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Microenvironmental pH control of drug dissolution

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Summary

Microenvironmental pH control has been used to modify the dissolution of pharmaceutical formulations in a predictive manner. An internal buffer system comprising disodium hydrogen orthophosphate and citric acid was incorporated at the 10% w/w level into a frusemide–polyvinylpyrrolidone (PVP) solid dispersion system which was X-ray amorphous, or non-crystalline, in nature. The dissolution rate, determined from constant surface area discs, was shown to be dependent on the phosphate/citric acid ratio of the internal buffer system. The approach proved successful for increasing the dissolution rate of a weakly acidic model drug in acidic media and retarding the dissolution rate in alkaline media. In an attempt to measure the pH at the "surface" of a dissolving compact a technique was developed that utilised a modified dissolution apparatus and a micro-pH probe. The data confirmed that the internal buffer system produced controlled changes in the measured surface pH. The surface pH–dissolution profiles for a series of internally buffered solid dispersions in two dissolution media (0.01 M sodium acetate and 0.01 M acetic acid) displayed a similar pattern to the pH–dissolution profile of an unbuffered X-ray amorphous frusemide–PVP solid dispersion in buffered dissolution media. This approach is proposed to be a useful method for producing controlled changes in the dissolution behaviour of pharmaceutical formulations and may be also applied to the prevention of crystallisation of drugs at the solid/liquid interface.

Introduction

The in vitro dissolution rate of a drug is a function of the drug solubility and, assuming a diffusion-controlled processes with a liquid film layer saturated with the drug, the diffusion of the drug through the layer. The solubility in the diffusion layer is that which most closely correlates with the dissolution behaviour (Gibaldi, 1984, Banker and Rhodes, 1979), and this can be a function of pH. This was effectively demonstrated in a study that compared pH–dissolution and pH–solubility data for salicylic acid and sodium salicylate using a pH-stat apparatus to control bulk pH (Serajuddin and Jarowski, 1985). When bulk pH data were used and the solubility measured at the same pH, pH–dissolution and pH–solubility profiles did not correlate. However, when solubility data at the pH of a saturated solution of the drug in the dissolution medium were used, pH–dissolution and pH–solubility data were found to correlate. This supports the concept that the pH of the diffusion layer resembles that

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of a saturated solution of the drug in the dissolution medium.

It would be advantageous to control the pH immediately surrounding a dissolving solid formulation and transfer dissolution control from a patient controlled pH variable to a pharmaceutical formulation variable. This would allow the controlled modification of a formulation to give the desired absorption profile which would then be more consistently achieved.

The use of drug salts can result in changes in the diffusion layer pH influencing the dissolution rate and clinical response (Gibaldi, 1984). Pharmaceutical additives have been included into formulations in order to modify the microenvironmental pH. Specific examples include aluminium glycinate or magnesium carbonate (Levy et al., 1965) and other alkaline compounds (Javaid and Cadwallader, 1972) in aspirin formulations and glycine, sodium bicarbonate, sodium carbonate or sodium citrate in penicillin formulations (Dwight, 1972a). Combinations of disodium hydrogen citrate and trisodium citrate have been claimed to provide a range of buffered pH environments in penicillin formulations (Dwight, 1972b).

It has been shown that the use of the salt of an acidic or basic drug can lead to precipitation of an insoluble layer on the surface of a dissolving tablet and this can hinder further dissolution (Higuchi et al., 1965). The use of additives has been indicated to alleviate these effects (Dwight, 1972a and b). The implied influence of the additives is to modify the microenvironmental pH but in most cases this has not been measured.

The present work reports the results of an initial study utilising microenvironmental pH control of dissolution of a frusemide–polyvinylpyrrolidone (PVP) solid dispersion system. The dissolution behaviour of this system has been described using constant surface area discs and buffered media (Doherty and York, 1987a, 1988). The X-ray amorphous frusemide–PVP solid dispersion was characterised by a different pH-dissolution profile than that for crystalline frusemide. A pronounced dissolution enhancement was observed when the solvent pH was greater than the pK_a of the drug and this involved the supersaturating effects of the drug dissolving from X-ray amorphous domains (Doherty and York, 1988). The decreased dissolution rates at pH values below the pK_a were associated with an obvious reversion phenomenon, involving recrystallisation of the drug at the solid–liquid interface, and this hindered further dissolution.

In this report a two-component phosphate/citric acid buffer system was included into a frusemide–PVP solid dispersion formulation containing an X-ray amorphous drug phase. By varying the phosphate/citric acid ratio it was proposed that the microenvironmental pH could be controlled and the dissolution enhancing effects of the amorphous solid dispersion sustained in a range of media with differing pH. An attempt was made to measure the surface pH by a micro-pH probe during the dissolution of constant surface area discs in media of differing pH to assess the capacity of the formulation buffer components to resist bulk pH changes.

Theoretical descriptions of single-component solid drug systems dissolving into reactive media have been proposed assuming the Nernst and Brunner film model (Higuchi et al., 1958, 1964). In addition, the diffusion layer pH gradient has been predicted for compressed discs containing a single component dissolving into reactive media using a pH-stat apparatus (Mooney et al., 1981). In the present work the situation is more complex. The buffered solid dispersion system contains 4 chemical entities; the drug, PVP and the acidic and basic elements of the buffer system. During dissolution these components can interact with each other and also with the reactive dissolution medium. In this initial report it is assumed that the dissolution rate is controlled by diffusion rates of each species through the diffusion layer and that the concentration gradient between the solid–liquid interface and the bulk medium provides the driving force for the dissolution process. It is proposed that formulation buffers can be incorporated to modify the microenvironmental pH in order to control the solubility of the drug in the diffusion layer and hence the concentration gradient with subsequent effects on the dissolution rate.

Materials and Methods

Frusemide B.P. (4-chloro-*N*-furfuryl-5-sulphamoyl-anthranilic acid, also termed furosemide) (lot 309277) was obtained from APS Ltd., Cleckheaton, U.K., and PVP as Kollidon 25 from BASF, F.R.G. The formulation buffer system comprised disodium hydrogen orthophosphate dihydrate (> 97%, BDH, Poole, U.K.) and citric acid (Analar grade, BDH, Poole, U.K.) according to literature tables (Diem and Lentner, 1972). All other reagents were of analytical grade and all water used was double distilled and deionised.

Sample preparation

The unbuffered and internally buffered frusemide–PVP solid dispersion samples were prepared by the solvent method (Chiou and Riegelman, 1971) from a 95 : 5% v/v methanol: water cosolvent. This process involved dissolving the drug and PVP in the methanol portion of the cosolvent, the buffer salts in the water component, and mixing the two solutions for 5 min. The cosolvent solution was evaporated to dryness in a vacuum oven at 50 °C and 1.5×10^3 Pa (Gallenkamp OVL 570). The resulting solids were size-reduced and the sub-250 μm sieve fraction retained. The sieved solids were dried for a further period (48 h) over molecular sieve 5A before use.

Dissolution

A dissolution method utilising constant surface area discs was used as previously reported (Doherty and York, 1987a). A flat-faced compact was produced from each powdered sample and retained in a stainless-steel holder in the base of a perspex cylinder. The hydrodynamics of the dissolution medium were controlled by a 3-bladed stirrer rotated at 50 rpm by a synchronous motor. Frusemide dissolution was analysed at least in duplicate by a diode array spectrophotometer (Hewlett Packard HP8451A) at 272 nm (37 °C) for 60 min, and the reproducibility of the experiment was estimated to be 2.29% CV from repeated testing of a solid dispersion sample.

A diffusion controlled process was assumed and the practical form of the Noyes–Whitney equation applied, with sink conditions prevailing (Noyes and Whitney, 1897);

$$d_m/d_t = k \cdot A \cdot S$$

where d_m/d_t is the measured dissolution rate and represents the slope of the linear mass dissolved–time plot (with units of mg/min), k is the intrinsic dissolution rate constant, A is the surface area of the solid or area of the diffusion layer and S is the concentration of the solute at the surface of the dissolving solid.

Surface pH measurement

The pH at the surface of a dissolving compact was estimated using an adaptation of the dissolution apparatus and a micro-pH probe. The synchronous motor was relocated to one side of the axis of the stirrer shaft and used to drive the shaft via a cog system (Fig. 1). The central core of the shaft was drilled out and a metal tube inserted, held rigidly at the top of the dissolution cell. The tube was located centrally over the dissolving compact and a micro-pH probe could be inserted down the shaft to allow measurement of the surface pH during a simulated dissolution run with the stirrer rotating. The micro-pH probe (Radiometer, Denmark, model number GK2801C, combined, miniature glass/reference electrode) had a hemispherical pH-sensitive tip and the measurements recorded reflected an average over this hemisphere.

To ensure that the whole hemisphere was in contact with the maximum area of the solid/liquid interface, compacts were produced on a base plate (Fig. 1) on which was fixed a protruding metal stud. This caused an indentation to be produced directly in the centre of the compact in which the probe could rest. The shape of the indentation was such that a small volume of fluid was present under the micro-pH probe tip. A standard glass/reference pH electrode (Russell, Scotland) was used to measure the bulk medium pH. Output from each pH probe was fed via a pH meter (Corning EEL, model 109) to a dual pen chart recorder (Rikadenki, model R12). The pH probes were calibrated at 37 °C using buffer solutions.

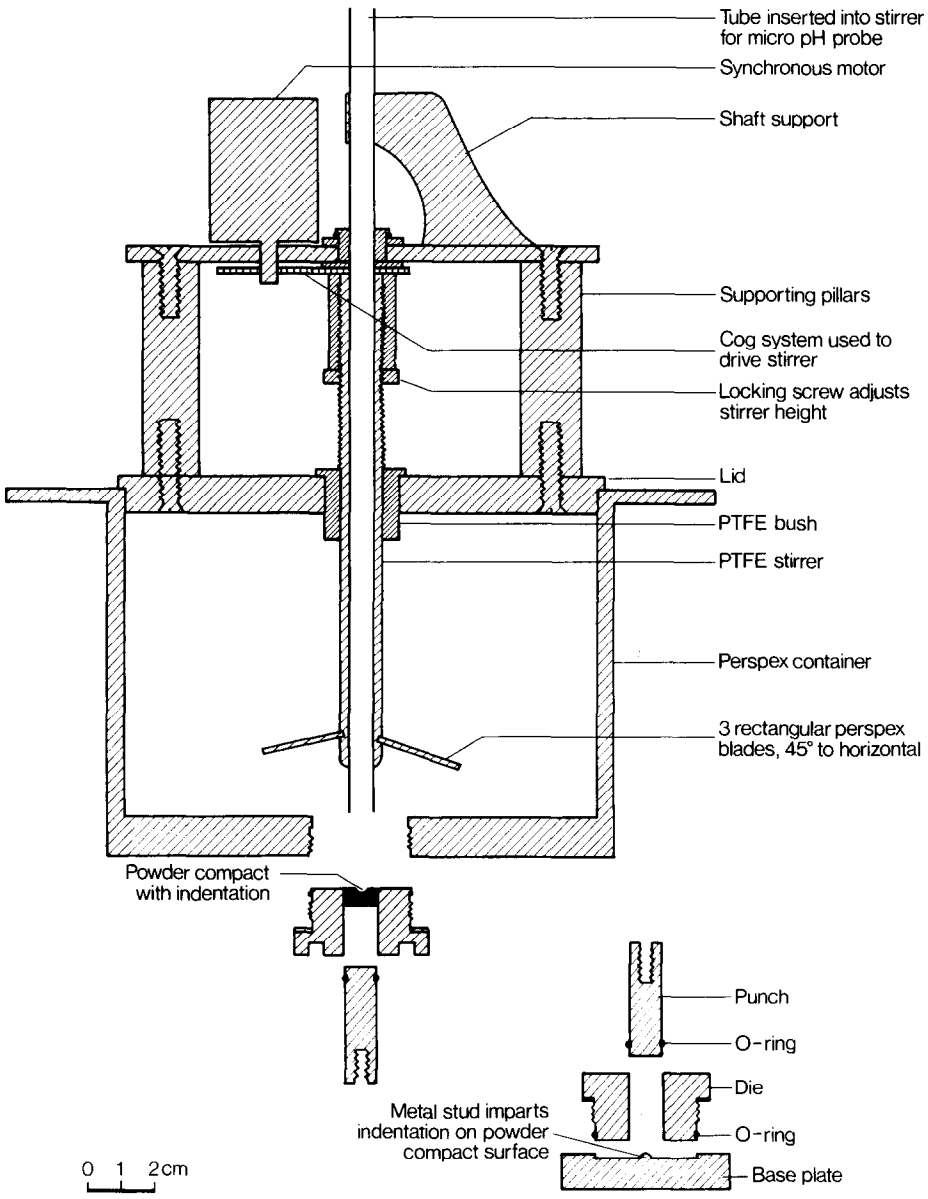

Fig. 1. Cross-section scale diagram of the dissolution apparatus modified to measure the pH at the surface of a dissolving compact using a micro-pH probe.

Three unbuffered dissolution media were used, 0.01 M acetic acid, water and 0.01 M sodium acetate. Surface pH data were recorded in 0.01 M acetic acid and 0.01 M sodium acetate. An optimised measuring system was developed to give a minimum disturbance to the hydrodynamics of the dissolving compact. Surface pH data were recorded every 5 min by bringing the micro-pH probe into contact with the solid/liquid interface for a 30 s period only, the probe being removed between measurements. Similar frusemide dissolution rates were shown from compacts with the indentation alone and those with simultaneous surface pH measurement indicating that the

surface pH measurement technique did not interfere significantly with the hydrodynamic and dissolution processes.

The final procedure for the measurement of surface pH involved compressing 500 mg of the powdered sample, using the base plate producing the indentation in the compact surface. The punch/die holder retaining the compact was screwed into the base of the dissolution cylinder and allowed to warm up in the apparatus to 37 °C for 30 min. The degassed dissolution medium at 37 °C was then added and the motor started. The micro and bulk pH probes were inserted and pH measurements recorded after 5, 10, 15, 20, 25, 30, 40, 50 and 60 min (to the nearest 0.05 pH unit). Each sample was analysed in duplicate. The surface pH data were correlated with dissolution rate data obtained from flat-faced compacts in a separate experiment.

Results and Discussion

Choice of the internal buffer system

In order to obtain a controlled pH range it was necessary to utilise a buffer system. Required properties included non-interference with the UV assay of frusemide and each buffer component to be in the solid form. The disodium hydrogen orthophosphate/citric acid system was chosen and shall be abbreviated to phosphate/citric acid. The ratio of the amounts of each buffer component required to achieve a desired pH were determined using the solution pH ratios (Diem and Lentner, 1972);

Nominal solution pH	Ratio $\frac{\text{phosphate}}{\text{citric acid}}$
2.2	0.021
3.0	0.414
3.6	0.780
4.0	1.035
4.6	1.463
5.0	1.758
6.0	2.846
7.0	7.200

Effect of the amount of buffer components in the formulation

An initial experiment assessed the effect of the amount of buffer components included in the formulation on the dissolution behaviour. This allowed determination of the optimum buffer concentration required to produce and maintain micro-environmental pH control.

Previous studies had shown that the porportion of PVP in the formulation was the critical factor in attaining an X-ray amorphous drug phase, and a minimum of 60% w/w PVP was indicated (Doherty et al., 1985). The PVP component was therefore kept constant at 60% w/w and the buffer components included at the levels of 1, 5, 10 and 15% w/w (equivalent to the sum of the masses of the phosphate and citric acid components), frusemide comprising the remaining proportion of the formulation. A phosphate/citric acid ratio of 2.846 was used and the resulting formulations were tested in 0.01 M acetic acid (bulk medium pH = 3.4). Dissolution data from duplicate experiments (Fig. 2) demonstrated that incorporation of 1% w/w buffer components resulted in a small dissolution rate increase in comparison with the unbuffered formulation (60% PVP and 40% frusemide). Further increases in the level of buffer components resulted in marked dissolution enhancement and a plateau region was apparent

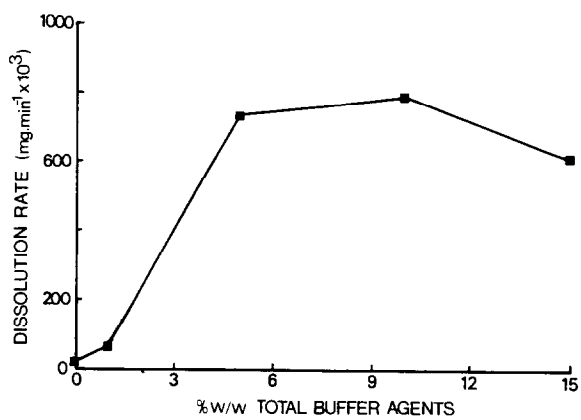

Fig. 2. The effect of the amount of total buffer components (defined as the sum of the masses of the phosphate and citric acid components) in a frusemide–PVP solid dispersion (phosphate/citric acid ratio = 2.846) on the dissolution rate from constant surface area discs in 0.01 M acetic acid at 37 °C.

between 5 and 15% w/w buffer components. The increase in the dissolution rate is attributed to a change in the microenvironmental pH, a consequence of the inclusion of buffering agents into the formulation. The surface recrystallisation effects observed for the unbuffered formulation in the acidic medium were not apparent for the internally buffered system and the dissolution enhancing effect of the X-ray amorphous drug phase was sustained.

The optimum buffered solid dispersion formulation, reflected in the dissolution rate data, comprised; 60% w/w PVP, 30% w/w frusemide and 10% w/w total buffer components. This formulation was used to assess the effect of modifying the phosphate/citric acid ratio of the internal buffer system on the frusemide dissolution rate.

Effect of modifying the buffer composition on the dissolution rate

A series of internally buffered frusemide–PVP solid dispersion formulations were produced containing phosphate/citric acid ratios in the range 0.021–7.200. It was proposed that the internal buffer system controls the microenvironmental pH and that the dissolution rate should then be independent of the bulk media pH. To test this hypothesis, frusemide dissolution rates were measured for the buffered formulations in 0.01 M acetic (pH 3.4), water (pH 5.8) and 0.01 M sodium acetate (pH 7.1) (Table 1). The dissolution rate from constant surface area discs was found to increase with increasing phosphate/citric acid ratio in the 3 solvents examined, i.e. increasing the basic element of the buffer system. However, the dissolution rates for a given sample were not equivalent in each solvent and this indicates that the solvent exerts a secondary effect on the dissolution behaviour.

The frusemide–PVP dispersion containing no buffering agents exhibited a slow dissolution rate, both in acetic acid and water, and increasing the proportion of the basic component of the internal buffer system increased the dissolution rate in the range 20.5–892.2 mg/min (×1000) (acetic acid) and 24.5–804.1 mg/min (×1000) (water). In contrast, the unbuffered formulation exhibited a markedly faster dissolution rate in the alkaline sodium acetate solution, consistent with the pH–dissolution profile (Doherty and York, 1988), and the internal buffer system reduced the dissolution rate in the range 838.4–144.5 mg/min (×1000) with increasing levels of the acidic component.

TABLE 1

Dissolution rate data

Phosphate/citric acid ratio in dispersion	Dissolution rate (mg/min × 1000)		
	Acetic acid	Water	Sodium acetate
Buffered samples			
0.021	20.5	24.5	144.5
0.414	26.9	32.4	199.7
0.780	30.1	41.4	521.1
1.035	30.3	47.2	650.1
1.463	36.8	734.5	672.8
1.758	678.5	755.7	713.3
2.846	791.7	845.6	735.7
7.200	892.2	804.1	838.4
Unbuffered samples			
frusemide	n.d.	5.3	53.7
40% frusemide–PVP dispersion	22.8	30.3	759.1

Average dissolution rate data from constant surface area discs for the series of internally buffered frusemide–PVP solid dispersions, pure frusemide and a 40% w/w frusemide–PVP dispersion (unbuffered) in 0.01 M acetic acid, water and 0.01 M sodium acetate at 37 °C.
n.d. = not detectable.

It was evident that inclusion of the internal buffer system into the formulation had a pronounced effect on the dissolution rate of the drug, with both enhancement and retardation of the dissolution process being feasible. The proposed mechanism involved a controlled change in microenvironmental pH.

An investigation of the solid state order within the buffered dispersion formulations was conducted by X-ray powder diffraction (XPD) and differential scanning calorimetry (DSC). These data demonstrated that frusemide was in an amorphous or non-crystalline state in the buffered dispersions, indicating that the presence of the internal buffering agents did not disrupt the frusemide–PVP interaction (Doherty and York,

1987b) and the PVP-induced inhibition of frusemide crystallisation. The internal buffer system subsequently modified the dissolution rate of the X-ray amorphous drug phase according to the pH–dissolution profile, the dissolution medium only exerting a secondary effect.

Surface pH measurements

Surface pH measurements were made for the series of internally buffered frusemide–PVP solid dispersions, frusemide alone and an unbuffered solid dispersion in 0.01 M acetic acid and 0.01 M sodium acetate. Example surface pH/time plots (Fig. 3) for 3 buffered dispersions in 0.01 M acetic acid demonstrate that the surface pH remained constant for at least 30 min, indent erosion modifying the data in the latter part of the experiment in fast dissolving systems. The surface pH was taken as an average of the data in the 0–30 min period. A small drift in the surface pH was observed when 0.01 M sodium acetate was used as a dissolution medium and this was accompanied by a small change in the bulk pH. It is evident that the internal buffer components modify the microenvironmental pH although the characteristics of the bulk medium maintain a small influence. To obtain surface pH data under equivalent conditions to those in 0.01 M acetic acid, the initial surface pH data in 0.01 M sodium acetate were extrapolated to zero time by linear regression and the extrapolated value defined as the surface pH.

TABLE 2

Surface pH data

Phosphate/citric acid ratio in the dispersion	Acetic acid			Sodium acetate		
	1	2	average	1	2	average
Buffered samples						
0.021	3.25	3.20	3.25	3.85	3.90	3.90
0.414	3.50	3.45	3.50	4.35	4.40	4.40
0.780	3.60	3.60	3.60	4.55	4.45	4.50
1.035	3.80	3.70	3.75	4.70	4.70	4.70
1.463	3.95	4.05	4.00	4.90	4.90	4.90
1.758	4.30	4.30	4.30	5.05	5.00	5.05
2.846	4.65	4.50	4.60	5.10	–	5.10
7.200	5.10	5.15	5.15	5.45	5.50	5.50
Unbuffered samples						
frusemide	3.20	3.35	3.30	5.40	5.45	5.45
40% frusemde PVP dispersion	3.30	3.35	3.35	4.45	4.50	4.50

Measured surface pH data for the series of internally buffered frusemide-PVP solid dispersions, pure frusemide and a 40% w/w frusemide–PVP dispersion (unbuffered) in 0.01 M acetic acid and 0.01 M sodium acetate at 37 °C. Duplicate data and average figures are shown. All surface pH data and the averaged values are quoted to the nearest 0.05 pH unit.

The surface pH data for the series of internally buffered formulations studied exhibited a similar range in each solvent (Table 2), pH 3.25–5.15 in 0.01 M acetic acid and pH 3.90–5.50 in 0.01 M sodium acetate, demonstrating that the internal buffers are acting to control the microenvironmen-

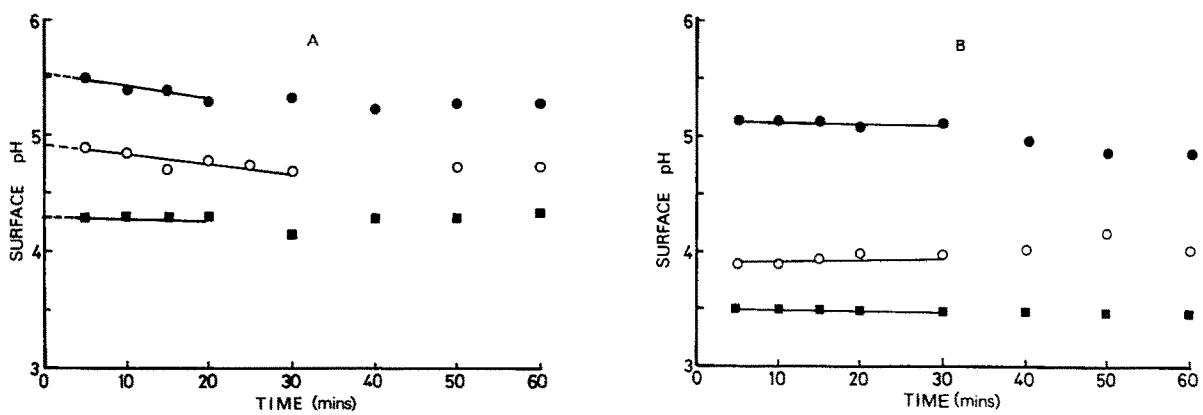

Fig. 3. Measured surface pH–time data for internally buffered frusemide–PVP dispersions containing phosphate/citric acid ratios of 0.414 (■), 1.463 (○) and 7.200 (●) in 0.01 M sodium acetate (A) and 0.01 M acetic acid (B). Dotted lines indicate extrapolation to zero time.

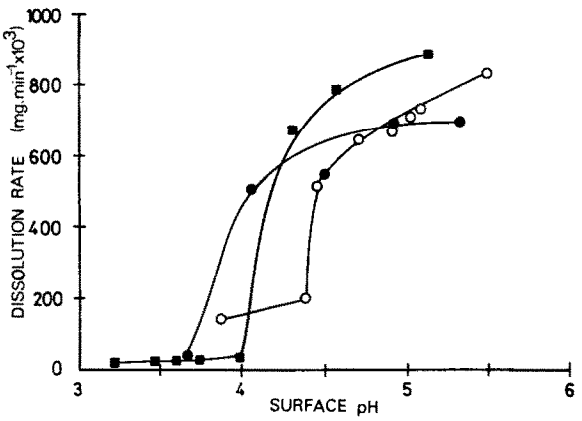

Fig. 4. The correlation between the measured surface pH and the frusemide dissolution rate from constant surface area discs for the series of internally buffered frusemide–PVP dispersions in 0.01 M acetic acid (■) and 0.01 M sodium acetate (●), compared with the pH–dissolution profile for a 40% frusemide–PVP dispersion in buffered solutions (○).

tal pH in each solvent. By comparison, the surface pH data for the unbuffered formulations, frusemide and the frusemide–PVP dispersion without added buffer agents, show larger differences in the two solvents examined. The data demonstrate that adjusting the phosphate/citric acid ratio of the internal buffer system resulted in a controlled change in the surface pH.

The correlation between the frusemide dissolution rate and surface pH data for buffered dispersions (Fig. 4) shows a similar pattern in the two dissolution media examined. Further, the profiles are of a similar form as the pH-dissolution profile of the unbuffered solid dispersion obtained using buffered dissolution media (Doherty and York, 1988). This implies that a common controlling parameter is effective in each system. The attainment and maintenance of a supersaturated frusemide solution in the microenvironment, shown to be a function of pH, was considered to be the dominant factor in the dissolution behaviour of the unbuffered dispersion (Doherty and York, 1988).

It has been inferred in other work that the bulk media pH differed from the diffusion layer pH when unbuffered media were used (Serajuddin and Jarowsky, 1985). In order to obtain a correlation between dissolution and solubility in accordance with the Noyes–Whitney equation, the pH of a saturated solution was measured and solubility data obtained at this pH. In the present work, saturated solution pH data were obtained for the unbuffered samples (frusemide and the frusemide–PVP solid dispersion without the internal buffer system) in 0.01 M acetic acid and 0.01 M sodium acetate by determining the pH of a saturated solution at the apparent equilibrium (37 °C, equilibration period of 6 days). An excellent correlation between the saturated solution pH and the measured surface pH during a dissolution run was observed for a pure frusemide compact in each solvent studied, confirming the predicted behaviour (Serajuddin and Jarowski, 1985) (Table 3). These data are of interest in the interpretation of dissolution data obtained in unbuffered media using pH-stat techniques where the recorded and maintained bulk pH will not represent the effective, controlling pH in the diffusion layer.

The surface pH data for the unbuffered 40% frusemide–PVP dispersion were lower than the saturated solution pH data in 0.01 M sodium acetate. This is consistent with the proposed mechanism of dissolution enhancement involving supersaturation effects in the microenvironment when the solution pH is above the pK_a of frusemide ($pK_a = 3.9$). This would result in a higher frusemide concentration in the diffusion layer than that present in a saturated solution at "equilibrium", although PVP may also exert an in-

TABLE 3

Comparison of the pH of a saturated solution and surface pH data

Sample	Saturated solution pH		Surface pH	
	Acetic acid	Sodium acetate	Acetic acid	Sodium acetate
Frusemide	3.29	5.47	3.30	5.45
40% Frusemide–PVP dispersion	3.38	5.08	3.35	4.50

pHs were measured during a simulated dissolution run, for the unbuffered samples, frusemide and a 40% w/w frusemide–PVP dispersion, in 0.01 M acetic acid (pH = 3.40) and 0.01 M sodium acetate (pH = 7.10) at 37 °C.

fluence in lowering the surface pH due to a weakly acidic nature. These factors may also account for the unbuffered dispersion exhibiting a lower surface pH than the crystalline frusemide in 0.01 M sodium acetate.

The comparison of the saturated solution pH and surface pH data for unbuffered samples supports the validity of the surface pH measurement technique in reflecting a microenvironmental pH.

The role of PVP in the formulation is considered to involve the production and stabilisation of an X-ray amorphous frusemide phase and the maintenance of a surpersaturated solution in the microenvironment during dissolution. In addition, as a consequence of the large PVP component in the formulation, an expanded diffusion layer is likely to produce a series of boundary layers at the solid–liquid interface associated with the dissolution of polymeric materials (Ueberreiter, 1968). These surface layers, and the intimate mixture of drug, polymer and internal buffer components are considered to be major contributing factors in the retardation of the dissolution of the water soluble buffer components such that they can exert an influence on the microenvironmental pH and subsequently on the dissolution of the amorphous frusemide phase.

Conclusions

The hypothesis that an internal buffer system in a frusemide–PVP solid dispersion system can be used to control the microenvironmental pH and consequently the drug dissolution rate has been tested. The use of an internal buffer system (incorporated at the level of 10% w/w total buffer components) resulted in marked dissolution changes dependent on the phosphate/citric acid ratio. This method of dissolution control was found to be effective for increasing the dissolution of frusemide in acidic media and reducing the dissolution rate in alkaline conditions. The pH of the bulk medium was considered to exert only a secondary influence.

Measurement of the pH at the surface of a dissolving compact by a method utilising a micro-pH probe confirmed the hypothesis that the dissolution rate changes associated with the inclusion of the internal buffer system into the solid dispersion formulation resulted from controlled changes in the microenvironmental pH. It may be predicted that the in vivo absorption of frusemide from a buffered solid dispersion would be dependent on the phosphate/citric acid ratio chosen and be more consistent than that from unbuffered formulations.

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