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OPTIMIZATION OF SLOW-RELEASE TABLET FORMULATIONS CONTAINING MONTMORILLONITE II. FACTORS AFFECTING DRUG RELEASE

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ABSTRACT

The influence of electrolytes, surfactants in the dissolution medium, and particle size of drug and montmorillonite on the in vitro release of the soluble model drug sodium sulfathiazole from directly compressed slow-release tablets containing 20% drug and 30% magnesium aluminum silicate was investigated. The presence of electrolytes in the dissolution media decreased the release from the tablets. A decrease in release was also observed in deionized water when sodium chloride was included in the tablet formulation. The surface tension of the media appeared to have little influence on the dissolution rate of the drug. Varying the particle size of the drug had a greater effect on release rates than varying the particle size of the montmorillonite clay.

INTRODUCTION

Magnesium aluminum silicate[1] has been used successfully to slow the *in vitro* release of sodium sulfathiazole from directly compressed tablets. The soluble model drug was included in the formulation at the twenty percent level. The incorporation of the montmorillonite clay into the formulation at a thirty percent level permitted the tablets to be wetted very slowly. The tablet formula and method of preparation were described in an earlier report (1).

In the first paper of this series (1), the effects of tablet hardness and rate of agitation during dissolution tests were reported. Tablet hardness had an insignificant effect on release, whereas release of drug increased as the stirring rate of the rotating basket was increased. It was also shown that the pH of the dissolution media influenced the release pattern for these tablets.

In the present study the effects of several other variables on the rate of release of sodium sulfathiazole will be discussed. These variables include electrolyte changes in the dissolution medium, the effect of including electrolyte in the formulation and changing the particle size of both drug and clay.

EXPERIMENTAL

The materials and techniques used in preparing tablets and studying release rates were described previously (1). Reagent grade sodium chloride[2] was pulverized, and passed through an 80 mesh screen

1. Veegum F®, R. T. Vanderbilt, Norwalk, CT 06855
2. Fisher Scientific, Fair Lawn, NJ 074103.

prior to use. It was incorporated into the formulation at a 15% level replacing dicalcium phosphate dihydrate. To investigate ionic strength effects of the dissolution media, this electrolyte was added to 0.1N HCl to make 0.5M and 4.0M solutions in sodium chloride. The surface tension of 0.1N HCl was reduced by the inclusion of a nonionic surfactant, polysorbate 80[3]. Magnesium aluminum silicate was received as the micronized montmorillonite clay, Veegum F®[1] ($\leq$ 50μ). This microfine clay was wet granulated with water to prepare granules of different particle sizes. The effect of the clay particle size was investigated by comparing tablets prepared with the 60-120 mesh (250-125 microns) fraction with those prepared with the micronized clay.

Sodium sulfathiazole[4] was received as very coarse granules. This eliminated the necessity of a granulating step to obtain the desired particle sizes. The drug was ground with a mortar and pestle and separated into two particle size ranges: 40-60 mesh (420-250 μ), and the fraction passing through a number 200 mesh (less than 74 μ) screen.

The prototype formulation (1) was used to prepare tablets in which sizes of both clay and drug were varied. The levels of all other ingredients and their particle sizes were held constant. Table 1 lists the particle sizes of drug and clay in the four tablet formulations.

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3. Tween 80, ICI, Wilmington, DE 19899

4. City Chemical Corp., New York, NY 10001

TABLE 1. Size Fractions of Drug and Clay for Tablet Formulas 1 to 4.

	Formula #1	Formula #2	Formula #3	Formula #4
Montmorillonite Clay[a]	60-120 mesh	60-120 mesh	<325 mesh	<325 mesh
Sodium Sulfathiazole	<170 mesh	40- 60 mesh	<170 mesh	40-60 mesh

[a] Veegum F®

Dissolution conditions, with the exception of differing media, were the same as previously described (1). The reported dissolution data represent the mean of three or more runs. Samples were assayed spectrophotometrically at the λ_{max} of sodium sulfathiazole in each dissolution medium.

RESULTS AND DISCUSSION

Tablets prepared with 30% magnesium aluminum silicate did not disintegrate when they were exposed to an aqueous medium. Instead, they slowly swelled to a larger volume and a thick gelatinous layer formed around the tablet matrix. This layer served as a barrier between the dissolution medium and the unwetted core. The release of sodium sulfathiazole from these tablets was very slow. It is probable that hydration of the clay played a significant role in the release characteristics of the drug. As the dissolution medium penetrated through the gel layer, the drug dissolved and diffused through the barrier into the bulk medium. Sodium sulfathiazole was very

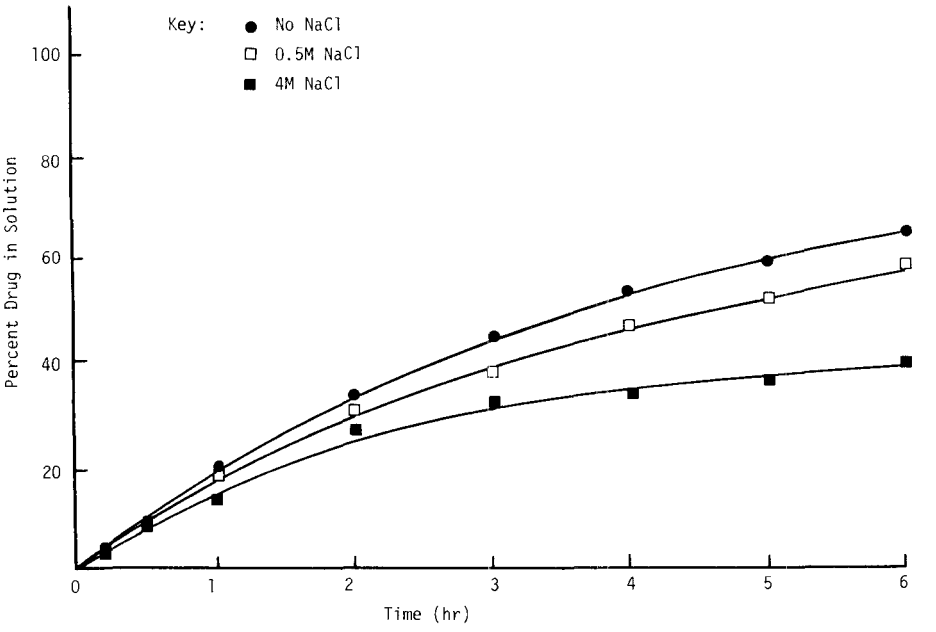

Figure 1 Influence of ionic strength of the medium on the dissolution rate of sodium sulfathiazole in 0.1N HCl at 37° and stirred at 50 rpm.

soluble in the dissolution medium and sink conditions prevailed during the dissolution studies.

Electrolytes are known to affect the swelling properties of montmorillonite clays (2,3). The presence of electrolytes was found to decrease the degree of swelling of the clay in proportion to the amount of electrolyte in solution. This is exemplified in Fig. 1 where the release rate decreased with increasing ionic strength of the dissolution media. These results indicate that the swelling of the tablet (hydration of the clay) was an important factor in controlling drug release from the dosage form.

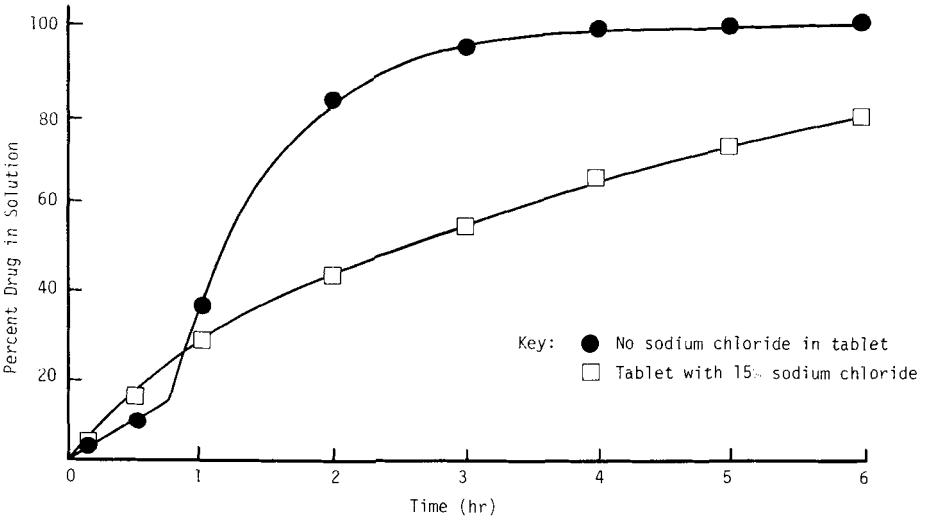

Figure 2 Influence of sodium chloride in the slow-release tablets on the dissolution rate of sodium sulfathiazole in deionized water at 37° and stirred at 50 rpm.

Inclusion of sodium chloride in the tablet formulation at the 15% level had a similar effect in deionized water as seen in Fig. 2. It should be pointed out that the initial linear phase previously observed (1) and reported in Fig. 2 did not occur with tablets containing sodium chloride. However, no electrolyte effect was observed when the dissolution test was carried out in 0.1N HCl, Fig. 3. The rate of hydration of the clay was reported to be slower at lower pH's (4). Therefore, the effect of the electrolyte may be overshadowed by this fact. There could also be a common ion effect, altering the solubility of sodium sulfathiazole as dissolution media penetrated the tablet. Since a great number of sodium ions were present in the penetrating media, the rate of dissolution of drug

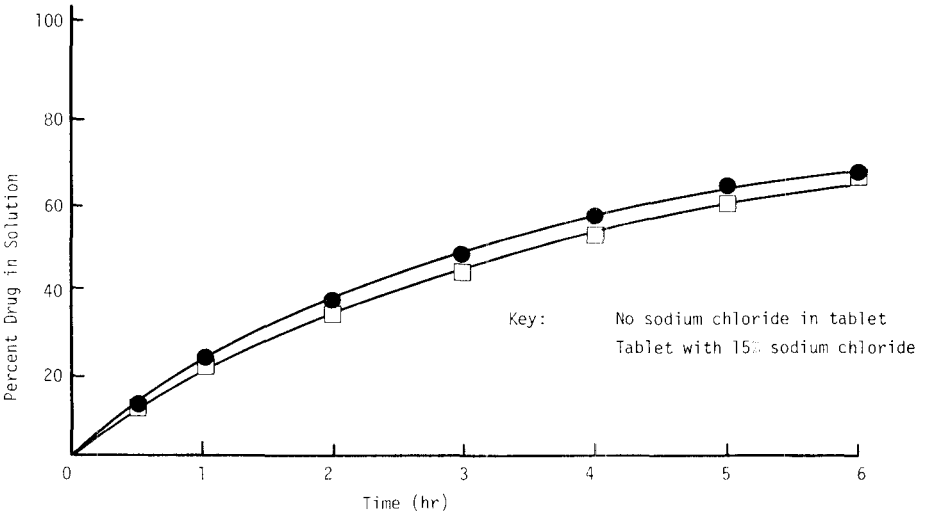

Figure 3 Influence of sodium chloride in the slow-release tablets on the dissolution rate of sodium sulfathiazole in 0.1N HCl at 37° and stirred at 50 rpm.

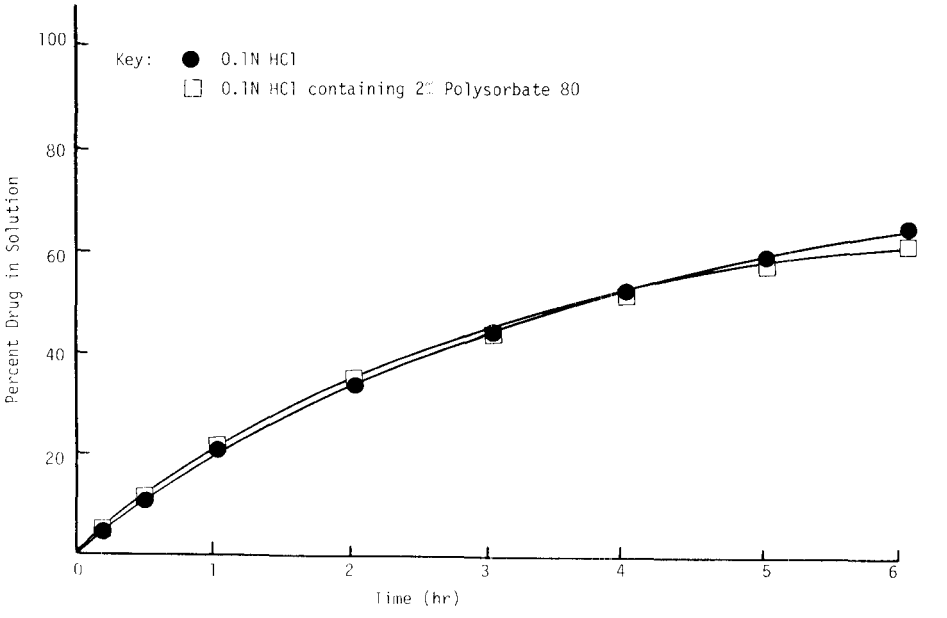

Figure 4 Influence of a surfactant in the medium on the dissolution rate of sodium sulfathiazole from slow release tablets at 37° and stirred at 50 rpm.

Table 2. Properties of Slow-Release Tablets

Tablet Formula	Weight Uniformity (mg) Mean ± S.D. (n=20)	Hardness (kg) Mean ± S.D. (n=6)	Friability % Loss (n=10)	Content Uniformity (mg) Mean ± S.D. (n=6)
1	562.26 ± 13.58	6.63 ± 0.52	0.24	102.15 ± 2.22
2	599.73 ± 2.67	5.33 ± 0.70	1.54	116.70 ± 6.62
3	560.61 ± 48.82	6.20 ± 3.20	1.80	128.62 ± 3.74
4	587.16 ± 27.54	4.50 ± 1.04	8.00	109.67 ± 5.44

at the gel-matrix interfacial layer may be decreased. (Sink conditions would still be maintained in the bulk medium, however.)

The influence of including a surfactant in the dissolution medium can be seen in Fig. 4. There was no significant effect on release of drug from the tablet when a nonionic surfactant was added to the dissolution medium at the 2% level.

The physical properties of tablets prepared with various particle sizes of drug and clay are given in Table 2. Tablet formula 1 is essentially the same as the prototype formula previously reported (1). Tablets were prepared to be approximately the same average weight (560-599 mg) and hardness (4.5-6.6 kg). Tablet formula 4 gave a very high friability value indicating poor bonding of the fine clay upon compression. It has been found that the moisture content of the montmorillonite granules and that of fine powder was not significantly different after similar treatments. Scanning electron microscopy has indicated that the surface morphology of both the clay granules and fine powder appear to be very similar. Therefore, it was assumed that the high friability was due mainly to the particle size of the clay. In addition, the high friability could have resulted from the low hardness.

Content uniformity data for tablet formulas 3 and 4 were obtained from tablets of approximately the same weight because of the large variation in weight uniformity. Tablets prepared from formulas 1 and 2 were chosen at random and analyzed for drug content. The inclusion of both drug and clay as very fine powders in formula #3, resulted in the greatest variation in mean tablet weight.

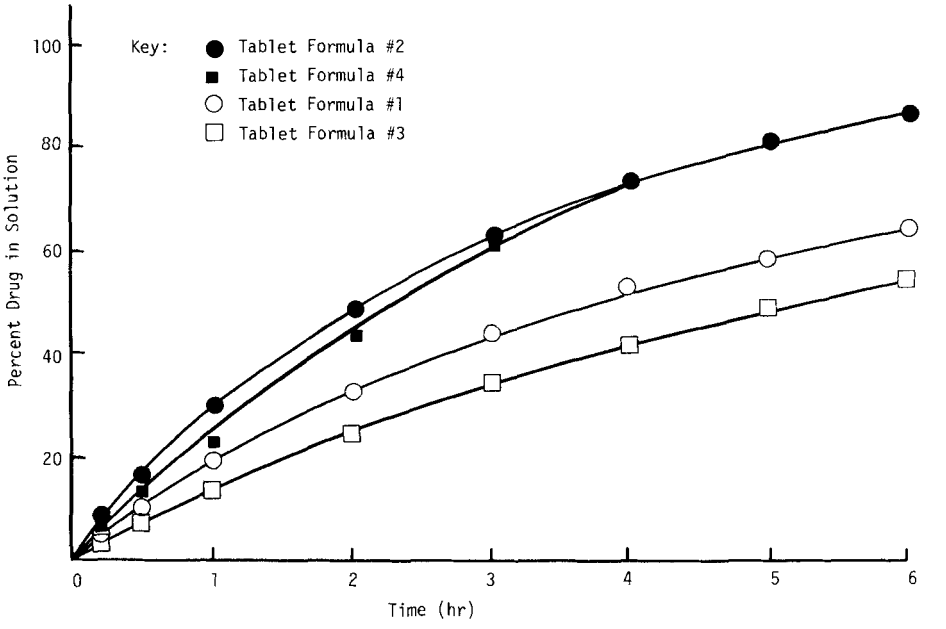

Figure 5 Influence of the particle size of sodium sulfathiazole and montmorillonite clay on the dissolution rate of sodium sulfathiazole from slow-release tablets in 0.1N HCl at 37° and stirred at 50 rpm.

The particle sizes of both drug and clay were found to alter the dissolution profiles of these tablets as shown in Fig. 5. The rank order of release rates from fastest to slowest was as follows:

Formula 2 > 4 > 1 > 3

The tablets containing coarse drug (2 and 4) gave the fastest release rates, whereas those containing fine drug (1 and 3) gave the slowest rates. Changing the particle size of the montmorillonite appeared to have an insignificant effect when coarse drug was included (2 and 4). However, a significant decrease in the release

rate was seen when the clay was included in the formula as a fine powder with fine drug (1 and 3).

In summary, tablets containing 30% montmorillonite have been prepared by direct compression and such tablets provide for a slow *in vitro* release of a soluble model drug, sodium sulfathiazole. The *in vitro* release rate of drug was not influenced by the presence of surfactants in the dissolution medium. However, it was found to be affected by the presence of electrolytes in the dissolution media and in the tablet, and the particle size of the drug and clay.

ACKNOWLEDGEMENTS

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