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RELATIONSHIP BETWEEN THE pH OF THE DIFFUSION LAYER AND THE DISSOLUTION RATE OF FUROSEMIDE

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ABSTRACT

Sodium bicarbonate and ascorbic acid, both highly water-soluble materials, were used to modify the initial dissolution rate of furosemide from tablet formulations in various dissolution media. The observed differences in the initial dissolution rates of the drug have been correlated with changes in the pH of the diffusion layer brought about by the diluents. The initial dissolution rate of furosemide was shown to be dependent on and controlled by the pH of the diffusion layer while the bulk exerted only a secondary effect by controlling the magnitude of the pH-change through its buffer capacity.

INTRODUCTION

According to Nelson[1,2] the pH of the diffusion layer surrounding a soluble acid or salt will be relatively independent of the bulk pH because of the buffering action of the material. The solution rate of the acid or salt would be mainly controlled by the pH of the diffusion layer rather than the bulk pH.

Researchers have used this buffering action of dissolving substances to improve the dissolution rates of low water-soluble acidic drugs by including various basic compounds[3,4] or buffer systems[5] in pharmaceutical formulations. The use of such systems lies in providing an environment near the dissolving drug in which it would be more soluble than the bulk medium in which dissolution was taking place[6].

The purpose of this study was to investigate the effect of highly water-soluble diluents on the dissolution rate of furosemide formulations and to relate these effects to changes in the pH of the diffusion layer during dissolution.

MATERIALS AND METHODS

Materials

Furosemide was obtained from Propan Pharmaceuticals (Pty) Ltd., Germiston, RSA (Lot A17333) and sodium bicarbonate and ascorbic acid from BDH Chemicals, Poole, England. All other chemicals were of analytical grade and all water used were double distilled.

Preparation of the tablets

Tablets containing 37,5 mg furosemide, 110 mg diluent (sodium bicarbonate [formulation A] or ascorbic acid [formulation B]), Ac-Di-Sol® as disintegrant, magnesium stearate as lubricant and starch mucilage as binder were prepared by wet granulation.

Compression

Tablets, each weighing approximately 150 mg, were compressed in a Beckmann hydraulic press fitted with a calibrated pressure gauge. Compression was done at 1500 KPa for 15 seconds between concave-faced punches in a 7 mm die. The tablets were manually pushed from the die with a punch.

Dissolution studies

Dissolution studies were done according to the method of the USP XXI (apparatus 2) using a six-station dissolution apparatus (Erweka, Model 6DTR). The dissolution medium consisted of 0,1 M HCl (pH 1,2); potassium acid phosphate/NaOH buffer (pH 5,8) or potassium acid phosphate/NaOH buffer (pH 7,4). All dissolution media were prepared according to the method of the USP XXI. Samples of 10 ml were withdrawn through a pre-filter (Sartorius, Göttigen, West Germany) at 1, 2, 4, 8, 16, 32, 64 and 90 minutes. The medium lost through sampling was immediately replaced with 10 ml fresh medium at 37 °C. The amount of furosemide dissolved at each sample time was determined at 271 nm against fresh medium as blank using a digital spectrophotometer (Hitachi, Model 100-10). Presented data are the mean of two runs on each formulation.

Determination of the pH of the diffusion layer (pH_d)

According to the definition[1,7], the diffusion layer is saturated with dissolving solids, which implies that it also contains other dissolved substances besides the drug. In this study it was assumed that the diluents, rather than

furosemide, would determine the pH_d since they have higher water solubilities, more pronounced acidic or basic properties and made up 70% of the tablet weight compared to only 25% of furosemide.

Saturated solutions of each diluent were prepared by adding an excess of the diluent to 200 ml of media at 37 °C. The samples were rotated until saturation was evident. The solutions were filtrated and the pH of the supernatants were measured using a digital pH-meter (Zeiss, Model 300).

Determination of the initial dissolution rate (I_{dr})

The rate at which furosemide dissolved was estimated by calculating the slope of a straight line through the data points between 0 and 8 minutes. The slope, called the initial dissolution rate, was calculated from the least square fit of the amount of furosemide dissolved against time. The calculations were done with a Lotus 123 computer program.

Statistical comparison

The mean I_{dr} of the formulations in the media were compared for significant differences at a 95% confidence level with the Student-Newman-Keuls multiple-range test. The calculations were done with a BMDP7d program (BMDP Statistical Software, California, USA).

RESULTS AND DISCUSSION

The effect of sodium bicarbonate and ascorbic acid on the pH_d and the I_{dr} of furosemide from the two formulations in the different media are summarized in table 1.

The I_{dr} from formulation A was significantly higher than from formulation B in both 0,1 M HCl and the pH 5,8-buffer, while no significant difference existed between the I_{dr} in the alkaline medium (pH 7,4).

It was expected that the I_{dr} could be correlated with the pH_d and that these pH_d's were determined by the basic/acidic properties of the dissolving diluents. The pH_d's in the presence of the diluents in each medium were determined as described under materials and methods. The effect of the diluents on the pH_d in the various media are shown in table 1.

The high I_{dr} from formulation A in 0,1 M HCl and the pH 5,8-buffer could be attributed to a rapid increase in the pH_d of 0,1M HCl and the pH 5,8-buffer. This increase was brought about by the highly water-soluble sodium bicarbonate.

TABLE 1

The pH of the diffusion layers (pH_d) in the presence of sodium bicarbonate and ascorbic acid and the initial dissolution rates (I_{dr}) of furosemide from formulations A and B in the various dissolution media.

Medium	Formulation A Sodium bicarbonate		Formulation B Ascorbic acid	
	$I_{dr} \times 10^{-3}$ (mg/ml/min)	pH_d	$I_{dr} \times 10^{-3}$ (mg/ml/min)	pH_d
0,1 M HCl (pH 1,2)	*3,397 (0,982)*[a]	*8,2*	*0,224 (0,953)*	*0,9*
Phosphate buffer (pH 5,8)	*6,645 (0,998)*	*8,4*	*2,645 (0,992)*	*1,7*
Phosphate buffer (pH 7,4)	*6,096 (0,999)*	*8,3*	*7,246 (0,907)*	*5,3*

[a] *Values in parentheses are the correlation coefficients of the straight lines through the dissolution data points between t_0 and t_8 minutes.*

Ascorbic acid, on the other hand, caused a decrease in the pH_d in the to media, resulting in a retardation of the I_{dr} of furosemide from formulation B.

The results suggested that the diluents changed the pH_d to such and extend that the I_{dr} of furosemide were mainly determined by the pH_d, while the bulk pH (pH_{bulk}) exerted only a secondary effect.

This hypothesis however, does not fully account for the significant slower I_{dr} from formulation A in 0,1 M HCl compared to the rate in the pH 5,8 buffer while the pH_d's were almost similar (Table 1).

According to Hoener & Benet[8] the solution rate of particles from a region where they are ionized (pH_d 8,2) to a bulk where they would become nonionized (pH_{bulk} 1,2) would be slow compared to the rate of a process where ionized particles in the diffusion layer (pH_d 8,4) diffuse to a region with a high capacity for ionized particles (pH_{bulk} 5,8), since the solubility for the ionized species (salt form) are much higher than for the nonionized molecules.

TABLE 2

The effect of the buffer capacities (β) of the phosphate buffers on the pH-change in the diffusion layer.

Medium	Buffer capacity (β)	pH_{bulk}	ΔpH Formulation A	ΔpH Formulation B
Phosphate buffer	*0,005*	*5,8*	*+2,6*	*-4,1*
Phosphate buffer	*0,020*	*7,4*	*+0,9*	*-2,1*

A significant difference was observed between the I_{dr} from formulation B in the two phosphate buffers, although the pH_{bulk} would suggest favorable dissolution in both media.

In the pH 5,8-buffer furosemide would be 99,37% ionized (pKa of furosemide taken as 3,6) compared to 99,98% in the alkaline medium (pH 7,4). Both these media would therefore favor the dissolution of furosemide. The I_{dr} in the pH 5,8-buffer however was almost 3 times slower than the rate in the pH 7,4 medium because of the significant difference between the pH_d's in the media. These results emphasized that the solution rate was governed/controlled by the pH_d rather than the pH_{bulk}.

The large difference between the pH_d's of formulation B (ascorbic acid) in the two phosphate buffers could be explained by the differences in the buffer capacities of the media.

The differences (ΔpH) between pH_{bulk} and pH_d for both formulations in the phosphate buffers are shown in table 2.

In the pH 5,8-buffer ascorbic acid could overcome the buffer capacity of the bulk medium in the diffusion layer, causing a large decrease in the pH_d. The higher buffer capacity of the alkaline medium neutralized the pH-lowering effect of the ascorbic acid which resulted in a smaller difference between the pH_d and the pH_{bulk}. It is safe to presume that the differences between the pH_d's and the pH_{bulk} were influenced by the buffer capacities of the dissolution

media. These differences were the main reason for the variations between the I_{dr} from formulation B in these media (Table 1).

The pH-increase caused by sodium bicarbonate was much more evident in the pH 5,8-buffer because of the low buffer capacity of the medium, while a smaller pH-difference was observed in the pH 7,4-buffer with the higher buffer capacity. Since the pH_d's were almost equal, the I_{dr} from the tablets in the two media did not differ significantly (Table 1).

An increase in the buffer capacity of the dissolution media improved the I_{dr} of furosemide in the presence of an acidic diluent because of a depression of the pH-lowering (negative) effect of the diluent which would retard the dissolution rate. For an alkaline diluent a higher buffer capacity of the bulk medium would minimize or neutralize the positive effect (pH-increase) of the diluent on the dissolution rate.

CONCLUSIONS

The results of the study showed that the:

- initial dissolution rate of furosemide, a poorly water-soluble acid, was dependent on the pH_d rather than the pH_{bulk};
- type of pH-change caused by the dissolving diluents depended on their basic or acidic properties;
- magnitude of the change in the pH_d was influenced by the buffer capacity of the bulk medium.

The results of the study confirmed the findings of Doherty and York[5] which showed that by governing the pH of the diffusion layer the dissolution rate of drugs could be controlled in a predictable way.

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