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Research paper

Rationale for ibuprofen co-administration with antacids: Potential interaction mechanisms affecting drug absorption

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Abstract

Ibuprofen is a widely used NSAID which is often co-administered with antacids because of its gastro-irritant effects. Literature data suggest that antacid interactions may increase or decrease the drug's absorption rate and onset of action and that the interaction may be formulation specific. In the present study, literature data on ibuprofen absorption were evaluated in order to gain insight into the nature of the in vivo effect. Solubility determinations in reactive media containing magnesium or aluminium and dissolution studies in the presence of antacid suspension were performed in an attempt to simulate in vitro the effects observed in vivo. The results obtained indicate that magnesium hydroxide enhances ibuprofen solubility, dissolution and bioavailability, while aluminium hydroxide has a retarding effect. Solubility studies indicated formation of a soluble solid ibuprofen phase in the presence of Mg^{2+}, in contrast, an insoluble ibuprofen salt was formed with Al^{3+}. The introduction of magnesium based antacid suspension into the dissolution media resulted in a formulation specific increase in drug dissolution rate with the most pronounced effect observed for the slowest release tablet formulation. The results obtained indicate the potential for in vitro studies to predict physicochemical interactions that are likely to influence drug absorption rate in vivo.

Keywords: Ibuprofen–antacid interaction; Absorption rate; Solubility; Dissolution; In vitro–in vivo correlation

1. Introduction

With the introduction of the Biopharmaceutics Classification System (BCS) and "biowaiver" concept, there is an increasing interest in the biopharmaceutical characterization of drug products with the aim of identifying and quantifying physicochemical, i.e. drug substance and formulation related factors that are likely to influence product in vivo behaviour. In this context, it was stated that "in vitro studies on drug dissolution or release rates from oral dosage forms and drug permeation across intestinal epithelia may be utilized to demonstrate the potential for drug interactions to influence a particular component of the absorption process" [1]. The same authors classified the mechanisms of drug–drug and/or drug–meal interactions into two categories: (i) physicochemical interactions involving changes in drug stability, solubility and diffusivity and (ii) physiological or biochemical interactions (e.g. alterations in gastric emptying rate, intestinal transit and intestinal, pancreatic and biliary secretion, effects on carriers and membrane bound enzymes, interactions with intestinal elimination pathways). Physicochemical interactions may occur as drug–drug, drug–food component and/or drug–excipient interactions. Furthermore, such interactions may be drug substance and/or dosage form related, as an effect on dosage form disintegration and/or drug dissolution may be encountered. Therefore, it is also important to evaluate whether the observed effect could be formulation specific.

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Ibuprofen is a well-known and widely used non-steroidal antiinflammatory drug (NSAID) regarded as one of the safest NSAIDs available [2,3]. It is often used as a self-medication drug, and, as it can cause gastro-irritant effects, it is often used concomitantly with some antacids. There are indications that co-administration with antacids can alter the drug's bioavailability and onset of action. There are a number of hypotheses regarding the possible mechanisms underlying NSAID interactions with antacids. A summary of these is given in Table 1.

The potential for NSAID–antacid interactions has been recognized and discussed in a number of review papers [1,9–13]. There are few reports of pharmacokinetic studies aimed at investigating the effect of co-administered antacid on ibuprofen absorption [14,15]. The addition of antacid and/or alkaline excipients has also been investigated as a formulation approach to enhance the absorption rate of ibuprofen after oral administration [16–19]. Formation of ibuprofen salts with metal ions such as sodium, potassium, magnesium, calcium, zinc and aluminium was also evaluated in an attempt to overcome the formulation problems with regard to its solubility, bitter taste and poor dispersibility as reported in the related patents [20–22]. However, only limited data on the in vivo bioavailability of these compounds are available [23,24]. Levis et al. [25] investigated the effect of buffer media composition on ibuprofen solubility and observed, in systems containing Ca^{2+}, visible precipitation due to the formation of the relatively insoluble salt.

There are, also, indications [26,27] that this type of drug interaction may be formulation specific, and discriminative in vitro dissolution test would be a useful tool in drug product development. Although potential ibuprofen interactions with antacids would probably not cause serious clinical implications, understanding of the underlying mechanisms would be of great importance in the cases when rapid onset of drug action is required, as well as in elucidation of its gastrointestinal absorption pathway.

In the present study, literature data on ibuprofen absorption were collected and evaluated in order to gain an insight into the in vivo situation. Solubility determinations in reactive media containing magnesium or aluminium and dissolution studies in the presence of antacid suspension were performed in an attempt to in vitro simulate the effects observed in vivo.

2. Materials and methods

2.1. Solubility study

Dynamic solubility studies of ibuprofen in reactive media containing magnesium or aluminium components were performed at 37 °C using the method of Chiou and Kyle [28], as previously employed to study the effects of buffer media composition on ibuprofen solubility [25]. Excess drug was added to 50 ml of media prepared by dispersing the defined amount of MgO, $Mg(OH)_2$, $MgCl_2$ or $Al(OH)_3$ in 0.1 M HCl or water (see Table 2, for details) in a jacketed vessel and the mixture was stirred at a constant rate by overhead stirrer. Three milliliter samples were removed at regular time intervals over a 2-h time period. After filtration and appropriate dilution, the samples were assayed spectrophotometrically at 221 nm. pH values of the filtered samples were recorded (pH meter Orion 250A). All the experiments were performed in duplicate. After the experiment, the excess solid phase was collected, dried at ambient temperature and examined by thermomicroscopy and differential scanning calorimetry (Mettler Toledo DSC 821).

2.2. Dissolution study

Four commercially available ibuprofen products, two film tablets (products A and B) and two sugar coated tablets (products C and D) were evaluated in the in vitro study. The study was performed in a rotating paddle apparatus (Erweka DT 70, Germany) at 50 rpm using 900 ml of USP phosphate buffer, pH 6.8, as dissolution media. In order to simulate the effect of co-administered antacid, 10.24 ml Milk of Magnesia® (GlaxoSmithKline, Ireland), corresponding to an 850 mg dose administered with 150 ml water in the reference in vivo study [15], was added to the dissolution media. Three milliliter samples were withdrawn at predefined time intervals, filtered and assayed UV-spectrophotometrically. The absorbance at 264 nm was employed for ibuprofen quantification [29], since it is less prone to interference from excipients than the corresponding absorbance at 221 nm. In the case of media containing Milk of Magnesia, correction of the measured absorbance with the absorbance of blank media (i.e. pH 6.8, phosphate buffer with antacid added) was performed. Dissolution profiles obtained in media with and without

Table 1
Possible mechanisms underlying NSAID interactions with antacids which may impact on bioavailability

Mechanism	Reference
Alteration in gastrointestinal motility and/or gastric emptying rate	[4–6]
Altered barrier properties of gastric mucus due to drug–mucus interaction	[7]
In vivo impact of carbonates on permeability of gastrointestinal mucus and/or paracellular transport	[8]
Increased ionization resulting in enhanced solubility, dissolution and in vivo absorption rate	[1,12,15]
Increased urinary excretion resulting from increased urinary pH	[11,12]
Formation of chelates, salts, ion-pairs and/or complexation with di- and tri-valent ions of both the drug substance and/or gastric mucus	[1,7,12]

Table 2
Summary of the dynamic solubility determinations

Alkalizing agent	Media	Amount of alkalizing agent added (mg/ml)	pH value		Solubility (C_{eq})		C_{eq}/C_0 [a]
			Initial	Final	mg/ml	mM	
MgO	0.1 M HCl	4	9.60	9.35	4.86	23.59	98.3
$Mg(OH)_2$	0.1 M HCl	6	9.10	8.24	6.57	31.89	132.9
$Mg(OH)_2$	Water	6	9.79	8.87	7.64	37.03	154.3
$MgCl_2$	Water	10	5.98	4.23	0.34	1.65	6.9
$Al(OH)_3$	0.1 M HCl	3.9	1.88	3.08	0.09	0.44	1.8

[a] Relative change in ibuprofen solubility (intrinsic solubility, $C_0 = 0.24$ mM).

added antacid were compared using the similarity factor, f_2.

2.3. In vitro/in vivo correlation

Literature in vivo data on the effect of co-administered $Mg(OH)_2$ on the absorption rate of ibuprofen reported by Neuvonen [15] were evaluated. Drug input kinetics in the form of percent of drug absorbed (Fa) were calculated by the Wagner–Nelson method from plasma concentration data as estimated from the data presented [15]. This was in accordance with other reports indicating that ibuprofen pharmacokinetics may be adequately represented by a one-compartment open model [30,31]. In order to develop an in vitro/in vivo correlation (IVIVC) model, time scaling of the in vitro data was performed. After the adjustment of the in vitro curves, interpolation of data was performed in order to assure enough data points for correlation purposes. Data on the fraction of ibuprofen absorbed in vivo were plotted against the percent dissolved in vitro with and without antacid. The obtained correlation plots were evaluated by linear regression analysis.

3. Results and discussion

3.1. Ibuprofen–antacid interactions in vivo: overview of the literature data

A survey of the literature data relating to ibuprofen–antacid type interactions indicates that concomitantly administered magnesium hydroxide, either in the form of antacid, or as tablet excipient, may to some extent increase the ibuprofen absorption rate in vivo. In contrast, aluminium hydroxide retards ibuprofen absorption, thus leading to the reduced drug bioavailability [23,24].The relevant literature is summarized in Table 3. Laska et al. [23] studied the correlation between blood levels of ibuprofen and clinical analgesic response. A clinical trial comparing different doses of ibuprofen with aluminium ibuprofen and placebo was conducted. It was shown that aluminium ibuprofen produced less analgesia as well as lower serum levels as compared with the same dose of ibuprofen alone. Eller et al. [24] reported the results from an in vivo bioavailability study of rectally and orally administered ibuprofen sodium solution and ibuprofen aluminium suspension. The results obtained indicated poor bioavailability of ibuprofen aluminium suspension irrespective of the route of administration. Hannula et al. [16] studied the absorption of ibuprofen from capsules containing aluminium hydroxide, calcium carbonate or sodium bicarbonate as the primary excipient. Their results demonstrated significant differences in absorption rate, with formulations containing calcium carbonate or sodium bicarbonate being rapidly absorbed (t_{max} 0.4 and 1.7 h, C_{max} 51.4 and 32.2 mg/l, for sodium bicarbonate and calcium carbonate containing formulations, respectively) and the aluminium hydroxide containing formulation being very poorly absorbed (t_{max} 3.1 h, C_{max} 25.6 mg/l). A rank-order correlation was observed between dissolution parameters and the in vivo data that reflect the rate of drug absorption. Gontarz et al. [14] evaluated the effect of co-administrated aluminum and magnesium hydroxide suspension on the pharmacokinetics of ibuprofen. The authors reported that, for the doses used, concurrent administration of aluminum and magnesium hydroxide suspension and ibuprofen does not alter ibuprofen pharmacokinetics. Neuvonen [15] investigated the effect of magnesium hydroxide on the oral absorption of ibuprofen (Burana 400 mg tablets). It was shown that absorption of ibuprofen was accelerated significantly when co-administered with magnesium hydroxide. A 65% increase of AUC_{0-1h} and 31% increase in peak concentration of ibuprofen in plasma were reported while the time to peak was shortened by about 0.5 h. However, the extent of drug absorbed was not changed. Furthermore, the author emphasized that the effect of magnesium hydroxide has been most pronounced in those subjects who normally had a slow absorption. The effect observed was ascribed to the increased solubility of ibuprofen at high pH. In a more recent study, Maenpaa et al. [18] reported that there was a trend toward faster absorption of ibuprofen when given in the form of magnesium hydroxide containing formulation, but the observed difference was not statistically significant. However, the magnesium hydroxide to ibuprofen ratio was notably lower compared to that applied in the study by Neuvonen [15] (i.e. 0.5 compared to 2.125) and it was stressed that the ratio between magnesium hydroxide and ibuprofen in the tablet should be higher to achieve a more significant increase in ibuprofen absorption rate. Similarly to ibuprofen, contrasting data were reported for ketoprofen co-administered with magnesium hydroxide. In the study by Neuvonen [15], no significant change in peak concentration, peak time or area under the plasma

Table 3
Survey of the literature data on ibuprofen interactions with alkalizing agents co-administered as antacid dosage forms or used as formulation excipients

	Alkalizing agent		Overall effect	Reference
Co-administered antacid	$Al(OH)_3$ and $Mg(OH)_2$	t_{max} lowered from 1.28 h to 0.95 h when co-administered with antacid	n.s.	[14]
	$Mg(OH)_2$	Increased absorption rate	↑	[15]
Ibuprofen aluminium salt administered in vivo		Lower serum concentration and lower analgesic response compared to ibuprofen free acid form	↓	[23]
		Lower absorption rate and bioavailability of aluminium ibuprofen suspension	↓	[24]
Alkaline excipients	$NaHCO_3$	t_{max} 0.4	↑	[16]
	$CaCO_3$	t_{max} 1.7	↑	
	$Al(OH)_3$	t_{max} 3.1	↓	
	$Mg(OH)_2$	A trend toward faster absorption	↑ (n.s.)	[18]
	$NaHCO_3$	Drug diffusion rate in gastric mucus	↓	[7]
	$CaCO_3$		↑	
	$Al(OH)_3$		↓	
	$Mg(OH)_2$		↑	
	MgO		↓	

n.s., not significant.

concentration–time curves was observed when fetoprotein capsules were administered with 850 mg Milk of Magnesia. However, the author commented that rapid absorption of ketoprofen (t_{max} 0.9 h) might have been the reason why the effect of magnesium hydroxide on the peak time and peak concentration of ketoprofen was not significant. Fuder et al. [32] reported that administration of buffered ketoprofen formulations (tablets containing $Mg(OH)_2$) resulted in marked and significant increase in C_{max}, while MRT was significantly reduced compared to the unbuffered tablets. The authors stressed that the influence of buffering may depend on the type of formulation.

The inconsistency of the results observed in the in vivo studies may be attributed to the intra- and inter-subject variability encountered, since most of the studies were performed as pivotal in vivo studies in a small group of volunteers. On the other hand, it may be hypothesized that the effect observed reflects a formulation specific drug–drug interaction, in which case the development of relevant media for simulation of drug interactions would be beneficial.

3.2. Interaction study: solubility

The results of solubility determinations in media containing magnesium and aluminium are summarized in Table 2. The theoretical pH-solubility curve for ibuprofen (pK_a 4.4, C_0 0.24 mM) is presented in Fig. 1 together with the experimentally obtained Cs values. Equilibrium solubility (C_{eq}) in reactive media containing 0.1 M HCl and magnesium oxide as an alkalizing agent was slightly above 20 mM (closed rectangles), while in media containing $Mg(OH)_2$ in 0.1 M HCl (open and closed circles) equilibrium solubility approached a value of approximately 32 mM (6.6 mg/ml). Similar results were obtained in media containing $Mg(OH)_2$ in water (closed diamond)

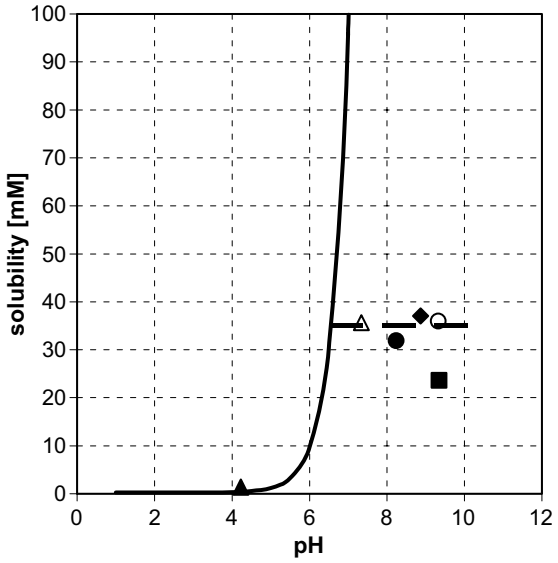

Fig. 1. pH solubility profile of ibuprofen in the presence of magnesium oxide (□), magnesium hydroxide (○), magnesium chloride (△). Solid line represents the theoretical pH-solubility profile (pK_a 4.4; C_0 0.24 mM). Closed symbols refer to ibuprofen acid, open symbols to ibuprofen sodium solubility.

($Cs \sim 37$ mM). Equilibrium solubility of ibuprofen acid in $MgCl_2$ aqueous solution (closed triangle) was 1.65 mM, which was in accordance with the value expected at the pH 4.23. Addition of an excess amount of MgO or $Mg(OH)_2$ to water or 0.1 M HCl resulted in a media pH value above 9 and under such conditions ibuprofen acid is completely ionized. It may be assumed that the observed equilibrium solubility values in media containing alkaline magnesium compounds represent the solubility of an ibuprofen magnesium salt/complex. The somewhat lower apparent solubility values observed in media containing magnesium oxide may be attributed to the slow rate of conversion of magnesium oxide to magnesium hydroxide.

DSC scans of the excess solid phases collected from the solubility experiments are shown in Fig. 2. DSC scans of the solid phase deposited in the presence of $Mg(OH)_2$ display a broad endothermic peak at ≈78 °C, which corresponds to the melting point of ibuprofen and a new endotherm with an onset value of 167 °C (Fig. 2). Such results are consistent with those reported on ibuprofen–magnesium solid-state reaction products by Kararli et al. [33] and Byrn et al. [34]. The results obtained indicate the formation of a solid state ibuprofen phase with increased solubility may also occur in vivo under the conditions of elevated microenvironmental pH upon concomitant administration of a magnesium hydroxide based antacid. In contrast, studies conducted in the reactive media containing aluminium hydroxide demonstrate the formation of a reaction product which was practically insoluble. This observation is consistent with the results of Shaw et al. [7] who reported that addition of aluminium hydroxide effectively eliminated the diffusion of ibuprofen investigated in gastric mucus in vitro. The poor solubility of ibuprofen aluminium is also in accordance with poor bioavailability observed in vivo [23,24].

The results obtained indicate that magnesium hydroxide enhances ibuprofen solubility and hence dissolution and bioavailability, while aluminium hydroxide has a retarding effect on these biopharmaceutically relevant parameters. With magnesium hydroxide a soluble ibuprofen solid phase is formed having equilibrium solubility (C_{eq}) of ~7 mg/ml and a dose number (Do) of ~0.228 (where Do = Dose/volume/solubility). In contrast, an insoluble ibuprofen complex is formed with Al^{3+} ($C_{eq} = 0.09$ mg/ml, $Do \sim 17$). The formation of this solid state composite species of ibuprofen, in the case of Al^{3+} results in non-sink conditions in the official dissolution test and results in conditions approaching solubility limited absorption, while with Mg^{2+}, absorption will be dissolution controlled and hence dependent on formulation/process variables [35].

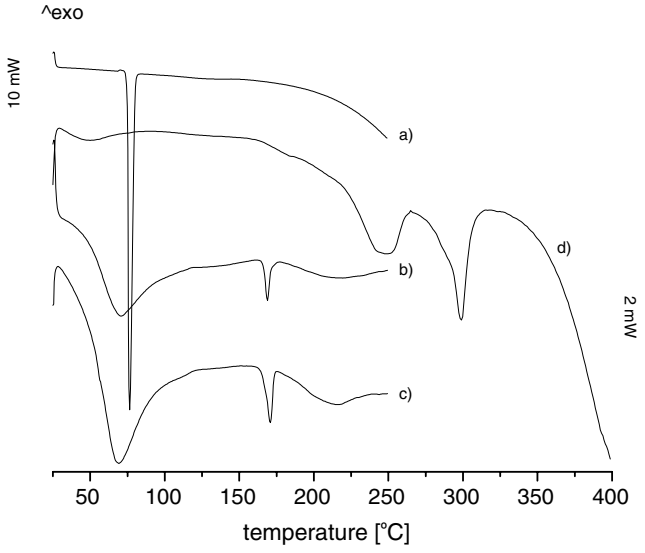

Fig. 2. DSC scan of ibuprofen (a) and solid phases deposited in the solubility study in reactive media containing $Mg(OH)_2$ (b,c) or $Al(OH)_3$ (d); (2 mW bar applies to (b–d) and 10 mW bar to (a)).

Solubility, as well as permeability of ibuprofen acid in different buffer media was also investigated [25,36]. Although a number of factors such as media composition, pH value, osmolarity and buffer capacity may contribute, it has been shown that ibuprofen permeability is enhanced in media with higher pH value and favored by the increased fluid flux across the epithelium. Such findings suggested that absorption of ionized ibuprofen takes place indicating the paracellular pathway as the predominating transport route.

3.3. Interaction study: dissolution

The solubility studies indicated that the formation of a new solid state species may be responsible for the altered absorption rate of ibuprofen when co-administered with certain alkalizing agents. It was of further interest to investigate if such interactions would affect ibuprofen dissolution from tablets, whether such interactions would be formulation specific, and, to evaluate the potential of dissolution test methodology as a predictive tool to simulate this type of drug–drug interaction in vitro.

Although USP phosphate buffer, pH 7.2, is officially recommended for dissolution testing of Ibuprofen tablets [37], there are also indications that media with lower pH value, such as, pH 6.8 phosphate buffer, may be more discriminative in a "biorelevant" manner [38]. Dissolution profiles of the investigated products studied in, pH 6.8, phosphate buffer, with and without Milk of Magnesia added, are presented in Fig. 3. Drug dissolution from film coated tablets was faster and less variable than was observed in the case of sugar coated tablets. Release can be described as "very rapid", with more than 85% drug dissolved in less than 15 min for product A and about 80% ibuprofen dissolved after 15 min in the case of film tablet B. In the case of sugar coated tablets, drug dissolution was slower and more variable. Ibuprofen dissolution from product C resulted in 80% of drug dissolved after 30 min, while product D exhibited slowest and most variable dissolution with 80% percent dissolution accomplished after 40 min. With the addition of antacid, the dissolution media pH value increased by approximately one pH unit (i.e. to pH 7.8). Drug dissolution rate was somewhat increased in the case of tablet samples B, C and D. The effect of antacid may be described as a relatively weak, but steady trend. A rank-order with the data reported in vivo by Neuvonen [15] was evident. The effect was not observed for the most rapidly dissolving tablets (product A). Drug release profiles observed in vitro with and without antacid suspension added to the dissolution media were compared according to the f_2 value (Table 4). A similarity factor was not calculated for product A which exhibited an amount of more than 85% dissolution in less than 15 min.

The highest increase in drug dissolution was obtained in the case of product D, which exhibited slowest dissolution

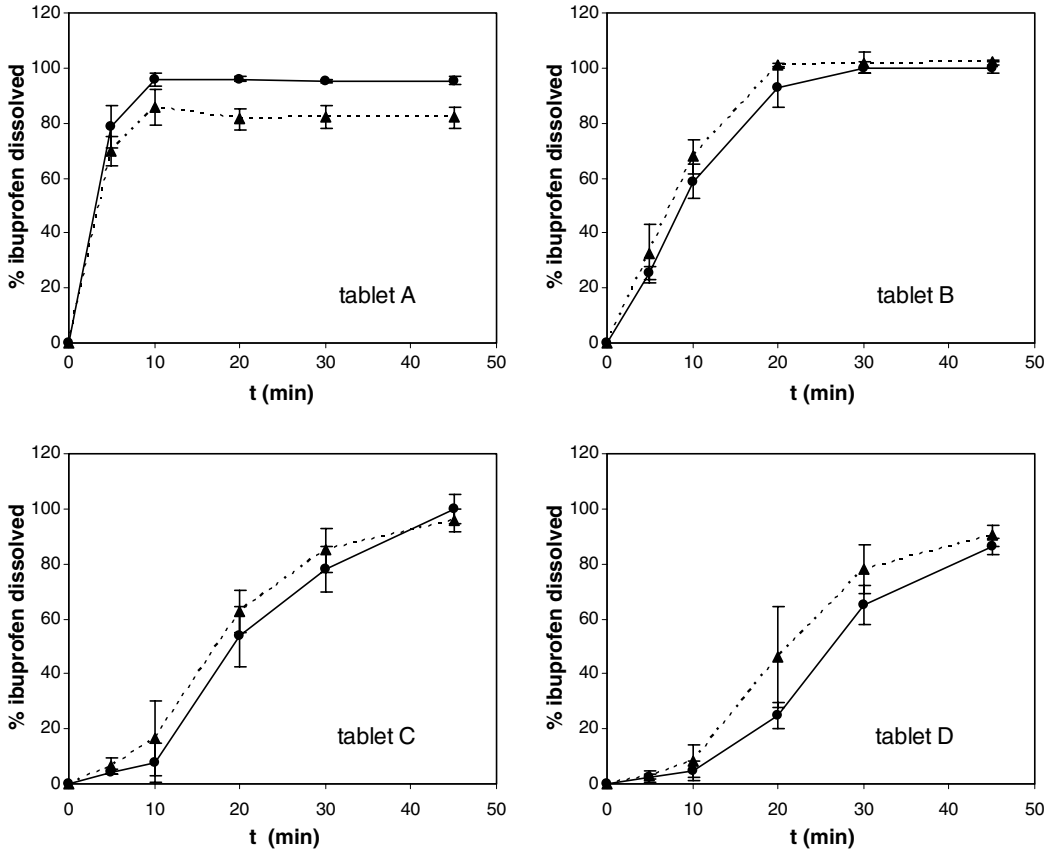

Fig. 3. Dissolution profiles in USP phosphate buffer, pH 6.8, without (solid line) and with Milk of Magnesia added (dashed line).

Table 4
Comparison of ibuprofen dissolution rate in media with and without antacid

	f_2
Product A	n.a.
Product B	59.9
Product C	58.3
Product D	47.1

n.a., not applicable.

rate among the samples investigated. Calculated values of the similarity factor further confirm such observations since the values obtained, when comparing dissolution profiles in simple buffer and in media containing antacid suspension, were higher than 50 indicating the similarity of profiles and, thus a lack of the effect of antacid, in the case of products B and C. In the case of product D, calculated f_2 value was 47.12 indicating significant differences between the dissolution profiles compared. The results obtained are in accordance with those reported by Cordoba-Diaz et al. [26,27] on the effect of pharmacotechnical design on the in vitro interactions of ketoconazole and norfloxacine with various antacids. The authors reported a decreased extent of interaction for formulations containing superdisintegrants. Such results indicate that rapidly dissolving formulations would be at lower risk of potential drug–drug and/or food–drug interactions.

3.4. In vitro/in vivo correlation

In vitro–in vivo comparison indicated a rank-order correlation between the in vitro data obtained for product D and in vivo data reported by Neuvonen. It has been demonstrated from a number of studies that different brands of conventional (i.e. immediate release, IR) ibuprofen tablets may show great differences in the pharmacokinetic behaviour due to the differences in formulation [3,39,40]. Formulation related differences in drug dissolution were clearly observed in vitro in the present study.

It may be postulated that the reported enhancement observed with concomitant antacid administration would be significant in the case of slowly dissolving tablets. Literature t_{max} values for ibuprofen tablets vary within the range 1–3 h [3], while Burana® tablets have been reported to exhibit the longest t_{max} values when compared with other commercially available preparations [39,41].

Therefore, in order to test the predictability of the proposed in vitro model, literature in vivo data on the effect of antacid on ibuprofen absorption were compared with the in vitro data obtained for product D which exhibited the slowest drug dissolution in the present study. Cumulative fractions of drug absorbed with and without co-administered antacid in vivo are shown in Fig. 4a. As expected for immediate release (IR) dosage forms, drug dissolution in vitro was considerably faster

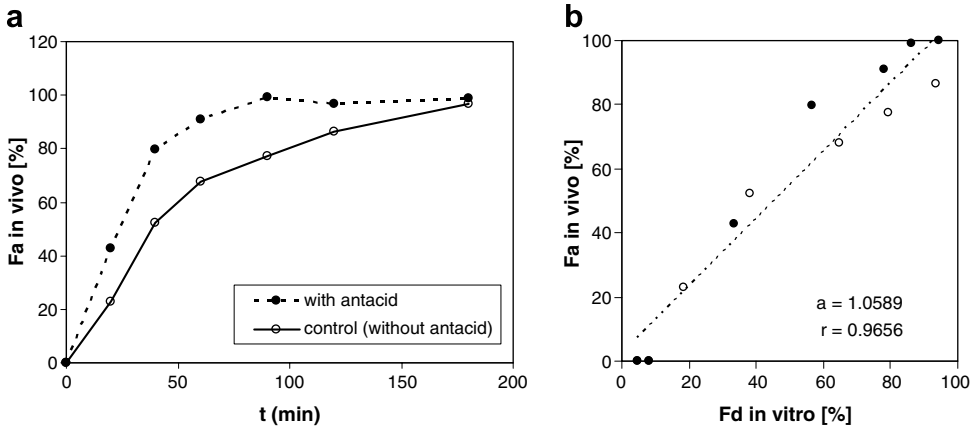

Fig. 4. In vivo fraction absorbed (a) and IVIVC plot (b) for ibuprofen tablets with and without co-administered Milk of Magnesia (close symbol, with antacid; open symbol, without antacid).

than in vivo drug absorption. Therefore, in order to establish level A in vitro/in vivo correlation, time scaling approach was applied [42–44]. Time scale of the in vitro data for product D, with and without antacid, was transformed according to Eq. (1).

$$T_{\text{vitro scaled}} = 3t_{\text{vitro}} - 30 \quad (1)$$

Correlation plots of percent absorbed in vivo (F_a) versus percent dissolved in vitro (F_d) were constructed and analyzed by linear regression analysis. The in vitro–in vivo correlations (IVIVCs) obtained are presented in Fig. 4b. A linear level A IVIVC was established with a correlation coefficient of 0.9759 and 0.9701 for the control study and the study with co-administered antacid, respectively, and 0.9656 for the pooled data set. The value of the slope of the regression line was 1.0589 for the pooled data set.

4. Conclusion

The results obtained support the existing idea that in vitro dissolution testing may serve as a screening tool to indicate potential drug–drug interactions. The increase in ibuprofen dissolution rate in vitro in the presence of magnesium based antacid was, in a formulation dependent manner, in rank-order with the data reported from the in vivo study. Although provisional, the obtained in vitro/in vivo correlation indicate the potential for in vitro studies to reflect physicochemical interactions that are likely to influence drug absorption rate in vivo. Findings from the solubility studies in reactive media suggest that the increase in ibuprofen plasma concentrations associated with the co-administration of magnesium antacid is not simply the result of elevated gastrointestinal pH value and may result from a direct physicochemical interaction. Such findings encourage further work on the in vitro simulation of drug–drug and drug–food interactions for poorly soluble, highly permeable drug substances.

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