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Mechanisms of dissolution of frusemide/PVP solid dispersions

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Summary

With a discriminating intrinsic dissolution apparatus the dissolution rates and profiles of frusemide-polyvinylpyrrolidone (PVP) mix and solid dispersion systems (10–100% w/w frusemide) have been examined together with scanning electron photomicrographs (SEM) of the dissolution surfaces of compressed discs before and after dissolution. Solid dispersion systems exhibited higher dissolution rates than corresponding mixes and untreated frusemide. The peak intrinsic dissolution rate, found for both mix and dispersion systems containing 40% w/w frusemide, was attributed to a balance of two opposing factors. In mix systems a dissolution-promoting effect of soluble complex formation with PVP is balanced by a viscosity-related retarding effect of increasing PVP content in the diffusion layer. In dispersion systems a large dissolution-promoting effect of the X-ray amorphous state of the drug at the 40% drug level produces a highly supersaturated diffusion layer demonstrated in time/solubility profiles which is also balanced by the increasing PVP content in the diffusion layer. These findings were further supported by the observed dependence of the dissolution rate on the molecular weight and related solution viscosity of the PVP used to form the X-ray amorphous solid dispersion and mechanical mix, in high polymer content systems. In addition, a filming effect over dissolved compact faces shown by SEM, when the drug level was 40% w/w or less was attributed to a PVP layer covering the dissolving face and the change from a crystalline drug-controlled dissolution mechanism to a polymer controlled system.

Introduction

Solid dispersion systems have been considered over the last 20 years as a means of increasing the solubility, dissolution and absorption of poorly water-soluble drugs. Surprisingly, to date only a few formulations have been marketed (e.g. Grispeg, Sandoz; Cesamet, Lilly).

While there is a large volume of experimental data showing dissolution rate improvements by solid dispersion formulations, little evidence is given to elucidate the mechanism(s) responsible. Many factors have been considered to be important. These include wetting (Kaur et al., 1980), polymorphic forms (Collett and Kesteven, 1978a), reduced particle size or particle agglomeration (Bates, 1969, El-Gindy et al., 1983), formation of high energy states (Simonelli et al., 1969, Corrigan et al., 1984a), amorphous states (Corrigan et al., 1984b), soluble complex formation in the microenvironment (Chiou and Riegelman, 1971, Bates, 1969) or supersaturation phenomena (O'Driscoll and Corrigan, 1982). The shortage of definitive evidence for specific mechanisms and misconcep-

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tions of solid dispersion stability and dissolution behaviour may be contributing factors to few preparations reaching the market. The aim of the present work is to examine the frusemide–PVP mix and solid dispersion system in depth to elucidate specific mechanisms effecting dissolution enhancement.

Materials and Methods

The materials used were:
frusemide B.P. (A.P.S., Cleckheaton)
polyvinylpyrrolidone (Kollidon 12, 17, 25, 90, B.A.S.F.)
methanol (H.P.L.C. grade, Rathburn, Scotland)

All other reagents used were of Analar or GPR grade.

Intrinsic dissolution apparatus

Dissolution behaviour was assessed in a modified intrinsic dissolution apparatus (Collett et al., 1972) (Fig. 1) comprising of a perspex cylinder, lid and compact holder in which powder samples were compressed directly (173 MPa for 1 min, Apex hydraulic press PMI) designed to reduce shaft wobble and motor speed variations providing precise dissolution data.

The holder screwed into the base of the cylinder advantageously minimising interference with the test surface. A stirrer, driven by a synchronous motor (Crouzet, Hants) at 50 rpm, was used and frusemide dissolution into 900 ml pH 4.95 acetate buffer at $37 \pm 0.5°C$ followed spectrophotometrically for 60 min by an automated diode array spectrophotometer (Hewlett Packard 8451A spectrophotometer and peristaltic pump 89052A) employing sink conditions and using calibration curves. Each sample was examined at least in duplicate. Reproducibility of data expressed as % coefficient of variance (S.D./mean $\times$ 100), was 2.29% ($n = 8$) for a 16% frusemide dispersion.

Solubility determination

Saturated solubility was determined by shaking an excess of powder sample with 100 ml pH 4.95 acetate buffer in a water bath (Grant, Cambridge) and analysing spectrophotometrically for frusemide content in the filtered supernatant at equilibrium (6 days at $37 \pm 0.5°C$). Solubility–time profiles were obtained by repetitive sampling. Each sample was analysed in duplicate.

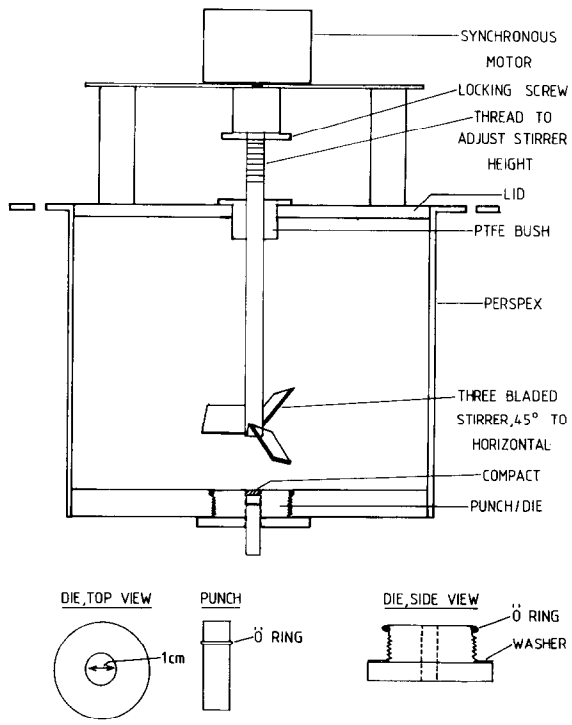

Fig. 1. Intrinsic dissolution apparatus.

Scanning electron microscopy (SEM)

A Cambridge stereoscan 600 scanning electron microscope was used to examine surface features of compacts before and after dissolution testing. Whole compacts were removed from the die and dried over molecular sieve 5A.

Sample preparation

Frusemide–PVP solid dispersions were prepared using the solvent method by evaporation to dryness from a methanolic solution (95% v/v methanol: 5% v/v water) in a vacuum oven (OVL 570, Gallenkamp, 50°C, 2.5×10^3 Pa) followed by grinding and the sieved 90–250 μM fraction was then dried over molecular sieve 5A for 48 h. A series of samples was prepared freshly prior to test containing 10–100% w/w frusemide and PVP

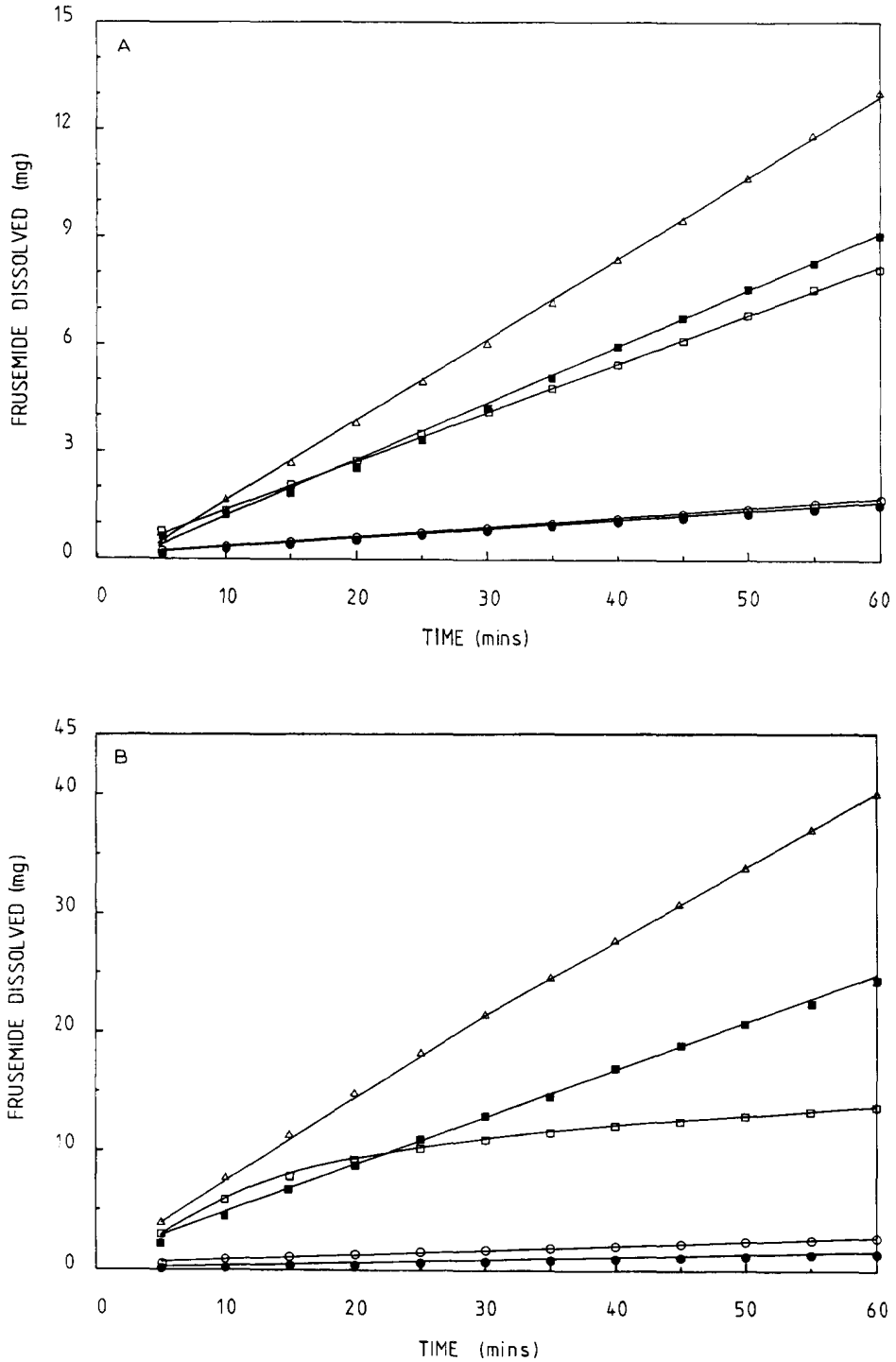

Fig. 2. Representative dissolution profiles for frusemide–PVP mix (A) and dispersion (B) systems in pH 4.95 acetate buffer (●), frusemide; (○), 80%; (□), 50%; (△), 40%; (■), 20% frusemide content.

(K25) in 10% increments. Frusemide was shown to be stable under the experimental conditions used by high-pressure liquid chromatography.

Frusemide–PVP mechanical mixes were prepared by trituration of the 90–250 μm sieve fraction of individual components.

Results and Discussion

The dissolution behaviour of the solid dispersions and mechanical mixes was examined using the practical form of the Noyes-Whitney equation for sink conditions.

$$M = K_i \cdot A \cdot C_s \cdot t \quad (1)$$

where M = mass (mg) dissolved at time t; K_i = intrinsic dissolution rate ($cm \cdot min^{-1}$); C_s = saturated solubility ($mg \cdot ml^{-1}$); and A = surface area of solid surface (0.7854 cm^2).

Representative profiles for solid dispersions and mechanical mixes using PVP–K25 (Fig. 2) show that the profile for crystalline frusemide is linear while other profiles exhibit biphasic release. The slope of the graphs or initial slope of biphasic profiles, termed the observed dissolution rate (Table 1), was used to calculate the intrinsic dissolution rate using Eqn. 1 and saturated solubility data (in cases where curves/biphasic release is seen, a 'final' slope is also given in Table 1). The shapes of the dissolution profiles were intensively examined using 3 time parameters, $T_{20\%}$, $T_{50\%}$ and $T_{80\%}$ where $T_{n\%}$ represents the time required for n% of the total mass dissolved to be dissolved. This technique has been reported to be an efficient method in defining the shape of dissolution–time profiles (Goldsmith et al., 1978).

The average time parameters of the dispersion and mix systems (Fig. 3) reveal that mix systems in the 60–80% drug region and dispersion systems in the 50–80% drug region show some negative curvature. All other profiles were linear ($r > 0.999$).

A 1% w/v PVP solution was found to increase the solubility of frusemide by 49.6% and this solubilising effect (Collett and Kesteven, 1978b) occurring in the diffusion layer will increase the dissolution rate. In mix samples with high frusemide content (> 50%) the dissolving surface may become depleted of PVP with time causing a subsequent reduction in PVP concentration in the diffusion layer and hence solubilising effect. This will result in a decrease in dissolution rate and a curved profile. SEM photomicrographs before and after dissolution of mechanical mixes (Fig. 4) confirm this hypothesis and the 'holes' seen in the dissolved surface correspond to dissolved PVP particles. Mix systems containing high PVP contents (> 50% PVP) do not show surface depletion of PVP with time and dissolution profiles are linear as reflected in the time parameters.

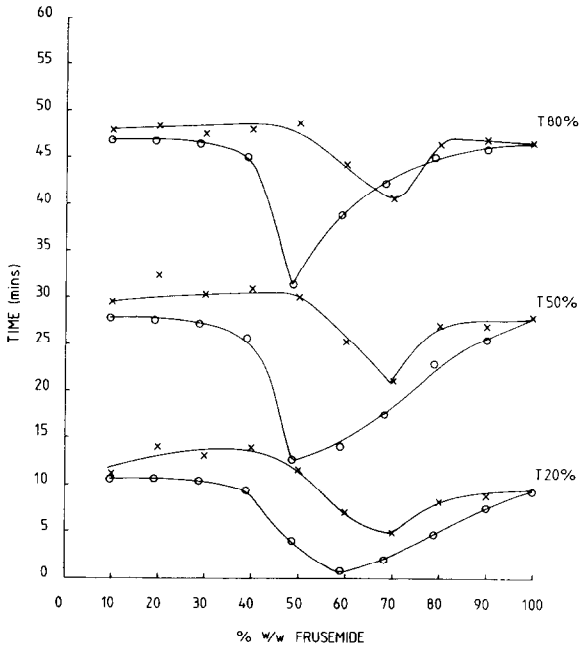

Fig. 3. Average time parameters, $T_{20\%}$, $T_{50\%}$, $T_{80\%}$ for frusemide–PVP mix (×) and dispersion (○) dissolution profiles.

Dissolution behaviour of polyphase mixtures has been discussed (Higuchi et al., 1965) and it was proposed that the initial dissolution rates of a mixture of two crystalline compounds are dependent upon their solubilities and diffusion coefficients, assuming a diffusion layer model according to the Noyes-Whitney equation. After a period, one of the phases may become depleted due to differential dissolution rates such that the surface is predominantly composed of one form. The

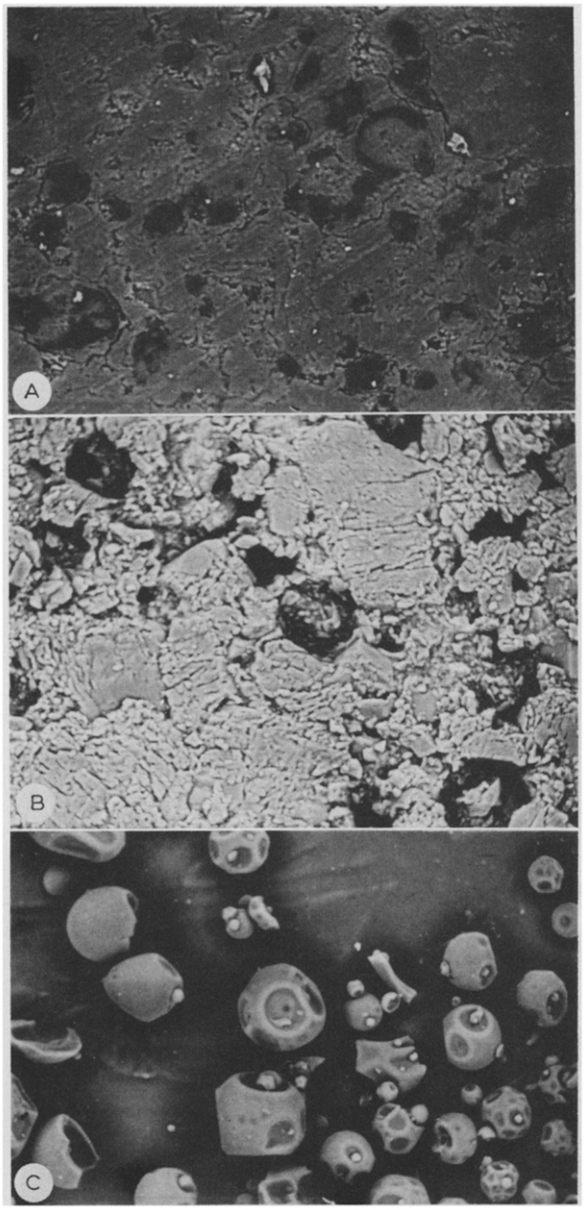

Fig. 4. SEM photomicrographs of 60% frusemide–PVP mix compact face before (A) and after (B) dissolution, with untreated PVP particles (C).

situation can be applied to the frusemide–PVP mix system with frusemide and PVP surface layers being formed in high drug and high polymer content samples, respectively, under steady-state conditions. The hypothesis may have limited application to the solid dispersion system which can comprise crystalline drug, amorphous drug and polymer phases.

The reductions in time parameters in dispersion systems (see Fig. 3), larger in magnitude than for mechanical mixes, occurred with different frusemide contents, and are not thought to be connected to PVP surface depletion effects. The reduction in crystallinity of frusemide in the dispersion system has been quantitively assessed by X-ray diffraction and differential scanning calorimetry (Doherty et al., 1985). Three regions were apparent, a crystalline region (90–100% w/w frusemide), semi-crystalline (50–80%) and an amorphous region (less than 40%). Amorphous frusemide would be expected to dissolve faster than crystalline material due to a 'high energy state', a generally undefined term but which can be interpreted as the prevention, by PVP, of the drug losing the exothermic enthalpy of crystallization and reduced inhibiting crystal forces. This explanation is supported by observed reductions in the endothermic enthalpy of solution for

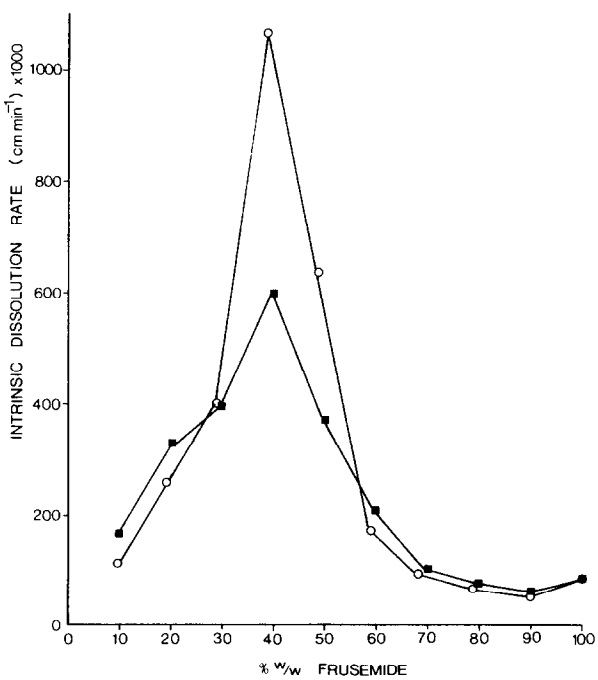

Fig. 5. Intrinsic dissolution rate data for frusemide–PVP mix (■) and dispersion (○) systems in pH 4.95 acetate buffer.

amorphous dispersions and an absence of endothermic events in differential scanning calorimetry traces, features to be discussed in a future report. A semi-crystalline sample may therefore expect to have a fast initial dissolution rate due to solution of the amorphous drug element which may become surface-depleted with time followed by a slower dissolution phase of the crystalline material. The biphasic release profile is seen in dispersions containing 50–80% frusemide which were classified as semi-crystalline. Fully crystalline and X-ray amorphous material show linear release profiles as reflected in the time parameters (see Fig. 3).

The intrinsic dissolution rates, calculated from Eqn. 1 are shown (Fig. 5) for mix and dispersion systems. In both cases maxima are seen at the 40% w/w frusemide level, with the dispersion dissolving faster than the mechanical mix. It should be noted that the slope of the dissolution profiles was in all cases larger for the dispersion than the

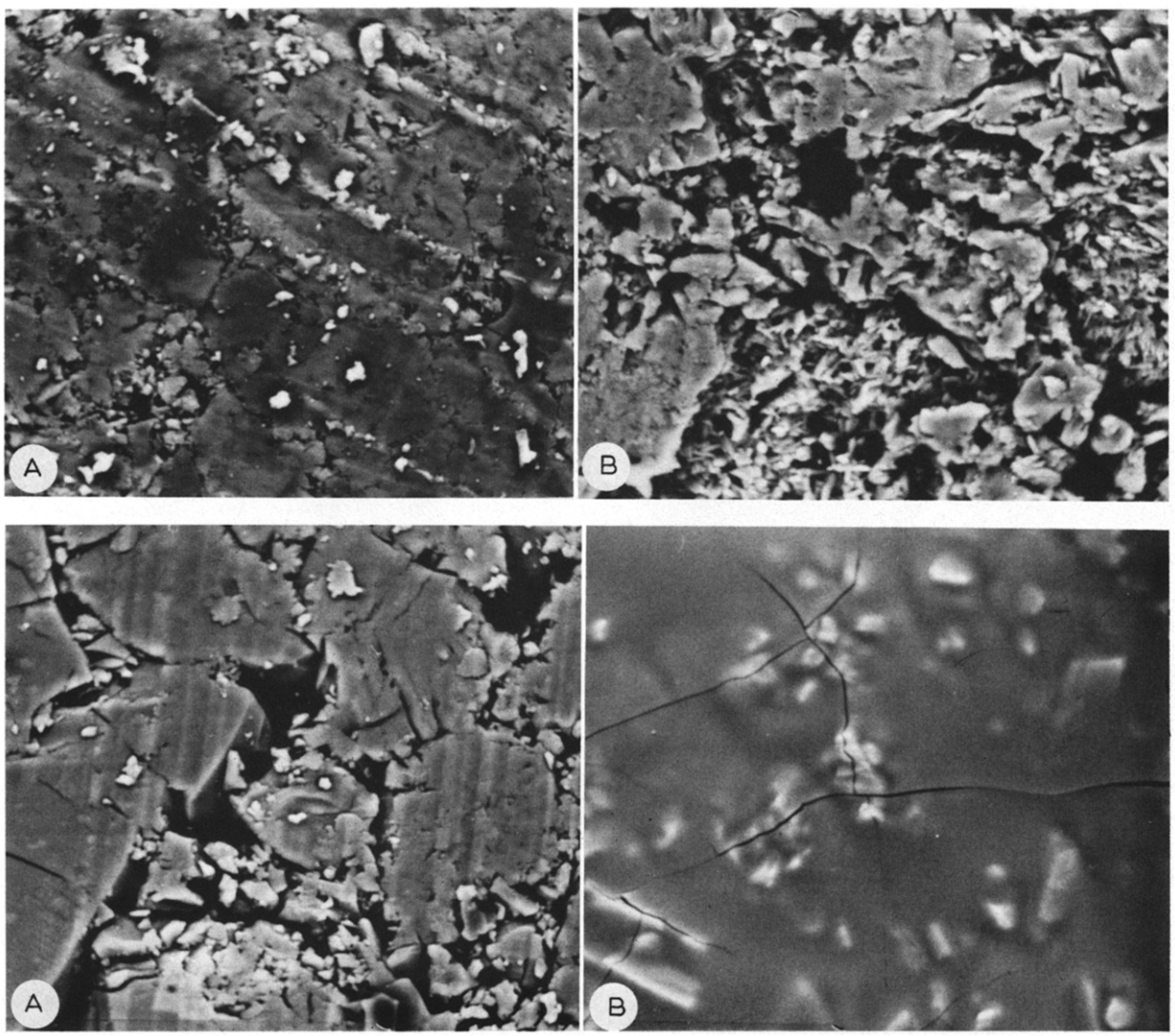

Fig. 6. SEM photomicrographs of compact faces before (A) and after (B) dissolution of 20% frusemide mix (top) and dispersion (bottom).

corresponding mix prior to calculation of the intrinsic dissolution rate (Table 1). The proposed mechanisms of dissolution increase are the solubilising effect of PVP in the mix and in the dispersion, in addition to this effect, a dissolution promoting effect of an X-ray amorphous drug phase. The maxima seen are due to a balance of these dissolution-promoting effects and the retarding effect of increasing PVP concentration in the diffusion layer.

Increases in bulk solution viscosity using PVP have been shown to retard the dissolution of model compounds (Kellaway and Najib, 1983) and these viscosity effects were found to dominate solubility increases due to drug–polymer binding. In addition, the retarded dissolution of paracetamol–PVP solid dispersions using high molecular weight PVP was related to an increased viscosity in the diffusional layer (Lipman and Summers, 1980). The relationship between viscosity and drug diffusion has been discussed (Sarisuta and Parrott, 1982, 1983) and an increase in polymer concentration was found to increase solution viscosity to a larger degree than it reduced drug diffusivity. The literature thus indicates that an increase in polymer concentration results in an increased solution viscosity and a retarded drug dissolution rate, although the exact relationship between viscosity and drug diffusion is complex.

The observed polymer-controlled retarding phenomenon will cause an increase in diffusion layer thickness associated with the change from crystalline drug-controlled dissolution to a polymer-controlled system (Ueberreiter, 1968) and a reduction in drug diffusion due to the viscosity effects. The PVP induced retarding effects will be common to both mix and dispersion systems. This is illustrated by dissolution data produced from amorphous dispersions and mix systems at the 20% w/w frusemide level using differing molecular weights of PVP (and hence viscosity). The observed dissolution rates (Table 2) reveal that the molecular weight of PVP at the 20% w/w frusemide level exhibits a dramatic effect on the dissolution behaviour and is considered to be the controlling factor in both mix and dispersion systems where the PVP content is high (> 40% w/w).

In addition, SEM photomicrographs before and after dissolution of 20% w/w frusemide mix and dispersion (Fig. 6) reveal a 'filming' effect attributed to the high PVP content of the expanded diffusion layer. The filming effect was only seen when PVP disc concentration was at least 40% w/w.

Examination of solubility–time profiles for X-ray amorphous and crystalline dispersions (Fig. 7) gave an insight into how the amorphous drug phase may manifest itself to increase the dissolution rate. These profiles indicate a supersaturation

TABLE 1

AVERAGE OBSERVED DISSOLUTION RATE DATA FOR FRUSEMIDE–PVP MIX AND SOLID DISPERSIONS; INITIAL AND FINAL RATES PRESENTED FOR CURVED PROFILES

% Frusemide	Observed dissolution rate ($mg \cdot min^{-1} \times 1000$)					
	Mix			Dispersion		
	Initial		Final [a]	Initial		Final
100	25.7	(2) [b]	–	25.7	(2)	–
90	21.3	(2)	–	29.8	(2)	–
80	28.7	(3)	27.9	47.4	(2)	36.6
70	38.7	(4)	33.1	65.4	(4)	38.4
60	76.7	(2)	49.6	114.3	(2)	49.0
50	140.4	(2)	–	480.6	(2)	81.7
40	232.5	(3)	–	741.8	(2)	–
30	169.8	(2)	–	522.1	(2)	–
20	142.8	(3)	–	395.6	(3)	–
10	74.7	(2)	–	242.3	(2)	–

[a] Final rate quoted only for biphasic profiles.
[b] Number of dissolution runs.

TABLE 2

AVERAGE OBSERVED DISSOLUTION RATE DATA FROM 20% w/w FRUSEMIDE MIX AND DISPERSIONS WITH VARYING PVP MOLECULAR WEIGHTS

PVP weight average molecular weight	K value PVP [a]	Observed dissolution rate ($mg \cdot min^{-1}$) $\times 1000$	
		Dispersion	Mix
2.5×10^3	12	1061.0	948.6
9.5×10^3	17	740.9	775.7
27.0×10^3	25	395.6	142.8
1.1×10^6	90	145.6	113.1

[a] Data from BASF 'Kollidon grades'.

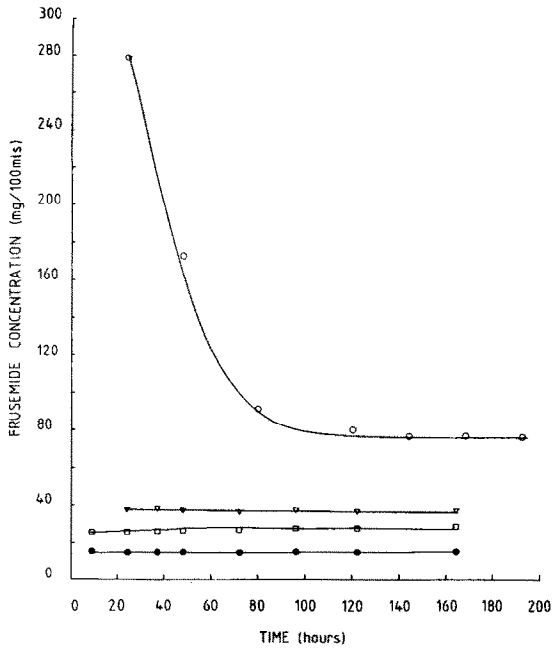

Fig. 7. Solubility–time profiles for frusemide PVP systems in pH 4.5 acetate buffer (●), frusemide alone; (□), 16% frusemide mix; (▽), 80% crystalline dispersion; (○), 16% amorphous dispersion.

phenomenon only for the amorphous dispersions. This mechanism would have a great influence on the dissolution rate by increasing the concentration gradient in the diffusion layer to the bulk media. The increased dissolution rates from amorphous phases in solid dispersions are therefore considered to be attributed to a supersaturating capacity of the drug material in the diffusion layer.

Conclusions

A discriminating intrinsic dissolution apparatus has been used to measure the dissolution of amorphous, semi-crystalline and crystalline frusemide–PVP dispersions and mechanical mixes.

In mix systems dissolution behaviour is shown to be a balance of the dissolution-promoting effect of increasing drug solubility due to interaction with PVP and a viscosity-related retarding effect of increasing PVP concentrations in the diffusion layer. The amorphous drug phase in solid dispersions enhances dissolution through a supersaturating phenomenon and this is balanced by the retarding effect of increasing concentrations of PVP in the diffusion layer in high polymer content systems.

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