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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.
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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]

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