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Impairment of the *in vitro* drug release behaviour of oral modified release preparations in the presence of alcohol

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ABSTRACT

Recently, there has been concern by regulatory authorities of the risk of alcohol-induced dose dumping of oral modified release (MR) formulations. The aim of this work was to use *in vitro* dissolution methodology to investigate the vulnerability of MR products to alcohol under different physiological conditions of the upper gastrointestinal tract. A variety of dissolution scenarios with ethanol concentrations in the range of 5–40% v/v were explored. Mesalazine (5-aminosalicylic acid) was selected as the model drug and the release behaviour of three commercially available MR, monolithic and multi-particulate preparations with pH-dependent or independent release mechanisms was evaluated (Salofalk®, Asacol® and Pentasa®). Each product was found to have a distinctive release profile and behaved differently in the scenarios screened. In the case of Pentasa, complete dose dumping occurred on exposure to 40% ethanol in acid for 2 h. Asacol, however, displayed a contrarian trend with drug release being substantially delayed in small intestinal media after pre-exposure to acid/ethanol for the same duration. Salofalk underwent accelerated drug release in the presence of ethanol in the dissolution media, with unexpected trends observed between the different scenarios. For the three preparations explored, there appears to be a complex interplay between the various formulation variables and ethanol in the dissolution media. The unpredictable release profiles under the different conditions makes it necessary to screen several *in vitro* scenarios of ethanol exposure for each preparation before a decision is reached on its susceptibility to drug release impairment on consumption with ethanol.

1. Introduction

Regulatory authorities have become aware of alcohol interactions with modified release (MR) formulations and the associated risk of dose dumping. The opiate drug, hydromorphone, formulated for controlled delivery over 24 h (Palladone ™) has recently been withdrawn from the US market by its manufacturers due to a potentially fatal interaction with alcohol (FDA, 2005). This drug was formulated into MR pellets through the use of ethylcellulose, Eudragit RS (ammonia methacrylate copolymer type B) and stearyl alcohol. A pharmacokinetic study was carried out by the company where different concentrations of alcohol were administered concomitantly with the extended release opiate. Patients were pre-treated with naltrexone to block the opiate effects. Co-ingestion with 240 ml of 40% v/v alcohol resulted in an approximate sixfold rise in mean C_{max} in comparison to when it was taken with water. In one volunteer, a 16-fold rise in C_{max} was observed. Co-ingestion of a 4% v/v alcohol beverage gave rise to a twofold increase in C_{max} in some subjects. Most opiates are narrow therapeutic index drugs and the main complications of dose dumping are respiratory depression and hypotension.

Based on this major interaction the FDA has decided to develop a regulatory decision framework to assess the risk of alcohol-induced dose dumping for oral MR formulations (Meyer and Hussain, 2005). *In vivo* pharmacokinetic studies are not routinely feasible as they pose a risk to patients; therefore, the FDA has recognised the necessity to develop *in vitro* tests to assess the 'vulnerability' or 'ruggedness' of formulations (Meyer and Hussain, 2005) so that any risks can be circumvented at an early stage in the development process by the formulators. Dissolution tests can be used in this regard to investigate the impairment of MR dosage forms arising from concomitant alcohol consumption.

The purpose of this study was to explore under physiological conditions the *in vitro* influence of alcohol on drug release from MR monolithic and multi-particulate preparations of mesalazine (mesalamine, 5-aminosalicylic acid). Mesalazine is indicated for the induction and maintenance of remission of inflammatory bowel diseases which include ulcerative colitis and Crohn's disease. These conditions predominantly affect the distal gut and mesalazine achieves its therapeutic efficacy by topically acting on the inflamed mucosa making it necessary for the active substance

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to be selectively released at the diseased areas. Mesalazine products available in the clinic attain MR either through dissolution of the pH-responsive polymer coating, or by drug diffusion through a water-insoluble polymer, or even a combination of both mechanisms (Basit, 2005). Three representative MR mesalazine products on the UK market were investigated in this study; they include: Asacol® 400 mg, Salofalk® 250 mg and Pentasa® 500 mg preparations. These have different drug release profiles both *in vitro* and *in vivo* (Stolk et al., 1990; Qureshi and Cohen, 2005; Klein et al., 2005).

Here we investigate different concentrations and durations of alcohol exposure that can guide industry and regulatory in the development of standard tests to screen the influence of alcohol on MR formulations. While other studies have explored the behaviour of MR formulations in hydro-ethanolic media (Roberts et al., 2007; Walden et al., 2007; Levina et al., 2007), they have not considered the patterns of alcohol distribution in the gastrointestinal tract and how they vary under different physiological states. Studies on alcohol distribution in the gastrointestinal tract suggest that on ingestion it is distributed in the stomach, duodenum and jejunum (Halsted et al., 1973). Administration of low concentrations (<5%) of ethanol solutions (as opposed to beverages) in the fasted state showed that its disappearance from the stomach was very fast as 96% of the total dose left the stomach by 23 min. Approximately 89% of the total dose left the stomach by emptying into the duodenum and 10% was absorbed into the blood across the gastric mucosa (Levitt et al., 1997). Guided by these patterns of alcohol distribution we designed *in vitro* dissolution tests for investigating the vulnerability of MR mesalazine products to alcohol.

2. Materials and methods

2.1. Materials

The mesalazine products studied were all purchased from their manufacturers. Salofalk® 250 mg tablets (Dr. Falk) and Asacol® MR 400 mg tablets (Procter and Gamble) are both coated with enteric methacrylic acid and methyl methacrylate ester copolymer however, the ratios of the acid to the ester in the polymers are different for the two products. Salofalk tablets are coated with Eudragit L (dissolution pH threshold of 6) thus start. Asacol tablets are coated with Eudragit S (dissolution pH threshold of 7). Pentasa® 500 mg tablets (Ferring) comprise compressed ethylcellulose coated granules where drug release is by diffusion through this insoluble polymer. Mesalazine was obtained from Sigma–Aldrich Chemicals, UK. Absolute alcohol was purchased from Fluka Chemicals, UK. Potassium dihydrogen orthophosphate and sodium hydroxide used to prepare the buffers and 5 M HCl were of analytical grade and obtained from VWR Chemicals Ltd., Poole, UK. 0.05 M phosphate buffer of 0.129 ionic strength and 23.0 mmol/L/ΔpH unit buffer capacity was used throughout.

2.2. Dissolution test conditions

Mesalazine release from the coated tablets was assessed by dissolution testing using USP Method II paddle apparatus (model PTWS, Pharma Test, Hainburg, Germany) controlled by IDIS EE software (Icalis Data Systems, Berkshire, UK). Tablets from within the same batch of each product were tested. Six tablets for each of the different ethanol concentrations under each scenario (see below) were tested. The volume of the dissolution media was 1000 ml maintained at 37 ± 0.5 °C and a paddle speed of 50 rpm was employed. Sink conditions were attained in all the test media used. The amount of mesalazine released from the dosage form was determined by an in-line UV spectrophotometer (Cecil 2020 model, UK) with 1 mm flow cells at 301 nm in acid and 330 nm in pH 6.8 and pH 7.4 buffer. As UV readings were automatically taken, no loss of medium occurred throughout the duration of the dissolution run.

Mesalazine products were exposed to a pH transition to simulate different regions of the gastrointestinal tract (Evans et al., 1988; Fallingborg et al., 1989; Ibekwe et al., 2008). 0.1 M HCl (pH 1.2) with different concentration of ethanol was used to simulate the gastric environment on ingestion of alcohol. Concentrations of ethanol in the range of 0–40% v/v were studied whereby 0% is the control and 40% is that found in spirits.

After pre-determined HCl/ethanol exposure times, dosage forms were transferred to pH 6.8 buffer for 2 h and then subsequently to pH 7.4 buffer to simulate the jejunum and distal gut, respectively. Different scenarios of HCl/ethanol exposure were explored in an attempt to simulate various *in vivo* conditions. The different scenarios we investigated are as follows:

Scenario A: HCl with or without ethanol for 2 h. This duration is the standard recommendation by the United States Pharmacopoeia for acid pre-exposure times for enteric-coated products.

Scenario B: HCl with or without ethanol for half an hour followed by 1.5 h in acid alone. This was developed as a more physiological alternative to scenario A; to account for alcohol emptying from the stomach. Following discharge of alcohol, the dosage form may remain in the stomach for upto 2 h in the fasted state until they are subjected to the phase III contractions of the migrating myoelectric complex.

Scenario C: HCl with or without ethanol for half an hour. This is to simulate a shorter residence time of the dosage form in the stomach.

Scenario D: HCl with or without ethanol for half an hour and then transfer to pH 6.8 buffer with or without half the concentration of ethanol in acid for 15 min followed by pH 6.8 buffer alone for the remaining 2 h. This is to reflect dosage form emptying with ethanol from the stomach into the jejunum. Exposure to ethanol in small intestinal media was only for 15 min as rapid absorption of ethanol occurs in the jejunum. Ethanol is more rapidly absorbed from the duodenum and jejunum than it is from the stomach (Nazer and Wright, 1983) and therefore, a rapid decline in small intestinal levels is observed. Peak ethanol levels in the proximal jejunum were on average half of gastric levels and declined by almost half-fold within half an hour (Halsted et al., 1973).

2.3. Media uptake by the tablets

To establish if media is uptaken by Asacol and Salofalk tablets during the acid with and without ethanol phase, tablets were subjected to this media under dissolution conditions for 2 h. After 2 h the tablets were removed and excess medium drained and blotted with filter paper. These tablets were weighed and the uptake calculated.

2.4. Scanning electron microscopy (SEM)

Tablets were cut in half and specimens coated with gold using a sputter coater (model K550, Emitech, Kent,UK) and mounted onto a sample holder and examined using an accelerating voltage of 5–15 kV depending on the magnification required. Examination was by SEM using a Phillips XL 20 scanning electron microscope (Philips, Cambridge, UK).

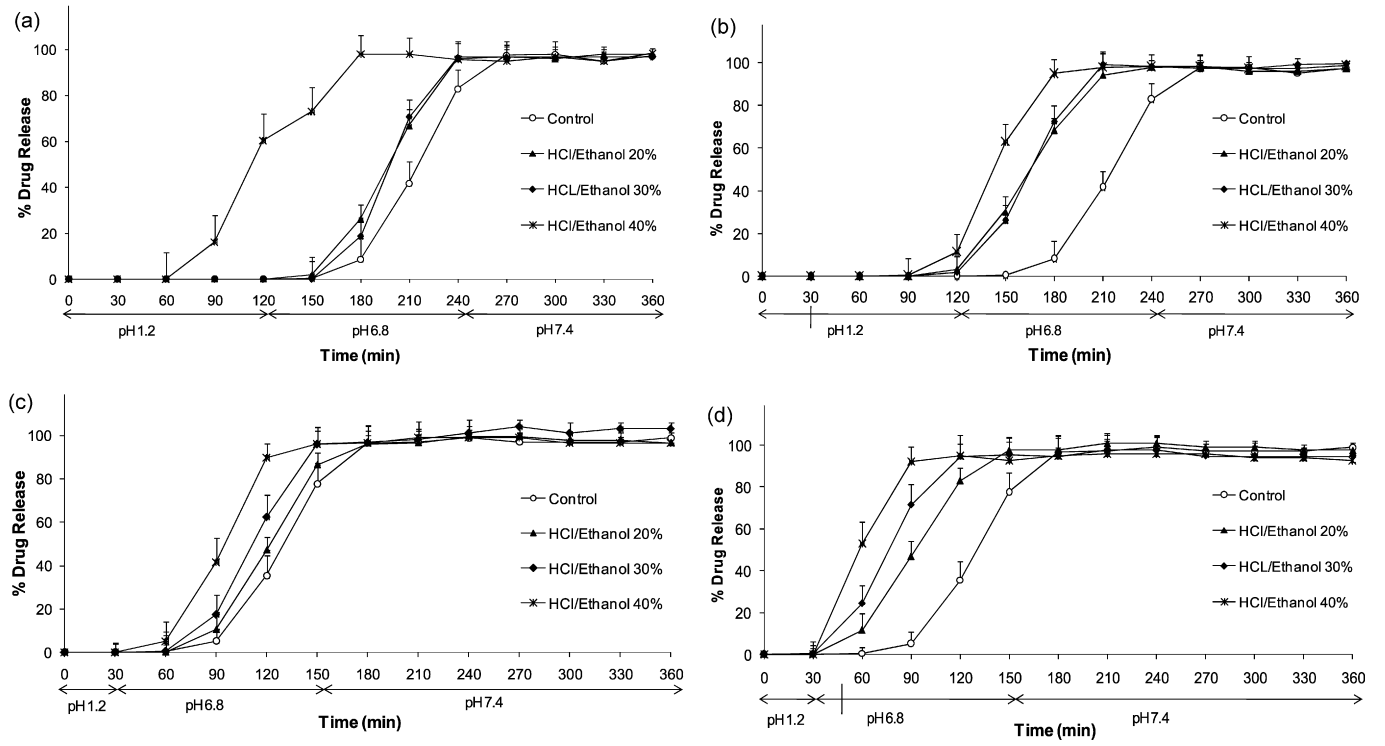

Fig. 1. Dissolution of Salofalk tablets in (a) 0.1 M HCl with ethanol for 2 h followed by pH 6.8 phosphate buffer for 2 h then pH 7.4 phosphate buffer, (b) 0.1 M HCl with ethanol for 30 min followed by 0.1 M HCl with no ethanol for 90 min followed by pH 6.8 phosphate buffer for 2 h then by pH 7.4 phosphate buffer, (c) 0.1 M HCl with ethanol for 30 min followed by pH 6.8 phosphate buffer for 2 h then pH 7.4 phosphate buffer and (d) 0.1 M HCl with ethanol for 30 min followed by pH 6.8 phosphate buffer for 2 h (first 15 min containing ethanol equivalent to half the concentration in acid) followed by pH 7.4 phosphate buffer. Dissolution profiles presented as mean (±S.D.).

2.5. Solubility determination

Solubility of mesalazine was determined in 0.1 M HCl and pH 6.8 phosphate buffer with different concentrations of ethanol (0–40%). Solubility was measured by adding excess mesalazine to the media and leaving it for 24 h on a shaking water bath at 37 °C. The excess drug was then filtered and UV absorbance of the solution measured at 301 nm for acid media and at 330 nm for buffer media.

3. Results and discussion

3.1. Drug release from Salofalk tablets

Salofalk tablets are coated with the enteric polymer, Eudragit L, which has a dissolution pH threshold of 6. Subjecting Salofalk tablets to scenarios A, B and C, where ethanol is included in HCl; reduces the lag-times and accelerates drug release in buffer (Fig. 1a–c). This faster release is proportional to the concentration of ethanol in the media. The most drastic effect of ethanol is seen on immersion of tablets for 2 h in HCl/40% v/v ethanol media; here the coating is impaired and 60% of the dose is liberated before exposure to small intestinal media (Fig. 1a). A concentration of only 5% ethanol in the dissolution media, however, appears not to influence the dissolution profile of this preparation and all the other mesalazine preparations we investigated (data not shown). Interestingly, scenario B in which the tablets are immersed in HCl/ethanol for half an hour followed by HCl alone for 1.5 h (Fig. 1b), gave rise to the fastest drug release in buffer (after removal from acid) in comparison to scenarios A and C. It appears that ethanol modifies the system rendering changes that are enhanced on the subsequent exposure to non-alcoholic media. Another likely transition *in vivo* is scenario D, where tablets empty along with ethanol from the stomach into the small intestine. Simulation of this drastically accelerates drug release even at 20% ethanol concentrations (Fig. 1d).

These accelerations of drug release are attributable to the formulation and not due to an enhancement of the drug's solubility. Solubility of mesalazine is similar or lower in HCl and phosphate buffer containing ethanol in comparison to the non-ethanolic forms of these media. Solubility in 0.1 M HCl without ethanol, or with 5%, 20%, 30% and 40% ethanol is 10.08, 9.54, 9.35, 9.11 and 8.62 mg/ml, respectively. While solubility in 0.05 M pH 6.8 phosphate buffer with no ethanol or 5%, 20%, 30% and 40% ethanol is 4.39, 4.35, 4.30, 4.20 and 3.83 mg/ml, respectively. The choice of model drug allows us to separate the influence of drug solubility from formulation on the effect of ethanol on MR product performance. This contrasts with the study by Roberts et al. (2007) where the model drug was aspirin and its solubility in HCl increases by several-fold in the presence of ethanol.

Eudragit L displays different solubility in the respective ethanol media. Cracks in the coating were revealed on exposure of Salofalk to HCl/ethanol for 2 h, however, cracks were absent on exposure to HCl alone. Leaching of plasticizer out of the film coat thus, causing it to become brittle., may have contributed to these cracks. According to the summary of product characteristics for Salofalk tablets, the plasticizer used is dibutyl phthalate; this is very soluble in ethanol and only very slightly soluble in water. Hence dibutyl phthalate is more likely to leach out when exposed to HCl/ethanol media than when exposed to HCl alone.

The site of delivery of mesalazine and its premature release will compromise therapeutic efficacy. In the event of the above scenarios occurring *in vivo*, drug release is likely to occur prematurely in the stomach or proximal small intestine with little reaching the inflamed mucosa of the distal small bowel and colon.

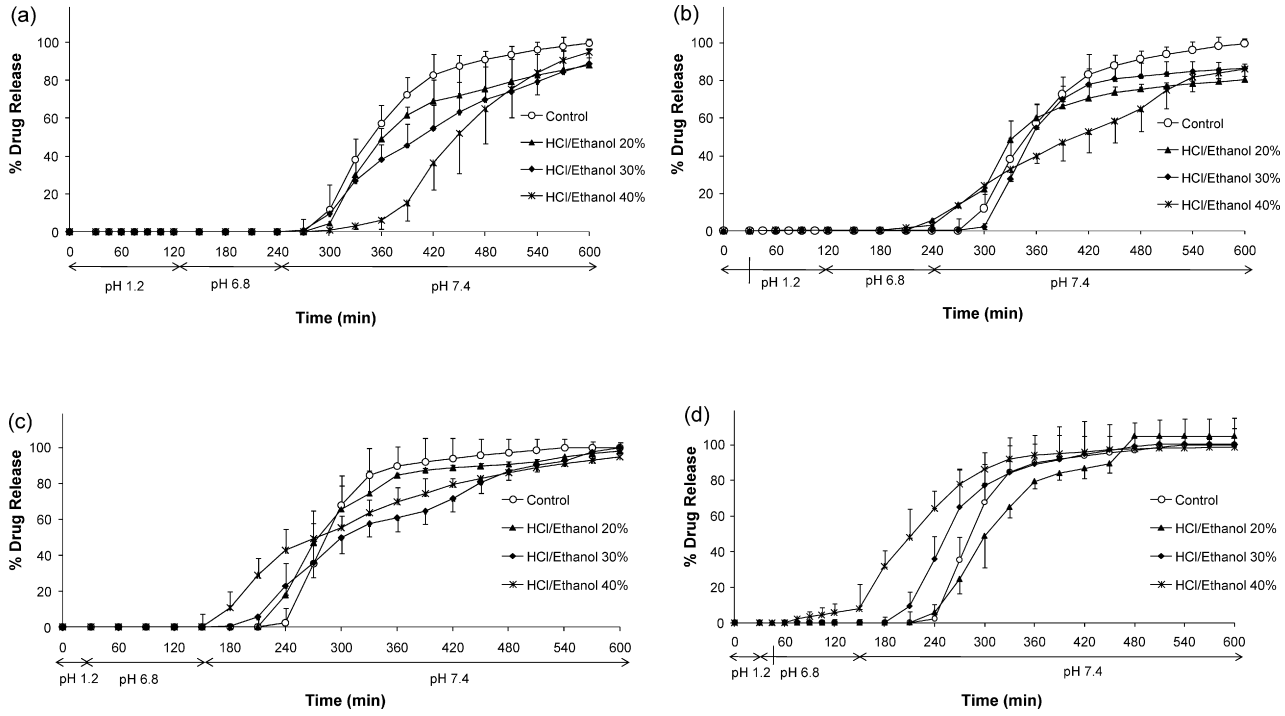

Fig. 2. Dissolution of Asacol tablets in (a) 0.1 M HCl with ethanol for 2 h followed by pH 6.8 phosphate buffer for 2 h then pH 7.4 phosphate buffer, (b) 0.1 M HCl with ethanol for 30 min followed by 0.1 M HCl with no ethanol for 90 min followed by pH 6.8 phosphate buffer for 2 h then by pH 7.4 phosphate buffer, (c) 0.1 M HCl with ethanol for 30 min followed by pH 6.8 phosphate buffer for 2 h then pH 7.4 phosphate buffer and (d) 0.1 M HCl with ethanol for 30 min followed by pH 6.8 phosphate buffer for 2 h (first 15 min containing ethanol equivalent to half the concentration in acid) followed by pH 7.4 phosphate buffer. Dissolution profiles presented as mean (±S.D.).

3.2. Drug release from Asacol tablets

Of the three mesalazine preparations screened, Asacol appears to display the highest variability in drug release profiles. This contrasts with the performance of Pentasa whereby uniform and consistent drug release profiles are observed. Intra-batch and inter-batch variability in the dissolution profiles of Asacol tablets have been previously reported and are associated with the variable coating thickness of these dosage forms (Fadda and Basit, 2005; Spencer et al., 2008).

Under control conditions, Asacol tablets did not release in pH 6.8 phosphate buffer for upto 2 h as the pH threshold of the Eudragit S polymer coating is pH 7. Exposure of Asacol tablets for 2 h to HCl with ethanol (scenario A) renders a delay in drug release in buffer in comparison to its subjection to the control media (Fig. 2a). However, the converse trend is observed in scenario C, in which the tablet is subjected to half an hour exposure to HCl with ethanol (Fig. 2c). Under this scenario, drug release is accelerated in the presence of ethanol. Although no particular trend can be seen with the different ethanol concentrations on subjecting Asacol tablets to half an hour of HCl/ethanol followed by 1.5 h HCl (scenario B) (Fig. 2b); nevertheless the release profiles are distinctive from that of scenarios A and C. Comparison of the different scenarios illustrates the complexity of the drug release patterns observed.

Percentage weight increase of Asacol tablets after exposure to HCl/40% ehanol for 2 h was at a mean of 22% compared to only 1.3% for the control (exposed to 0.1 M HCl alone). Shearing these hydrated tablets across the middle revealed a high viscosity liquid interior in contrast to the control tablets, where the core was still dry and intact. It appears that imbibation of HCl/ethanol into the core results in the dissolution of mesalazine. Mesalazine is a zwitterionic drug; the carboxyl group has a pK_a of 2.30 and the amino group has a pK_a of 5.69 (French and Mauger, 1993). At a low pH, these groups are protonated and the cationic form of the drug is generated. This dissolved mesalazine reduces the pH at the drug (tablet core)/polymer interface thus, retarding dissolution of the enteric polymer. We crudely measured the pH of these hydrated Asacol cores with partially dissolved interiors using pH strips and found it to be at a value of approximately 5. The slower dissolution rate of enteric dosage forms with acidic drugs in the core is well recognised (Ozturk et al., 1988). The main excipient comprising the core of Asacol tablets is lactose, whereas it is sodium carbonate in Salofalk (ABPI compendium, 2008). Sodium carbonate is a buffering agent and will therefore suppress the reduction in pH at the core/polymer interface.

Media uptake could not be measured for Salofalk tablets under these conditions of 2 h HCl/40% ethanol exposure as the tablet undergoes considerable dissolution. The contrasting behaviour of Asacol to Salofalk tablets is also likely to be attributable to the different dissolution rates of Eudragit L and S in ethanol and hydro-ethanolic media; despite that organic film coats are used in both these products. It has been reported that the time taken for 15 g of polymer to dissolve in 100 g of ethanol at 20 °C on a laboratory shaker is 15 and 50 min for Eudragit L and S, respectively (Pharma Polymers, 2001). The observed drug release patterns could therefore, be due to the effect of ethanol on the coating itself, including polymer and plasticizers, coupled to its effect on excipients in the core. Although we know the composition of these preparations qualitatively we do not have quantitative information. Plasticizers have been shown to affect dissolution of Eudragit S enteric polymer films under standard dissolution conditions (Fadda et al., 2008).

In the event of scenario A occurring *in vivo*, Asacol will display a converse therapeutic problem to Salofalk tablets. The rather high pH threshold of Eudragit S which may not be attained in certain subjects (Ibekwe et al., 2006; Ibekwe et al., 2008), particularly in patients with ulcerative colitis (Fallingborg et al., 1993), and

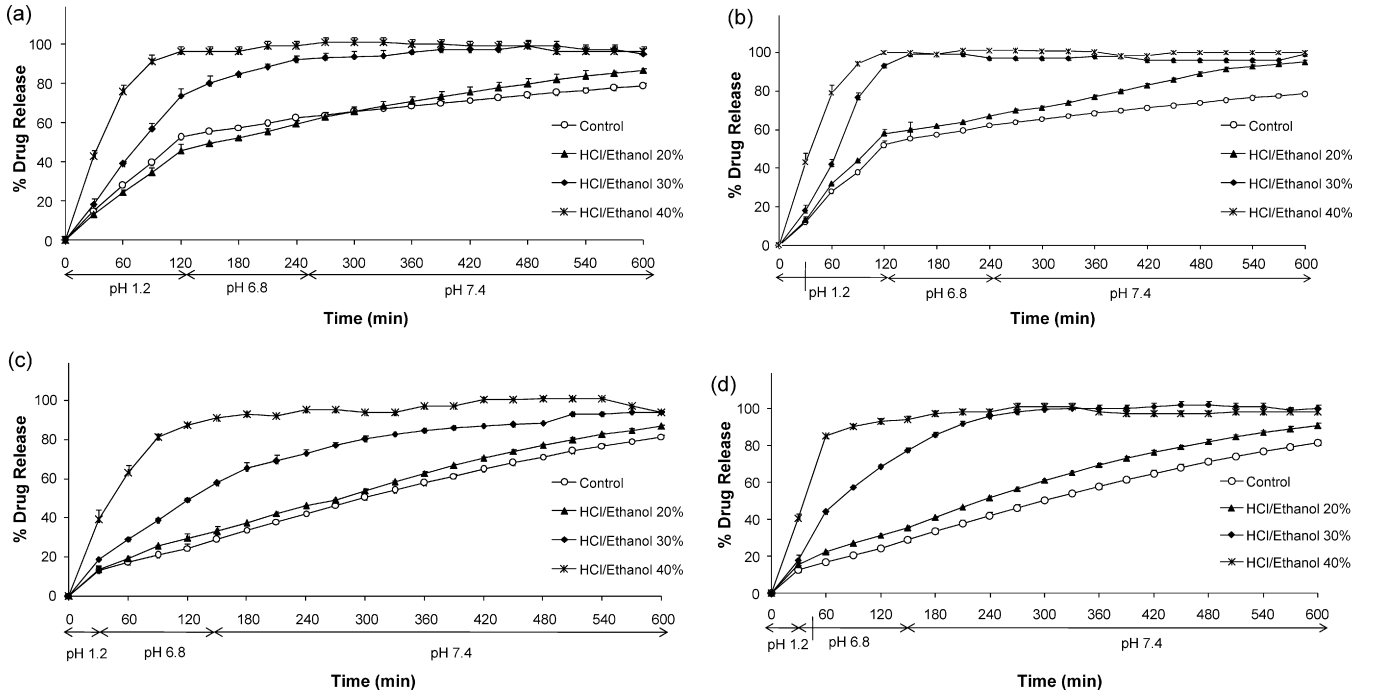

Fig. 3. Dissolution of Pentasa tablets in (a) 0.1 M HCl with ethanol for 2 h followed by pH 6.8 phosphate buffer for 2 h then pH 7.4 phosphate buffer, (b) 0.1 M HCl with ethanol for 30 min followed by 0.1 M HCl with no ethanol for 90 min followed by pH 6.8 phosphate buffer for 2 h then by pH 7.4 phosphate buffer, (c) 0.1 M HCl with ethanol for 30 min followed by pH 6.8 phosphate buffer for 2 h then pH 7.4 phosphate buffer and (d) 0.1 M HCl with ethanol for 30 min followed by pH 6.8 phosphate buffer for 2 h (first 15 min containing ethanol equivalent to half the concentration in acid) followed by pH 7.4 phosphate buffer. Dissolution profiles presented as mean (±S.D.).

the limited fluid availability in the colon (Gotch et al., 1957) all contribute to the well recognised phenomenon of Asacol failing to disintegrate in some patients (Schroeder et al., 1987; Wilding, 1999). In a study by (Safdi, 2005) fragments of tablets were retrieved from volunteers' faeces and assayed: on average they were found to contain 97.2 ± 47.1 mg mesalazine, which is 24% (± 11.8) of the 400 mg administered dose (Safdi, 2005). This incomplete drug delivery from Asacol may be further intensified on the concomitant consumption of alcohol.

Exposure of Asacol tablets to HCl/ethanol for half an hour followed by pH 6.8 buffer with ethanol for 15 min (scenario D) (Fig. 2d) results in faster dissolution which is proportional to the concentration of ethanol in the medium. Drug release occurs below the pH threshold of the polymer. These results further consolidate that very different profiles can be obtained depending on the kinetics of alcohol absorption and the position of the dosage form relative to alcohol in different regions of the gastrointestinal tract.

3.3. Drug release from Pentasa tablets

Pentasa tablets rapidly disintegrate into granules on exposure to fluid. Drug release occurs from these granules by diffusion of mesalazine through the ethylcellulose coating. Ethylcellulose is a water-insoluble, non-ionic polymer and is therefore, insensitive to pH however, it appears to be very vulnerable to ethanol as complete dose dumping of the drug occurs on exposure to HCl/40% ethanol for 2 h (scenario A) (Fig. 3a). Moreover, whether the coating material is based on an organic solution or aqueous dispersion will have a bearing on its permeability. Organic films are tougher and less permeable due to the greater extent of polymer–polymer interpenetration (Lecomte et al., 2004).

Fig. 3a–d illustrates that ethanol in the dissolution media generally accelerates drug release in proportion to the concentration present. This can be explained by the freely soluble nature of ethylcellulose in ethanol and its practical insolubility in water (Rowe et al., 2003). Mesalazine can diffuse through an intact ethylcellulose coat and through a discontinuous coat with pores. Evidence for this exists from SEMs (data not shown) whereby pores in the granule coating were only observed in granules subjected to HCl/ethanol media and not the control media. An interesting, unexpected trend is the faster drug release observed on exposure of Pentasa granules to half an hour HCl/ethanol followed by 1.5 h acid alone (scenario B) in comparison to 2 h exposure to HCl/ethanol media (Fig. 3a and b). Further studies would be necessary to understand these unexpected observations.

Although substantial drug release from Pentasa occurs in HCl media, this is considerably accelerated in the presence of ethanol. Consequently most of the drug will be released in the proximal GI tract; systemic absorption and adverse effects will therefore be enhanced.

3.4. General discussion

The hydromorphone product (Palladone ™) that underwent alcohol-induced dose dumping and subsequent withdrawal from the US market was evaluated *in vitro* through dissolution tests in acid with different concentrations of ethanol for 2 h. The *in vitro* dissolution profiles attained and the *in vivo* pharmacokinetic data are summarised by Walden et al. (2007). The most substantial effect on the mean peak plasma drug concentration was induced by consuming a 40% ethanol drink. *In vitro* drug release data was suggestive of a dose dumping effect which was seen in the *in vivo* study. *In vitro* dissolution screening of alcohol-induced drug release impairment appears to provide a surrogate for the behaviour *in vivo*.

Our study was not confined to one dissolution scenario for alcohol distribution, however, several scenarios were explored which gave rise to different release patterns for the same preparation. It can thus, be inferred that the *in vivo* outcome will be highly depen-

dent on the kinetics of alcohol absorption and emptying. While we tried to model dosage form transit in the stomach and small intestine in relation to the position of alcohol; the scenarios explored are by no means exhaustive as several factors are likely to interfere. Food is known to change the emptying patterns of alcohol from the stomach. In the fed state, it has been observed that 10% of the ingested dose of alcohol empties from the stomach every 15 min and removal is complete at 126 min (Levitt et al., 1997). A study by Franke et al. (2004) showed that alcoholic beverages inhibit gastric emptying due to the presence of ethanol, calorific content and non-alcoholic ingredients produced by fermentation. Alcoholic beverages will also be diluted in the stomach as the fluid content in the fasted state has been measured to be at a mean of 45 ml (Schiller et al., 2005). Moreover, the rate of consumption of the beverage will determine the concentration and quantity of alcohol the dosage form is exposed to. All these variables will have implications on drug release from the preparation.

The FDA has issued draft guidance for industry on the dissolution of various extended release preparations in the presence of different concentrations of ethanol in HCl equivalent to 5%, 20% and 40% for 2 h (FDA, 2007). To date, draft guidance has been issued for tramadol, oxymorphone, morphine sulphate, bupropion and the non-opiate: metoprolol succinate. Although 2 h exposure to ethanol in HCl is conceived to be an extreme challenge to the preparation and is likely to be the worst-case scenario; we have shown using MR mesalazine preparations that this is not necessarily the scenario that stresses the formulation most and induces the greatest impairment to drug release.

4. Conclusions

Ethanol influences drug release from mesalazine MR preparations *in vitro*. There appears to be a complex interplay between the formulation, the release medium and the duration to its exposure; as the form and extent of impairment induced by ethanol cannot be predicted. Each preparation responds differently to the four different scenarios of ethanol exposure. A scenario which induces the most impairment in drug release for one product is not necessarily the most stressful for another product. Currently, it is therefore, not sufficient to select a potential 'worst-case' scenario. Several tests need to be screened before a decision is reached on a preparation's susceptibility to ethanol impairment.

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