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The In-vitro pH-Dissolution Dependence and In-vivo Bioavailability of Frusemide-PVP Solid Dispersions

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Abstract—The dependence of the dissolution rate on the pH of the buffered medium, using constant surface area discs, has been examined for crystalline frusemide, a semi-crystalline frusemide-polyvinylpyrrolidone (PVP) solid dispersion and an X-ray amorphous frusemide-PVP dispersion. The marked changes observed in the pH-dissolution profiles indicate that differing dissolution mechanisms operate in the amorphous regions. This conclusion was further supported by the comparison of pH-dissolution and pH-equilibrium solubility profiles that suggested a supersaturation effect to be the relevant term in describing the dissolution enhancing effects of amorphous regions. A marked dissolution enhancement, relative to crystalline frusemide, was shown by the X-ray amorphous solid dispersion in weakly acidic solutions. A similar effect was observed in the dissolution characteristics of gelatin capsule formulations in simulated gastric and intestinal media. In a human bioavailability study, the X-ray amorphous frusemide-PVP solid dispersion exhibited a significant reduction in the time for maximum effect in comparison to crystalline frusemide and a semi-crystalline solid dispersion. This effect, demonstrated by the primary end organ response in seven healthy subjects, concurred with the in-vitro prediction of dissolution enhancement in weakly acidic media.

The rationale for the use of solid dispersion formulations is to improve the in-vivo dissolution and absorption rate. An extensive literature is evident describing the in-vitro dissolution behaviour of solid dispersion systems and this has been reviewed at intervals (Hajratwala 1974; Corrigan 1984; Ford 1986). However, an equivalent examination of the in-vivo dissolution behaviour is not apparent, and of the studies reported many workers use laboratory animals as the test subjects.

The relationship between pH and in-vitro dissolution enhancement, an important factor in the prediction of in-vivo behaviour, has not been extensively investigated for solid dispersion systems. The dependence of the dissolution rate at a single pH, using constant surface area discs, on the drug fraction in the frusemide-polyvinylpyrrolidone (PVP) solid dispersion system has been correlated with changes in crystallinity (Doherty et al, 1985, 1986). The present work, extending an initial publication (Doherty et al 1986) examines the pH-dissolution and pH-equilibrium solubility profiles for frusemide-PVP solid dispersions and correlates these with the in-vivo dissolution and absorption in human subjects by monitoring the primary end organ response.

The oral bioavailability of frusemide preparations is reported to be in the range 50–70% of an intraveneous dose (Branch et al 1977; Cutler & Blair 1979). Solid and liquid preparations have been reported to be bioequivalent (Kelly et al 1974; Cutler & Blair 1979) while other authors have shown tablets to have between 66–96% bioavailability of an equal dose oral solution (Eggers et al 1983; Kingsford et al 1984; McNamara et al 1987). The dose-response curve for frusemide in man, using sodium ion excretion rate as the response, shows a characteristic sigmoidal pattern (Chennavasin et al 1979; Cutler & Blair 1979). Dosage regimens in the 12–50 mg range have been shown to be on the linear section of the curve (Kleinfelder 1963). Consequently, many workers have found the electrolyte excretion rate (sodium or potassium ion) to parallel the frusemide urinary excretion rate using oral doses of 20–40 mg (e.g. Branch et al 1977; Chennavasin et al 1979; Keller et al 1981; Ogata et al 1983). With this evidence workers have measured the urinary sodium ion excretion rate to assess the bioavailability of frusemide formulations in human subjects (20–40 mg oral doses) (McNeil et al 1977; Paton 1980). This kinetic-effect method of analysing bioavailability has the advantage of being non-invasive and allows a rapid analysis of samples.

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Materials and Methods

Frusemide BP was obtained from APS Ltd., Cleckheaton, UK, PVP as Kollidon 25 from BASF, West Germany and frusemide oral liquid as Lasix Paediatric liquid (Hoecht, batch no's. 0185RTB/0185RTC, 1 mg mL^{-1}). All other reagents were of Analar grade and all water used was double distilled and deionized.

X-ray amorphous and semi-crystalline frusemide-PVP solid dispersions were prepared using the solvent method (Chiou & Riegelman 1971) from vacuum evaporation of a methanolic solution (50°C, 2.5×10^3Pa) (Doherty & York 1987). Recovered solids were sieved and the 90–250 μm fraction dried over molecular sieve 5A for 24 h before testing.

Intrinsic dissolution apparatus

An intrinsic dissolution apparatus utilising constant surface area discs (1 cm diameter) was used as described by Doherty & York (1987). 900 mL of degassed sodium acetate-acetic acid (pH 3·5–5·4) or disodium hydrogen orthophosphate dihydrate-citric acid (pH 2·2, pH 5·5–7·0) buffer solutions (Diem & Lentner 1972) were used as dissolution media. Frusemide dissolution was monitored automatically at 272 nm (37°C) using a diode array spectrophotometer (Hewlett Packard HP 8451A) from calibration graphs. Each sample

was analysed at least in duplicate and the coefficient of variance (CV) was found to be 2·29% (Doherty & York 1987). A diffusion controlled process was assumed, the dissolution rate being related to the concentration gradient across the diffusion or film layer. Assuming sink conditions the practical form of the Noyes-Whitney equation can be applied, where m is the mass dissolved at time t:

$$dm/dt = k.\ A.\ S$$

The measured dissolution rate (DR) is equal to dm/dt, having units of mg min^{-1}, k is the intrinsic dissolution rate constant, A is the surface area of the solid (assumed to be constant in this work) and S is the concentration of solute at the solid surface. The comparison of pH-dissolution and pH-equilibrium solubility profiles examines the validity of using equilibrium solubility data to estimate the term S in the given equation for samples of differing crystallinity.

Solid dose form dissolution apparatus

Filled capsules of the test formulations (size 3, white opaque, Capsugel, UK) were examined using a pharmacopoeial apparatus (BP 1980) comprising a six stage dissolution unit with flat bottom glass vessels (Caleva 6ST) and UV spectrophotometer (Uvikon 810, Kontron). Each capsule was placed in a stainless steel mesh basket and rotated at 100 rev min^{-1} for 2 h. The dissolution fluid (37°C) was constantly circulated through in-line filters to the spectrophotometer which analysed drug content every two minutes at 272 nm. Each sample was examined at least in duplicate. Simulated gastric fluid (SGN, pH 1·02 without enzymes, sodium chloride 2·0 g, concentrated hydrochloric acid 7·0 mL, water to 1000 mL) and simulated intestinal fluid (SIN, pH 7·5, without enzymes, potassium dihydrogen phosphate 6·8 g, sodium hydroxide 1·0 M 39·0 mL, sodium chloride 2·0 g, water to 1000 mL) were used as dissolution fluids.

Equilibrium solubility

Equilibrium solubility was assessed, using the same buffer systems described above, by mechanically shaking 1·0 g of powder in 50 mL of buffer solution at 37°C for 6 days, filtering the supernatant through 0·2 μm membrane filters (Whatman, UK) and diluting with 0·01 M sodium hydroxide. Frusemide content was determined by UV spectroscopy at 272 nm (Hewlett Packard diode array spectrophotometer, HP 8451A) from calibration curves.

Bioavailability trial protocol

The bioavailability trial, approved by the Bradford University Ethical Committee, involved seven male caucasian volunteers aged between 23–40 years (average 26·6 years), weighing between 65–83 kg (average 71·4 kg) and of good physical condition. Each subject was required to take a 20 mg oral frusemide dose either of an oral frusemide solution or a white opaque capsule containing 20 mg frusemide or equivalent of the two frusemide-PVP test solid dispersions on a single blind basis. Volunteers were asked to refrain from smoking, excessive exercise, drinking alcohol, tea or coffee on each study day. A wash out period of one week was included between consective study days. Volunteers emptied their bladders at 08.30 h, the urine being discarded. At 09.00 h, each subject received the test formulation or oral liquid and 200 mL of water. All urine was collected at 0, 0·5, 1·0, 1·5, 2·0, 2·5, 3·0, 4·0, 5·0, 6·0, 7·0 and 8·0 h after administration. A light lunch was taken not before 3 h after administration, fluid replacement achieved by taking 300 mL of water at the 1·5 and 3·0 h stages and then as desired. Urine samples were analysed for sodium ion using a precision flame photometer designed for the analysis of biological samples (Instrument Laboratories IL943, Cheshire, UK). The instrument was standardised using a sodium ion solution (100 mmol L^{-1}). Each sample was automatically diluted and analysed in duplicate. Reproducibility of the sodium ion concentration data was assessed to be 0·19% CV by injecting an individual urine sample ten times.

On a separate occasion the sodium ion excretion rate was monitored in the absence of any treatment in five volunteers to assess basal sodium ion excretion levels throughout the day.

Results and Discussion

Intrinsic dissolution and equilibrium solubility

pH-dissolution profiles were investigated for the untreated crystalline frusemide, a semi-crystalline dispersion (50% w/w drug) and an X-ray amorphous dispersion (40% w/w drug) using constant surface area discs. Dissolution profiles for crystalline and X-ray amorphous frusemide-PVP dispersions were linear. Semi-crystalline dispersions gave biphasic plots and representative profiles are shown in Fig. 1. Calculated average dissolution rates are plotted in Fig. 2 as a function of the pH of the buffer solution. Dissolution data could not be obtained for untreated crystalline frusemide below pH 4·2 due to low UV absorbances.

The semi-crystalline frusemide-PVP dispersion exhibited biphasic or curved release over a specific pH range and linear release profiles outside this range. This effect is demonstrated by the convergence of the initial and limiting dissolution rate profiles (Fig. 2).

The X-ray amorphous dispersion pH-dissolution profile appeared to show a discontinuity in the trend at pH 4·5. A second batch of the X-ray amorphous dispersion of equal composition was studied (batch b) and gave a similar pattern

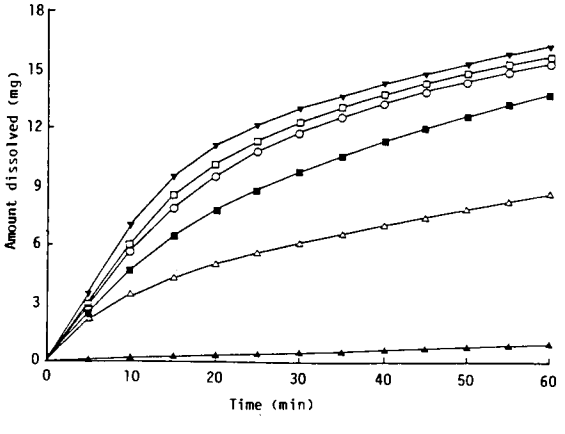

FIG. 1. Representative dissolution profiles as a function of the pH of the buffer solution (37°C) for a semi-crystalline frusemide-PVP solid dispersion (50% w/w drug). pH values; (▼) 5·32; (□) 4·92; (○) 4·50; (■) 4·06; (△) 3·68; (▲) 2·24.

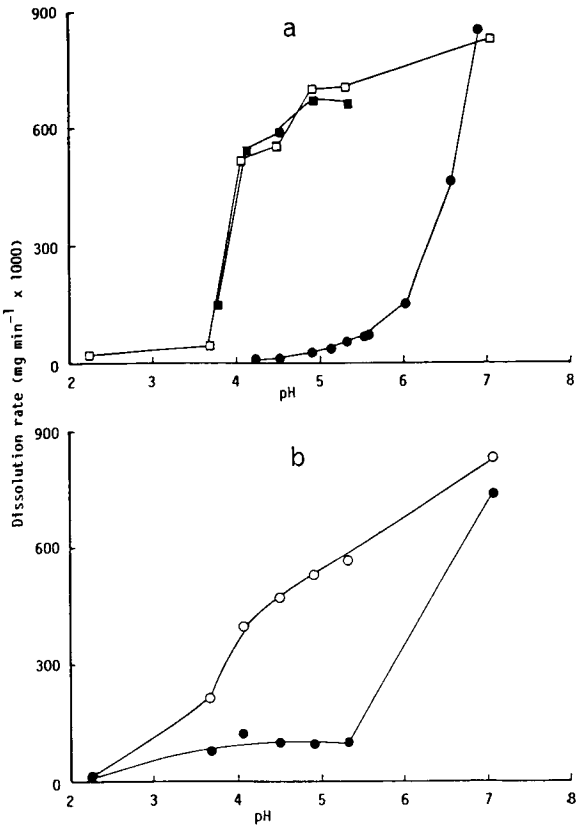

FIG. 2. Comparison of pH-dissolution rate profiles (37°C); (a) crystalline frusemide (●) and two batches of an X-ray amorphous frusemide-PVP dispersion (batch a (□) and b (■)) containing 40% w/w drug; (b) initial (○) and limiting (●) dissolution rates for a semi-crystalline dispersion (50% w/w drug) exhibiting biphasic release.

(Fig. 2) establishing that this was not an experimental artifact.

The X-ray amorphous frusemide-PVP dispersion exhibits a different pH-dissolution profile from crystalline frusemide and a similar pattern is also shown in the initial and limiting slopes of the semi-crystalline dispersion. This difference supports the conclusion of previous work (Doherty & York 1987) that the initial fast dissolution rate from the semi-crystalline sample is due to the dissolution of an amorphous drug phase and the slower limiting rate due to the dissolution of a predominantly crystalline drug phase.

The changes in the pH-dissolution profiles can be considered in relation to the proposed qualitative dissolution model for the X-ray amorphous frusemide-PVP dispersion (Doherty & York 1987). The principal dissolution enhancing effect was considered to be the supersaturating behaviour of the drug in the diffusion layer. When this occurs at a solution pH where the crystalline drug is sparingly soluble then dramatic dissolution improvements can be seen (pH 4–6). As the media pH rises the solubility and hence dissolution of the weakly acidic pure drug increases such that approaching neutrality the drug solubility is no longer likely to be the rate limiting step in dissolution. At this point the X-ray amorphous dispersion and crystalline drug have similar dissolution rates (Fig. 2) as the supersaturating effects are unable to exert an influence on the dissolution rate.

At low pH (pH 2·2–3·5) recrystallization of the drug at the solid-liquid interface of X-ray amorphous dispersion compacts resulted from an inability of the drug to retain the supersaturated state and the buffering of the dissolution layer by frusemide below the pK_a. The data imply a pH-dependence of the solution phase stability of the metastable supersaturated solution possibly associated with the pK_a of the drug (pK_a frusemide = 3·9). This observation may explain the absence of the supersaturation effect in previous models of dissolution enhancement where non-buffered media were employed (e.g. Simonelli et al 1969).

It is conceivable that the surface recrystallization of the drug from X-ray amorphous dispersions at low pH may inhibit subsequent dissolution in favourable environments. To examine this effect compacts of X-ray amorphous frusemide-PVP dispersion were first exposed to SGN (pH 1·02) for 1 h and then the solvent was changed to a pH 4·95 acetate buffer for a further hour using the intrinsic dissolution apparatus. The dissolution rate data obtained indicated that there was neither a lag time for dissolution in the favourable buffer (pH 4·95) nor any change in the overall rate due to the exposure to the SGN media.

The ionic strength of the dissolution medium can modify the dissolution rate. This effect was examined by comparing dissolution data in the presence of added sodium chloride (3·6 g in 900 mL pH 4·95 acetate buffer, 37°C). An increase in the ionic strength was not found to affect the dissolution of the drug alone and only resulted in a slight reduction in the dissolution rate of the 40% w/w frusemide-PVP dispersion. This modest change in dissolution rate may reflect the influence of the ionic strength on viscosity or drug diffusion effects in the diffusion layer but cannot account for the change in pH-dissolution profile for the X-ray amorphous frusemide-PVP solid dispersion.

pH-equilibrium solubility data were obtained (at 37°C) for frusemide alone and the X-ray amorphous 40% w/w frusemide-PVP dispersion using the same buffer systems as the pH-dissolution studies. The pH-dissolution and pH-equilibrium solubility profiles can be compared (Fig. 3). A close correlation can be seen for the crystalline frusemide indicating that equilibrium solubility changes readily account for the dissolution change with pH, according to the standard Noyes-Whitney relationship.

The pH-dissolution and pH-equilibrium solubility profiles for the X-ray amorphous dispersion show markedly different patterns over the pH range studied (pH 3·6–5·3 using sodium acetate-acetic acid buffer solutions). The data indicate that the equilibrium solubility of the X-ray amorphous dispersion is not related to the dissolution change with pH. This finding supports the proposed hypothesis (Doherty & York 1987) that the mechanism of pronounced dissolution increase for the X-ray amorphous regions in solid dispersions is a supersaturation effect operating in the diffusion layer.

Solid dosage form dissolution testing

Capsule formulations containing 20 mg frusemide or equivalent of the semi-crystalline (60% w/w drug) and X-ray amorphous (40% w/w drug) frusemide-PVP dispersions were prepared and tested using the BP (1980) apparatus with SGN and SIN media. Sieved powder fractions were used (90–250 μm) and fill weights were ±0·5 mg. The average %

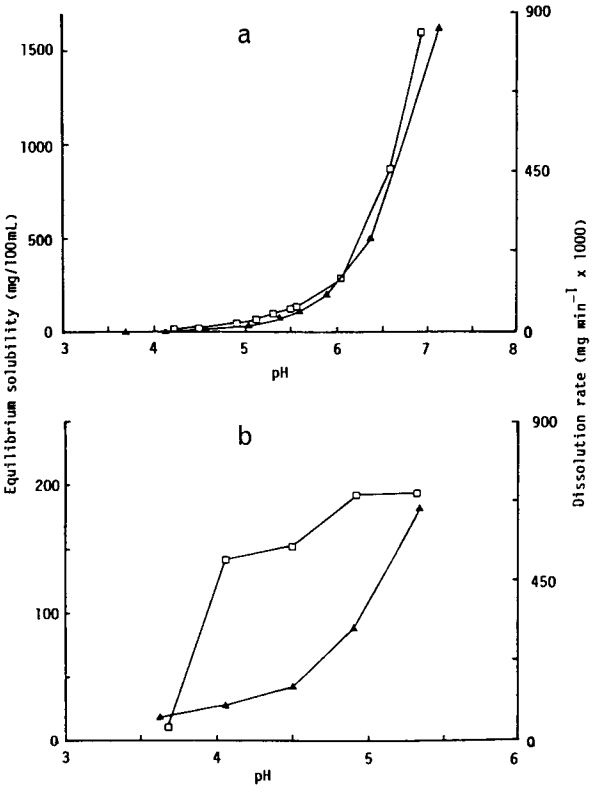

FIG. 3. Comparison of pH-equilibrium solubility (▲) and pH-dissolution (□) profiles (37°C) for; (a) crystalline frusemide, (b) X-ray amorphous frusemide-PVP dispersion (40% w/w drug) using buffer solutions.

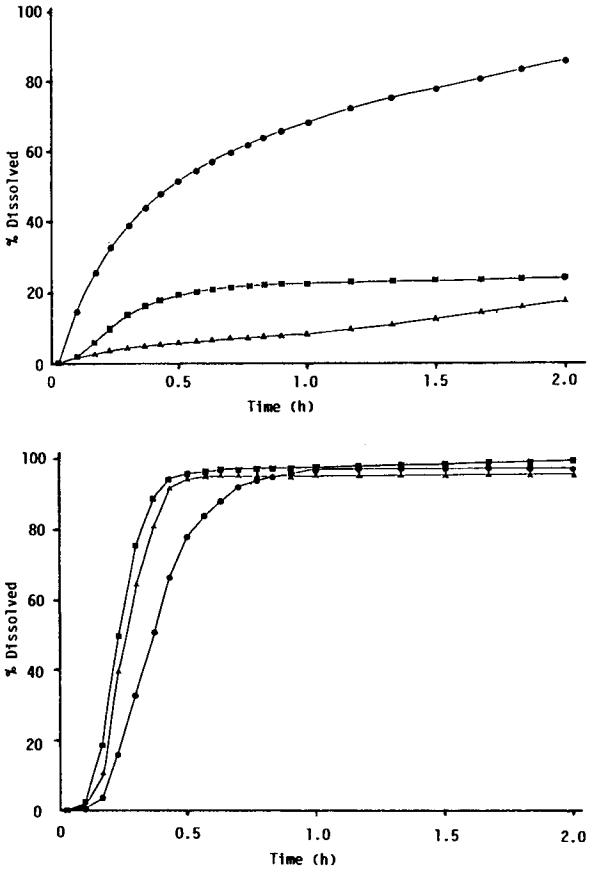

FIG. 4. Capsule dissolution data in (top) SGN, (bottom) SIN; (■) crystalline frusemide, (●) X-ray amorphous frusemide-PVP dispersion (40% w/w drug), (▲) semi-crystalline frusemide-PVP dispersion (60% w/w drug).

released-time data for a two hour dissolution run in each media are shown in Fig. 4. The profiles, which show differing release patterns, can be assigned the following rank orders:

SGN. Amorphous dispersion >>crystalline frusemide->semi-crystalline dispersion

SIN. Crystalline frusemide > semi-crystalline dispersion > amorphous dispersion

The dissolution data demonstrate a frusemide dissolution enhancement, relative to crystalline drug, from capsule formulations of the X-ray amorphous frusemide-PVP dispersion in the acidic SGN medium. In alkaline conditions the drug solubility increases such that it is no longer the rate limiting factor in the dissolution process and under these conditions increasing the levels of PVP in the formulation will reduce drug diffusion and dissolution rate. Hence the crystalline drug dissolved faster in SIN than the 60% and 40% w/w frusemide-PVP dispersions.

The pH-dissolution studies have shown that frusemide dissolution improvements are demonstrated by the X-ray amorphous frusemide-PVP solid dispersion, relative to the crystalline drug, in acidic media. The magnitude of the increase was found to be most pronounced between pH 4–6 where a supersaturation effect is thought to be the principal enhancing factor. At lower pH levels both intrinsic and capsule dissolution data indicated an enhancement over frusemide alone but of a smaller magnitude. The data predict an increased in-vivo dissolution rate from areas of the gastrointestinal tract possessing weakly acidic pH resulting in an increased initial absorption rate and reduced time for maximum effect.

Bioavailability trial

The objectives of the trial were to compare the biological effects due to administration of capsule formulations of X-ray amorphous (40% w/w drug) and semi-crystalline (60% w/w drug) frusemide-PVP solid dispersions and untreated crystalline frusemide to a frusemide oral solution in seven healthy male caucasians.

The average urinary volume and urinary sodium ion excretion data are shown in Table 1. The average sodium ion excretion rate-time profiles are shown in Fig. 5 with standard error bars. The urinary sodium ion excretion rate in the 30 min preceding each test was taken as the basal excretion rate in each individual on each study day. This was subtracted from subsequent excretion data for that day such that the calculated area-under-the-curve (AUC) data (Table 1) reflect increased sodium ion output due to administered frusemide. The validity of the correction procedure was shown using urinary sodium ion excretion data determined in the absence of frusemide administration which, after being treated in the same manner, showed negligible sodium ion excretion above base level in the 6 h period examined (5 volunteers). The

Table 1. Average urinary volume and electrolyte excretion data, calculated AUC, T_{max} and % bioavailability relative to an oral solution following administration of the test frusemide formulations (±standard deviation).

Formulation	Cumulative vol. of urine (mL)	Cumulative Na^+ excreted (mmol)	AUC (0–8 h)	T_{max} (min)	% Bioavailability to oral solution
Liquid	1581±310	126·4±33·0	5818±1596	53·7±16·1	100
Amorphous dispersion	1871±584	128·6±19·8	5564±772·0	67·0±22·4	95·6
Crystalline frusemide	1842±725	136·6±64·6	5977±2650	90·4±26·4	102·7
Semi-crystalline dispersion	1463±591	113·9±52·1	5080±2442	94·3±29·4	87·3
Blank (0–6·0 h)	548±158	43·0±18·0	226	—	—

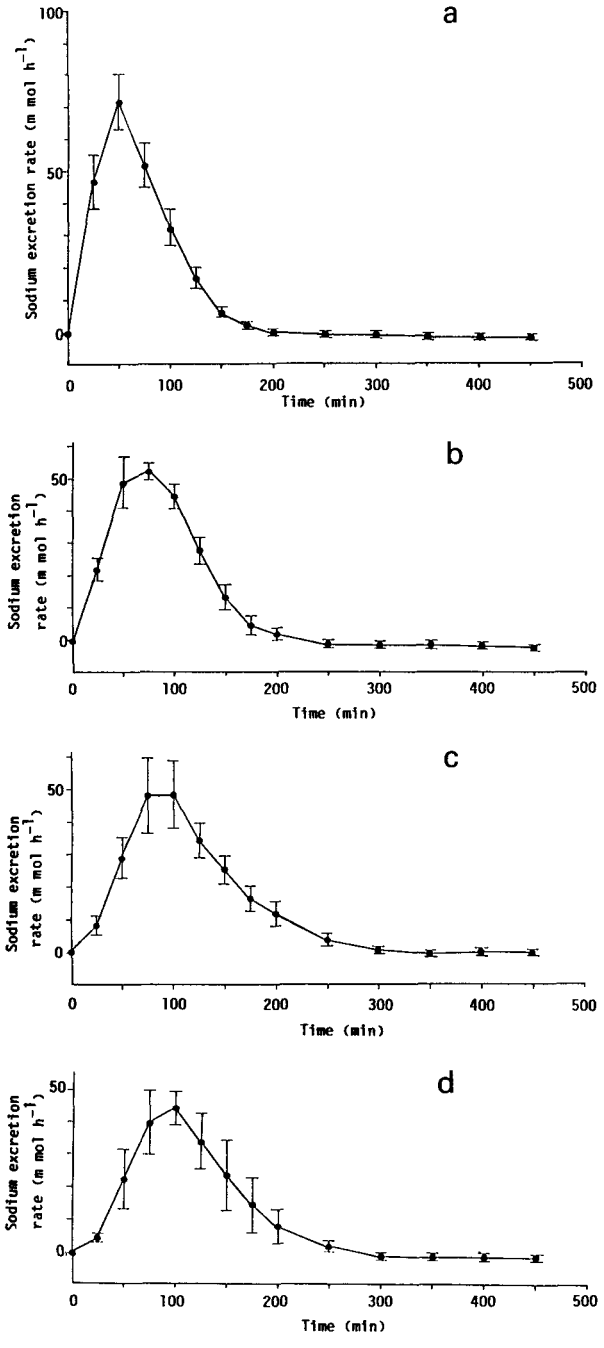

FIG. 5. Average sodium ion excretion data above base level (standard error bars) for frusemide formulations; (a) frusemide liquid, (b) X-ray amorphous frusemide-PVP dispersion (40% w/w drug), (c) crystalline frusemide, (d) semi-crystalline frusemide-PVP dispersion (60% w/w drug).

corrected sodium ion excretion rate-time profiles were examined for AUC (trapezoidal rule) and the time for maximum effect (T_{max}).

The average sodium ion excretion-time profiles reveal the liquid formulation to display a different pattern from the crystalline frusemide, exhibiting a rapid onset of action consistent with the high bioavailability of drugs in liquid form.

To assess the differences between the means of two populations from small sample sizes and with equal but unknown population variance (T_{max} data), a two sample *t*-test was used (Iman & Conover 1983).

The results of the statistical analyses revealed:

(1) The T_{max} for the liquid frusemide preparation and X-ray amorphous frusemide-PVP dispersion were significantly lower (99% and 95% confidence levels, respectively) than the T_{max} for the semi-crystalline dispersion and crystalline frusemide.

(2) No significant differences were found between the AUC data for any sample, which were in the range 87–103% of an oral frusemide solution.

(3) The variance associated with the AUC data for the X-ray amorphous frusemide-PVP solid dispersion was significantly lower (97·5% confidence level) than that for crystalline frusemide (F-distribution test).

The administration of the model drug frusemide in an X-ray amorphous solid dispersion resulted in an increased initial absorption rate and improved consistency of absorption in comparison to a semi-crystalline dispersion or crystalline frusemide formulation, reflected in the measured primary end organ response. Frusemide absorption from solid dosage forms has been shown to be characterized by large intersubject variability (McNamara et al 1987) and improvements in the consistency of absorption demonstrated here for the X-ray amorphous dispersion reflect the applicability of solid dispersion technology. The extent of absorption was not found to be significantly different in the formulations tested, concurring with literature reports of the bioequivalence of solid and liquid frusemide preparations (e.g. Cutler & Blair 1979).

The in-vivo results are in agreement with the in-vitro dissolution data which demonstrated improvements, relative to crystalline drug, from X-ray amorphous solid dispersions when the media was pH 4–6 (constant surface area disc dissolution) and to a lesser extent pH 1 (capsule dissolution). These pH environments would be found in the stomach and upper sections of the small intestine (Gibaldi 1984). Consequently, the X-ray amorphous frusemide-PVP solid dispersion dissolves and is absorbed at a faster initial rate than

either the semi-crystalline dispersion or crystalline drug providing a reduction in the T_{max}. Similar effects on the T_{max} have also been shown for other sulphonamide-PVP dispersions in experimental animals (for tolbutamide, Said & Saad 1975; for chlorpropamide, Desphande & Agrawal 1985).

Conclusions

1. A pronounced dissolution enhancement from constant surface area discs was shown in the range pH 4–6 for an X-ray amorphous frusemide-PVP solid dispersion in comparison with the crystalline drug. A similar effect was shown by comparing the initial and limiting dissolution rates for biphasic dissolution profiles of a semi-crystalline dispersion, reflecting the heterogeneous solid state nature of this sample.

2. Comparisons of pH-dissolution and pH-equilibrium solubility profiles suggested that a supersaturation effect was the most relevant term in describing the dissolution enhancement from amorphous regions in solid dispersion systems.

3. A kinetic-effect human bioavailability study, monitoring the frusemide primary end organ response, revealed the X-ray amorphous frusemide-PVP dispersion to have a significantly reduced time for maximum effect, concurring with the in-vitro dissolution prediction in weakly acidic media.

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