disintegration and drug dissolution rate in vitro and its relevance to the situation observed in vivo in the presence of food. An attempt to develop level A in vitro–in vivo correlation (IVIVC) model that would be predictive of drug products in vivo behaviour was made. Paracetamol was selected as a well-known, highly soluble model drug for which extensive literature in vivo data are available.

2. Materials and methods

2.1. Dosage forms

Five commercially available paracetamol immediate release tablet formulations were investigated: P0, P1 and P2 were conventional uncoated tablets (product P0 was reported to be used in the in vivo study published by Souliman et al. (2006)), P3 were film-coated and P4 were designated as “rapidly absorbed”. The formulation compositions of the investigated products are given in Table 1.

Table 1
Formulation compositions of the investigated drug products (500 mg paracetamol per tablet)

Product	Formulation composition
P0	L-Hydroxypropylcellulose, povidone, talc, colloidal silicium dioxide, magnesium stearate
P1	White gelatin, polyethylene glycol 6000, talc, croscarmellose sodium, hydrogenated ricinum oil, microcrystalline cellulose, magnesium stearate
P2	Microcrystalline cellulose, povidone, croscarmellose sodium, colloidal silicium dioxide, magnesium stearate
P3	Starch, polyvidone, potassium sorbate, talc, stearic acid; film coating: hydroxypropylmethylcellulose, triacetin; printing ink: ethanol, propylene glycol, shellac, sodium lactate, dimethylpolysiloxane
P4	Sodium bicarbonate, soluble starch, povidone, maize starch, potassium sorbate, microcrystalline cellulose, magnesium stearate, carnauba wax, titanium dioxide, polydextrose, hypromellose, glycerol triacetate, polyethylene glycol

2.2. Media composition

USP phosphate buffer pH 5.8 (as described in the USP monograph for dissolution testing of Acetaminophen Tablet) without and with addition of 0.5 and/or 1.0% of viscosity increasing agent was used throughout the study. After performing the preliminary screening study, hydroxypropylmethylcellulose (Methocel K4M, Colorcon Co., UK) was selected as a chemically inert, water-soluble, relatively easily dispersible non-ionic polymer aimed to mimic the effect of increased viscosity. To prepare the viscous media, required amount of HPMC K4M was dispersed in one third of the amount of purified water needed for media preparation preheated to 80 °C and allowed to cool. The rest of water in which the required amounts of KH_2PO_4 and NaOH were dissolved was than added to the HPMC dispersion.

2.3. Rheological measurements

Rheological measurements were performed on the rotational rheometer Rheolab MC 120 (Paar Physica, Germany) coupled with the rotating cylinder measuring device Z2 within the shear rate range 0–300 s^{-1}. Media samples were preheated at 37 °C. All measurements were performed in triplicate. Values of apparent viscosity (at the shear rate 100 s^{-1}) were used for viscous media characterization.

2.4. Solubility determination

Equilibrium solubility of paracetamol in simple buffer and viscous media was determined at 37 °C. Excess amount of drug was added to the 50 ml of the investigated media and mixed with the magnetic stirrer for 2 h. 3 ml samples were withdrawn at predetermined time intervals (5, 15, 30, 60, 90 and 120 min), filtered, properly diluted and assayed for paracetamol UV spectrophotometrically at 243 nm. Solubility determinations were performed in duplicate.

2.5. Diffusion study

Diffusion studies of paracetamol in simple buffer and viscous media were performed in the rotating paddle dissolution apparatus equipped with the enhancer cell assembly (Vankel, USA). Accurately weighed amount of paracetamol (i.e. 2 mg/ml) was dissolved in the investigated media. 2 ml samples of the prepared paracetamol solutions were placed in the enhancer cell, covered with the semipermeable cellulose membrane (Cuprophan®, Akzo, Germany) and the cell was immersed in the dissolution vessel prefilled with 500 ml of purified water termostated at 37 °C. Paddle rotational speed was set at 100 rpm. In the predetermined time intervals (5, 15, 20, 30, 45 and 60 min), 3 ml samples were withdrawn from the vessels, filtered and assayed for paracetamol UV spectrophotometrically at 243 nm. Determinations were performed in triplicate. Drug diffusivity was expressed as the flux calculated from the slope of the initial portion of the cumulative amount of paracetamol diffused per unit area vs. time plot.

2.6. Tablet disintegration

Tablet disintegration was determined in the Tablet Disintegration Tester (Erweka ZT 32, Germany) using both simple buffer and viscous media. Tests were carried out in 800 ml of the investigated media at 37 °C.

2.7. Dissolution study

Dissolution studies were performed in the rotating paddle apparatus using 900 ml of simple buffer and/or viscous media at the paddle stirring speed of 50 and/or 25 rpm. All experiments were performed at 37 °C. A 3 ml samples were withdrawn at the predetermined time intervals (5, 15, 20, 30, 45, 60, 90 and 120 min), filtered, properly diluted and assayed for paracetamol UV spectrophotometrically at 243 nm. All determinations were performed in triplicate. Mean dissolution time (MDT) was calculated as parameter describing kinetics of drug dissolution in vitro under various experimental conditions (Eq. (1)).

$$\mathrm{MDT} = \frac{\sum_i \bar{t}_i \Delta M_i}{\sum_i \Delta M_i} \quad (1)$$

where: $\bar{t}_i$ is the central point of the observed time interval and ΔM_i is the differential amount of drug dissolved.

2.8. In vivo data

Literature data on the effect of food on paracetamol absorption in vivo were collected and analyzed (Paintaud et al., 1998; Rostami-Hodjegan et al., 2002; Kelly et al., 2003; Souliman et

Table 2
Overview of the literature in vivo data

Dosage form	$t_{max\ (fed)}/t_{max\ (fasted)}$	$C_{max\ (fed)}/C_{max\ (fasted)}$	AUC_{fed}/AUC_{fasted}	Reference
Solution	1.33	0.98	1.0	Paintaud et al. (1998)
Rapidly absorbed tablet	1.80 [a]	0.54 [a]	0.98 [a]	[a] Rostami-Hodjegan et al. (2002)
	1.85 [b]		0.94 [b]	[b] Kelly et al. (2003)
Film-coated tablet	2.18 [a]	0.61 [a]	0.95 [a]	
	2.14 [b]		1.01 [b]	
Conventional tablet	1.98	0.8	0.94	Souliman et al. (2006)

al., 2006). Drug input kinetics in vivo expressed in the form of fraction of drug absorbed (F_a) reported by Souliman et al. (2006) were employed for the in vitro–in vivo correlation studies.

3. Results and discussion

3.1. In vivo data

Literature reports show that, in the case of paracetamol tablets, large differences in drug absorption kinetics in the fed state as compared to the fasting conditions were observed both in human and canine studies. Co-administration with food has led to the reduced rate of paracetamol absorption, although the extent of absorption was not affected in most of the cases. There was no food effect observed, or it was negligible when paracetamol was administered as a solution or an effervescent tablet (Paintaud et al., 1998; Walter-Sack et al., 1989) and it was more pronounced in the case of film-coated tablets when compared to fast absorbed tablets (Rostami-Hodjegan et al., 2002). Kelly et al. (2003) studied the rates of tablet disintegration, gastric emptying and drug absorption following administration of a new, rapidly absorbed, and a conventional film-coated paracetamol formulation. They postulated that faster drug absorption from a new paracetamol formulation containing sodium bicarbonate resulted from a combination of enhanced gastric emptying and improved disintegration/dissolution. Mean gastric emptying times for the new tablets were faster than those for conventional tablets in both fasted and fed state, although these differences were not statistically significant. However, the differences in gastric emptying were more pronounced in the fasted state and the differences in disintegration were more pronounced in the fed state. Kalantzi et al. (2005) investigated paracetamol tablet disintegration in canine stomach and reported that intragastric disintegration is slower in the fed than in fasted state for film-tablet formulation, while for the uncoated paracetamol tablets difference was minimal. The effect of food on the in vivo disintegration of the two products was in agreement with the differences observed in the in vitro dissolution profiles of

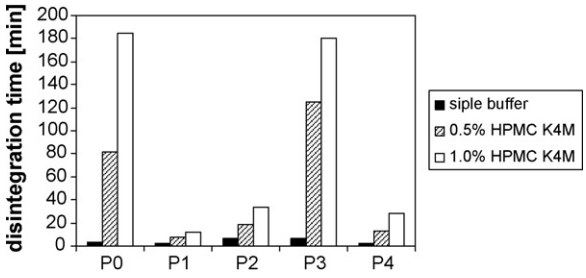

Fig. 2. Tablet disintegration times in various media.

the two tablets in milk. An overview of the literature data on paracetamol pharmacokinetics in the fasted and fed state is presented in Table 2. Although total drug exposure, measured by the AUC value, was almost the same in both fasted and fed state conditions nevertheless of the type of dosage form administered, notable differences in t_{max} and C_{max} values were observed. Co-administration with food resulted in the lowered maximum concentration and delayed drug absorption as indicated by the ratio of $t_{max\ (fed)}$ to $t_{max\ (fasted)}$. Dosage form specific effect of food was reflected by the t_{max} ratio in fed vs. fasted state ranging from 1.33 in the case of paracetamol solution to 2.18 in the case of film-coated tablets.

3.2. In vitro results

Characteristics of the investigated dissolution media are given in Table 3. Apparent viscosity of media containing 0.5% HPMC K4M was 20 cP. Its rheological behaviour may be described as, so-called "upper Newtonian", as there was certain deviation from the linearity observed in the initial portion of the flow curve, at low shear rates (below 50 s^{-1}), while at higher shear rates the flow pattern was Newtonian. Media containing 1% HPMC K4M was characterized by the apparent viscosity value of approximately 150 cP and it exhibited pseudoplastic flow behaviour. Solubility determinations and drug diffusion studies have shown that the presence of HPMC as the viscosity increasing agent did not influence paracetamol solubility nor its diffusion rate in the

Table 3
Characteristics of the dissolution media employed

Media	η (cP)	PAR solubility (SD) (mg ml^{-1})	PAR flux (SD) (mg cm^{-2} s^{-1})	Rheological behaviour
"Simple" buffer	1	18.1 (1.16)	2.37×10^{-4} (1.06×10^{-5})	
0.5% HPMC K4M	20	17.6 (2.11)	1.95×10^{-4} (2.09×10^{-5})	"Upper" Newtonian
1.0% HPMC K4M	150	17.9 (2.58)	2.18×10^{-4} (1.92×10^{-5})	Pseudoplastic

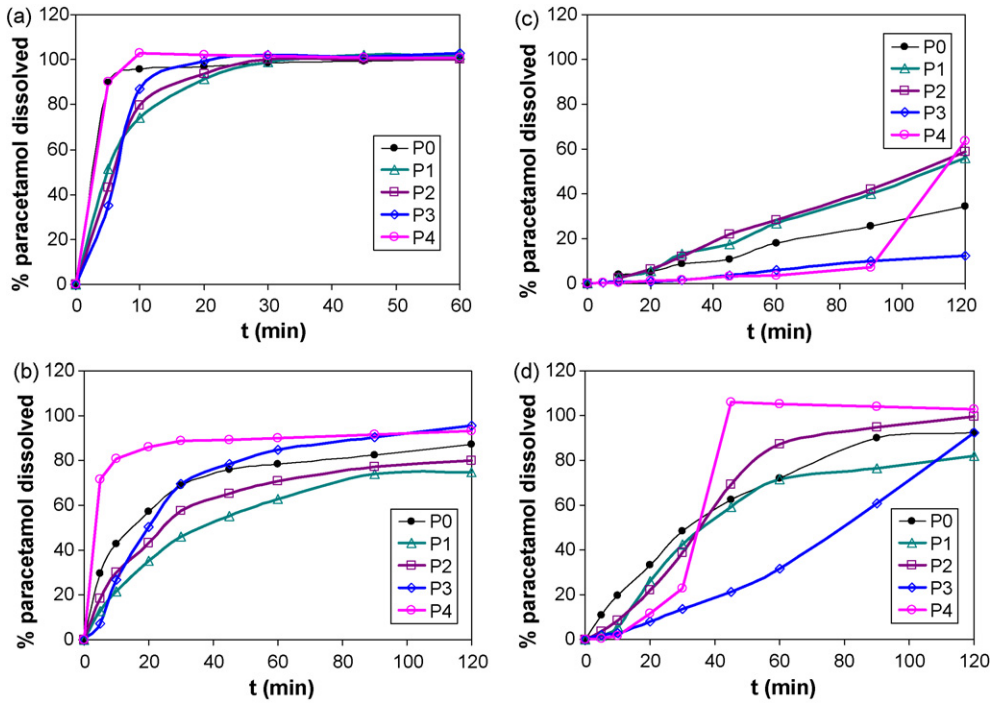

Fig. 3. Dissolution data obtained under various experimental conditions: (a) simple buffer, 50 rpm; (b) simple buffer, 25 rpm; (c) viscous media containing 1% HPMC K4M, 50 rpm and (d) viscous media containing 0.5% HPMC K4M, 50 rpm.

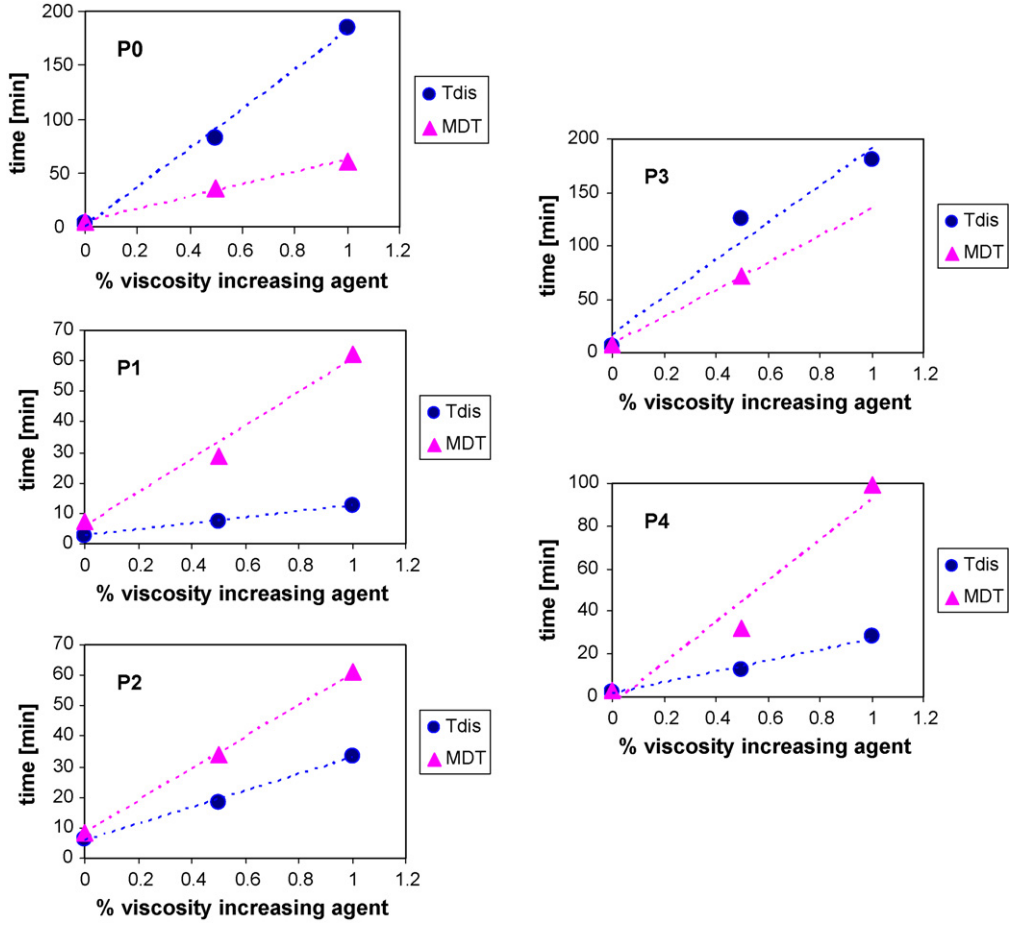

Fig. 4. Influence of viscosity increasing agent concentration in the investigated media on tablet disintegration time (T_{dis}) and mean dissolution time (MDT).

investigated media. Such findings are in accordance with data reported by Nelson and Shah (1987) showing that solute diffusivity in dilute polymeric solutions was not affected by the bulk viscosity of the media.

Results of tablet disintegration testing are presented in Fig. 2. Tablet disintegration times were significantly prolonged in viscous media as compared to simple buffer. The results of dissolution studies in various media are presented in Fig. 3a–d. Under the compendial conditions (USP phosphate buffer pH 5.8 and paddle rotation speed of 50 rpm) all the investigated products exhibited very fast dissolution with only slight differences between individual formulations and somewhat faster dissolution rate observed for P4 ("rapidly absorbed tablets") (Fig. 3a). Employment of lower stirring speed (25 rpm) resulted in the slower dissolution rate and more pronounced differences between the investigated products (Fig. 3b). Regarding the influence of media viscosity, drug dissolution in media containing 1% HPMC K4M was considerably delayed and prolonged to an extent which would question its biorelevance (Fig. 3c). However, in media containing 0.5% HPMC K4M (Fig. 3d) it was possible to distinguish the differences between the formulations and the results obtained were in rank-order with those reported from the in vivo fed state studies. Dissolution rate of conventional paracetamol tablets was least affected by the increased media viscosity, while there was a 30 min delay in drug dissolution in the case of rapidly absorbed tablets. In the case of film-coated tablets, dissolution rate was reduced to an extent that only 30% of drug was dissolved after 1 h. It may be presumed that poor wetting and reduced hydrodynamic shear rate in viscous media contributed to the phenomena observed due to the slow and incomplete dissolution of film coating in media with increased viscosity when compared to simple buffer. Also, it was apparent that dissolution profiles in viscous media reflected the prolonged disintegration time of the investigated paracetamol tablets. The effect of media viscosity on tablet disintegration time and mean dissolution time (MDT) is presented in Fig. 4.

3.3. *In vitro–in vivo correlation*

In order to test the "biorelevance" of the proposed dissolution method, an attempt to develop level A in vitro–in vivo correlation was made. Literature in vivo data on the effect of food on paracetamol absorption from conventional tablets, reported by Souliman et al. (2006), were evaluated. Souliman et al. (2006) reported level A IVIVC using artificial digestive system as an in vitro model to estimate the "availability of acetaminophen IR tablets for absorption in fasted and fed states". After performing time scaling of the in vitro data (corresponding to the gastric emptying time of 30 min in the fasted state and 60 min in the fed state), high level of linear correlation was accomplished (i.e. $r = 0.9128$ in the fasted and $r = 0.9984$ in the fed state).

In vitro–in vivo correlation plots obtained when in vivo data on paracetamol absorption reported by Souliman et al. (2006) were plotted against the in vitro data obtained in the present study are shown in Fig. 5. It was found that in vitro results

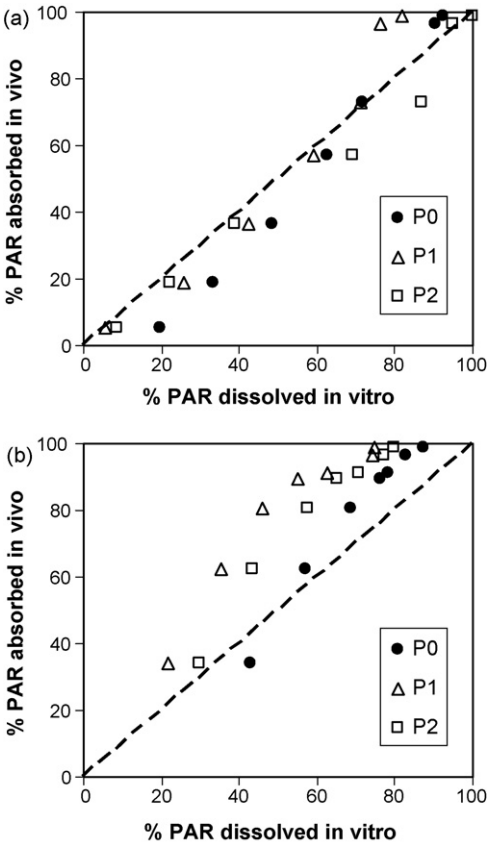

Fig. 5. In vitro–in vivo correlation plot for conventional uncoated paracetamol tablets (products P0, P1 and P2) fed state simulation (a) and fasted state simulation (b).

obtained for conventional uncoated tablets (P0, P1 and P2) in media containing 0.5% HPMC K4M were in excellent correlation with the in vivo data reported for paracetamol absorption in the fed state (Fig. 5a). Furthermore, in vitro results obtained in the simple buffer at 25 rpm corresponded well with the reported in vivo input in the fasted state (Fig. 5b). The obtained correlation plots were characterized by the coefficient of correlation values 0.9899, 0.9499 and 0.9778 (referring to the fasted state) and 0.9978, 0.9764 and 0.9876 (referring to the fed state) for the investigated conventional uncoated tablet preparations P0, P1 and P2, respectively. Corresponding values for the pooled data sets (i.e. products P0, P1 and P2) were 0.8870 and 0.9700 for the fasted state simulation and the fed state simulation, respectively. The slopes of the regression lines for the pooled data sets were close to unity (i.e. 1.0528 for the fasted state simulation and 1.1311 for the fed state simulation of the preparations P0, P1 and P2) indicating high level A IVIVC. Certain deviations from the ideal 1:1 linear correlation observed in the simple buffer at 25 rpm should be attributed to the methodology "artifact" rather than the real discrepancy due to the coning effect observed in the dissolution vessel under the low agitation intensity. Other authors have also reported good in vitro–in vivo correlation for the immediate release tablet preparations using standard dissolution paddle apparatus and lower stirring speed, such as 25–30 rpm (Radovanović et al., 1998; Rostami-Hodjegan et al., 2002a).

4. Conclusions

Experimental results from both in vivo and in vitro studies indicate that increased viscosity may be identified as an important factor causing delayed onset in plasma of highly soluble drugs co-administered with food. This effect is less likely to be attributed to the drug substance properties (drug solubility and diffusivity were not affected). It may be postulated that the effect observed results from the prolonged disintegration time of tablet formulations due to the poorer wetting of the tablet surface and the reduced hydrodynamic shear stress encountered. Furthermore, this effect may be formulation-specific, leading to the potential bioinequivalence in the fed state. An attempt to in vitro simulate food effect observed in vivo using dissolution media containing 0.5% HPMC K4M as the viscosity increasing agent, resulted in a high level A IVIVC. The proposed media exhibited the potential to differentiate formulation specific food effect observed in the case of paracetamol immediate release tablets. Such findings indicate that relatively simple and reproducible dissolution media may be used to simulate increased postprandial luminal viscosity and contribute to the existing idea that well-defined media or set of test conditions in vitro may be used to distinguish the potential food effect during the course of drug product development and approval.

Acknowledgment

This work was done under the project TR6719 supported by the Ministry of Science, Republic of Serbia. The authors would like to thank Marijana Knežević for the assistance in conducting the dissolution studies.

References

Abrahamsson, B., Albery, T., Eriksson, A., Gustafsson, I., Sjoberg, M., 2004. Food effects on tablet disintegration. Eur. J. Pharm. Sci. 22, 165–172.

Abrahamsson, B., Pal, A., Sjoberg, M., Carlsson, M., Laurell, E., Brasseur, J.G., 2005. A novel in vitro and numerical analysis of shear-induced drug release from extended-release tablets in the fed stomach. Pharm. Res. 22, 1215–1226.

Anwar, S., Fell, J.T., Dickinson, P.A., 2005. An investigation of the disintegration of tablets in biorelevant media. Int. J. Pharm. 290, 121–127.

Charman, W.N., Porter, C.J.H., Mithani, S., Dressman, J.B., 1997. Physicochemical and physiological mechanisms for the effects of food on drug absorption: the role of lipids and pH. J. Pharm. Sci. 86, 269–282.

FDA/CDER, 2002. Guidance for industry: food-effect bioavailability and fed bioequivalence studies.

Fleisher, D., Li, C., Zhou, Y., Pao, L.H., Karim, A., 1999. Drug, meal and formulation interactions influencing drug absorption after oral administration. Clin. Pharmacokinet. 36, 233–254.

Galia, E., Nicolaides, E., Horter, D., Lobenberg, R., Reppas, C., Dressman, J.B., 1998. Evaluation of various dissolution media for predicting in vivo performance of class I and II drugs. Pharm. Res. 15, 698–705.

Jaffe, J.M., Colaizzi, J.L., Barry, H., 1971. Effects of dietary components on GI absorption of acetaminophen tablets in man. J. Pharm. Sci. 60, 1646–1650.

Junginger, H.E., Verhoeven, J., Peschier, L.J.C., 1990. A new in vitro model to detect interactions between controlled release dosage forms and food. Acta Pharm. Technol. 36, 155–160.

Kalantzi, L., Polentarutti, B., Albery, T., Laitmer, D., Abrahamsson, B., Dressman, J., Reppas, C., 2005. The delayed dissolution of paracetamol products in the canine fed stomach can be predicted in vitro but it does not affect the onset of plasma levels. Int. J. Pharm. 296, 87–93.

Kelly, K., O'Mahony, B., Lindsay, B., Jones, T., Grattan, T.J., Rostami-Hodjegan, A., Stevens, H.N.E., Wilson, C.G., 2003. Comparison of the rates of disintegration, gastric emptying and drug absorption following administration of a new and a conventional paracetamol formulation, using γ scintigraphy. Pharm. Res. 20, 1668–1673.

Koch, P.A., Schultz, C.A., Wills, R.J., Hallquist, S.L., Welling, P.G., 1978. Influence of food and fluid ingestion on aspirin bioavailability. J. Pharm. Sci. 67, 1533–1535.

Li, Z., Vachharajani, N.N., Krishna, R., 2002. On the assessment of effects of food on the pharmacokinetics of drugs in early development. Biopharm. Drug Dispos. 23, 165–171.

Macheras, P., Koupparis, M., Apostolelle, E., 1987. Dissolution of four controlled release theophylline formulations in milk. Int. J. Pharm. 36, 73–79.

Maturu, P.U., Prasad, V.K., Worsely, W.N., Shiu, G.U., Skelly, J.P., 1986. Influence of a high fat breakfast on the bioavailability of theophylline controlled release formulations. An in vitro demonstration of an in vivo observation. J. Pharm. Sci. 75, 1205–1206.

Nelson, K.G., Shah, A.C., 1987. Mass transport in dissolution kinetics I: convective diffusion to assess the role of fluid viscosity under forced flow conditions. J. Pharm. Sci. 76, 799–802.

Paintaud, G., Thibault, P., Queneau, P.E., Magnette, J., Berard, M., Raumbach, L., Bechtel, P.R., Carayon, P., 1998. Intraindividual variability of paracetamol absorption kinetics after a semi-solid meal in healthy volunteers. Eur. J. Clin. Pharmacol. 53, 355–359.

Persson, E.M., Gustafsson, A.S., Carlsson, A.S., Nilsson, R.G., Knutson, L., Forsell, P., Hanisch, G., Lennernas, H., Abrahamsson, B., 2005. The effects of food on the dissolution of poorly soluble drugs in human and in model small intestinal fluids. Pharm. Res. 22, 2141–2151.

Radovanović, J., Djurić, Z., Jovanović, M., Ibrić, S., Petrović, M., 1998. An attempt on establishing in vitro–in vivo correlation: case of paracetamol immediate release tablets. Eur. J. Drug Metab. Pharmacokinet. 23, 33–40.

Reppas, C., Eleftheriou, G., Macheras, P., Symillides, M., Dressman, J.B., 1998. Effect of elevated viscosity in the upper gastrointestinal tract on drug absorption in dogs. Eur. J. Pharm. Sci. 6, 131–139.

Rostami-Hodjegan, A., Shiran, M.R., Ayesh, R., Grattan, T.J., Burnett, I., Darby-Dowman, A., Tucker, G.T., 2002. A new rapidly absorbed paracetamol tablet containing sodium bicarbonate. I. A four-way crossover study to compare the concentration-time profile of paracetamol from the new paracetamol/sodium bicarbonate tablet and a conventional paracetamol tablet in fed and fasted volunteers. Drug Dev. Ind. Pharm. 28, 523–531.

Rostami-Hodjegan, A., Shiran, M.R., Tucker, G.T., Conway, B.R., Irwin, W.J., Shaw, L.R., Grattan, T.J., 2002a. A new rapidly absorbed paracetamol tablet containing sodium bicarbonate. II. Dissolution studies and in vitro/in vivo correlation. Drug Dev. Ind. Pharm. 28, 533–543.

Schmidt, L.E., Dalhoff, K., 2002. Food–drug interactions. Drugs 62, 1481–1502.

Singh, B.N., 1999. Effects of food on clinical pharmacokinetics. Clin. Pharmacokinet. 37, 213–255.

Singh, B.N., 2005. A quantitative approach to probe the dependence and correlation of food-effect with aqueous solubility, dose/solubility ratio and partition coefficient (log *P*) for orally active drugs administered as immediate-release formulations. Drug Dev. Res. 65, 55–75.

Souliman, S., Blanquet, S., Beyssac, E., Cardot, J.M., 2006. A level A in vitro/in vivo correlation in fasted and fed states using different methods: applied to solid immediate release oral dosage form. Eur. J. Pharm. Sci. 27, 72–79.

Stillings, M., Havlik, I., Chetty, M., Clinton, C., Schall, R., Moodley, I., Muir, N., Little, S., 2000. Comparison of the pharmacokinetic profiles of soluble aspirin and solid paracetamol tablets in fed and fasted volunteers. Curr. Med. Res. Opin. 16, 115–124.

Walter-Sack, I.E., De Vries, J.X., Nickel, B., Stenzhorn, G., Weber, E., 1989. The influence of different formula diets and different pharmaceutical formulations on the systemic availability of paracetamol, gallbladder size, and plasma glucose. Int. J. Clin. Pharmacol. Ther. Toxicol. 27, 544–550.

Wearly, L., Karim, A., Pagone, F., Streicheer, J., Wickmann, A., 1988. Food-induced theophylline release/absorption changes from controlled-release formulations. A proposed in vitro model. Drug Dev. Ind. Pharm. 14, 13–28.