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OPTIMIZATION OF SLOW-RELEASE TABLET FORMULATIONS CONTAINING MONTMORILLONITE I. PROPERTIES OF TABLETS

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ABSTRACT

Slow-release tablets containing 20% sodium sulfathiazole and 30% magnesium aluminum silicate were prepared by direct compression techniques. Dissolution studies indicated that tablet hardness exerted a negligible influence on drug release from the tablets. During the dissolution process the clay slowly swelled to form a gelatinous hydrated layer around the tablet matrix. At faster stirring speeds, friction between the dissolution basket and the tablet rapidly removed the hydrated boundary region and resulted in a more rapid dissolution rate of the sulfonamide. Faster rates of dissolution were seen in deionized water than in dilute acid since the clay hydrated more readily at the higher pH.

INTRODUCTION

Montmorillonite, (Veegum ®) a complex colloidal magnesium aluminum silicate is widely used in pharmaceutical dosage forms

as a suspending agent and a tablet disintegrant. The availability of several grades of the clay with varying physical and chemical properties has increased the potential use of montmorillonite in formulations for special applications.

Previous studies by McGinity et al., (1-3) have been concerned with the interaction of montmorillonite with various pharmaceuticals and the in vitro/in vivo release characteristics of drugs from these drug-clay adsorbates. The surface of the montmorillonite being negatively charged interacts strongly with positively charged drugs (1). This interaction has been demonstrated to prolong the release and absorption in vivo of cationic drugs (2). The drugs were displaced from the clay via a cationic exchange mechanism by electrolytes present in the gastrointestinal tract (3). Recent studies by Porubcan et al. (4), showed that digoxin was adsorbed onto montmorillonite by a reversible adsorption mechanism at pH 2 and 6. Earlier mechanistic studies by the same workers showed that the cationic drugs, clindamycin and tetracycline were adsorbed by cation exchange under pH conditions favoring the cationic form of the drug (5).

The improved dissolution rate of poorly soluble nonionic and negatively charged drugs by adsorption to montmorillonite was recently reported by McGinity and Harris (6, 7). The rapid release of drug from the surface of the clay was due to the weak physical bonding between the two materials and to the swelling of the clay in aqueous media. The hydrophilic and swelling pro-

perties of the montmorillonite clay in aqueous media was found to also help facilitate the wetting of the hydrophobic drug substances.

The present study describes the development of slow-release tablet formulations by adding high levels of the montmorillonite clay, Veegum®, to the dosage form. Since the lattice of the clay swells in aqueous media, low levels of montmorillonite have been successfully employed as a disintegrant in the manufacture of compressed tablets. However, as the level of clay in the tablet was increased the rapid hydration of the clay prevents moisture penetrating the tablet matrix, resulting in drastic increases in disintegration time. Tablet formulations were developed using sodium sulfathiazole as the soluble, model drug.

EXPERIMENTAL

Materials - The following materials were used: colloidal magnesium aluminum silicate[1], sodium sulfathiazole[2], dicalcium phosphate dihydrate[3], dextrose[4], starch[5], magnesium stearate[6], polysorbate 80[7]. All other chemicals and solvents were reagent grade and were used as received.

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[1]Veegum F®, R.T. Vanderbilt, Norwalk, CT 06855
[2]City Chemical Corp., New York, NY 10001
[3]Emcompress®, Edward Mendell Co., Carmel, NY 10512
[4]Emdex®, Edward Mendell Co., Carmel, NY 10512
[5]StaRx® 1500, Colorcon Co., West Point, PA 19486
[6]Alfa Division, Ventron Corp., Danver, MA 01923
[7]Tween 80

Methods - Preliminary screening evaluations of tablets containing varying levels of montmorillonite resulted in the following prototype formulation:

Magnesium aluminum silicate	180 mg
Sodium sulfathiazole	120 mg
Dicalcium phosphate dihydrate	90 mg
Dextrose	84 mg
Starch	120 mg
Magnesium stearate	6 mg

Tablets of the above formulation were compressed using direct compression techniques with a Stokes Model F single punch tablet machine, using 7/16" flat face bevel edge punches. The microfine magnesium aluminum silicate was granulated by the addition of water. The dried granules were screened and the 60 to 120 mesh fraction was used in the prototype formulation. The sodium sulfathiazole had been passed through a 60 mesh screen before blending with the excipients. All other materials in the tablet were used as received from the manufacturer.

Dissolution studies were conducted using the official U.S.P. basket apparatus. One liter flasks containing 900 ml of medium were maintained at 37°. The basket was vertically centered and lowered to a depth of 2.5 cm above the bottom of the flask. The shaft was attached to a synchronous motor and (unless otherwise stated) was rotated at 50 rpm. Dissolution media of varying pH were evaluated for their influence on the dissolution properties of the tablets. Three milliliter samples were withdrawn at various time intervals and assayed for drug content using ultra-

violet spectroscopy at the wavelength corresponding to the maximum absorbance of sodium sulfathiazole in each dissolution medium studied. To maintain a constant volume of dissolution medium, 3 ml volumes of fresh medium were replaced after the removal of each sample. The reported data are the average of at least triplicate dissolution runs.

RESULTS AND DISCUSSION

Tablets containing 20% sodium sulfathiazole and 30% montmorillonite clay (magnesium aluminum silicate) were compressed at three hardness levels. The dissolution profiles of drug from these tablets in dilute hydrochloric acid and deionized water are shown in Figs. 1 and 2 respectively. The drug was found to be freely soluble in both media. As can be seen in Fig. 1, there was very little difference in the release patterns for the three tablets, suggesting that in acidic media, the dissolution rate of sodium sulfathiazole from the slow release tablets was independent of tablet hardness. Approximately 50% of the drug was released into solution after 3 hr. After 6 hr, 70-75% of the active moiety had passed into solution.

The profiles in Fig. 2 represent the dissolution behavior of the tablets in deionized water. It is interesting to note that in this medium, there was a linear increase in the amount of drug released during the first 0.75 hr of the study, after which time there was a dramatic increase in the dissolution rate. During the linear phase, the tablet surface appeared to

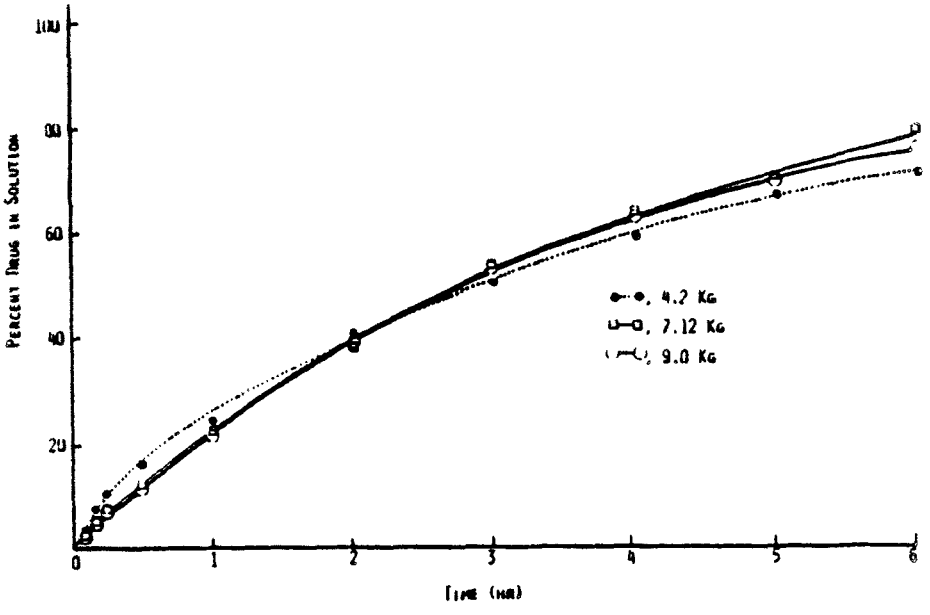

Figure 1 - Influence of tablet hardness on drug release from slow release sodium sulfathiazole tablets in 0.1N hydrochloric acid at 37° and stirred at 50 rpm.

wet very poorly, resulting in a slow hydration of the tablet components. However, after 0.75 hr, the tablet hydrated much more rapidly. This increase was probably due to the faster hydration of the clay in water as compared to the acidic media. In both media, the clay slowly swelled and formed a gelatinous layer around the tablet matrix. The matrix or tablet core remained solid and intact. During the dissolution process, the hydrated layer was slowly removed by the agitation of the ro-

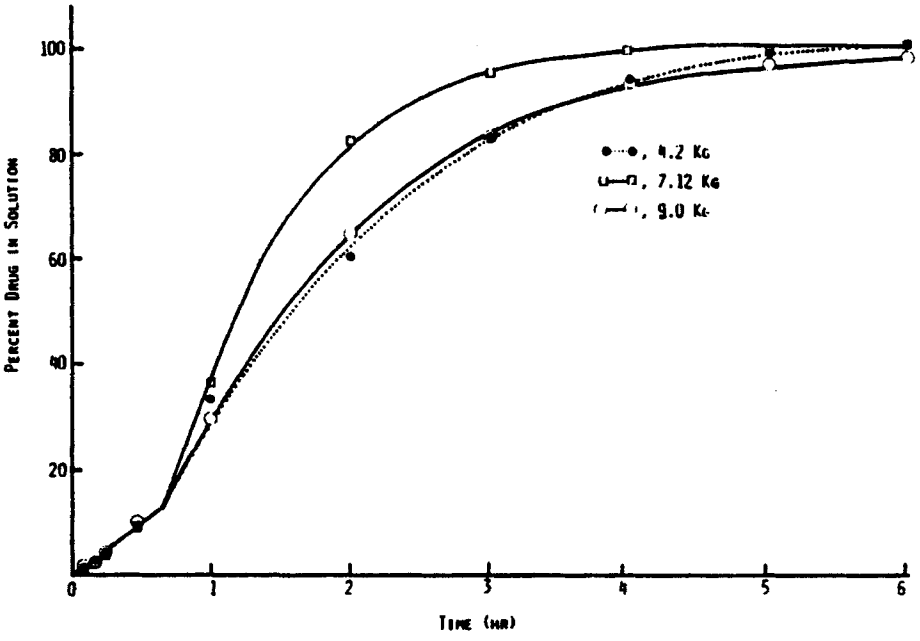

Figure 2 - Influence of tablet hardness on drug release from slow release sodium sulfathiazole tablets in deionized water at 37° and stirred at 50 rpm.

tating basket. Further hydration of the clay resulted in a decrease in the size of the tablet matrix until the entire tablet was hydrated.

The profiles of Fig. 3 demonstrate the influence of the agitation conditions on the dissolution rates of sodium sulfathiazole from the slow release tablets, in dilute acid. As the stirring rate increased from 50 to 200 rpm, there was a two fold difference in the amount of drug in solution after 2 and 3

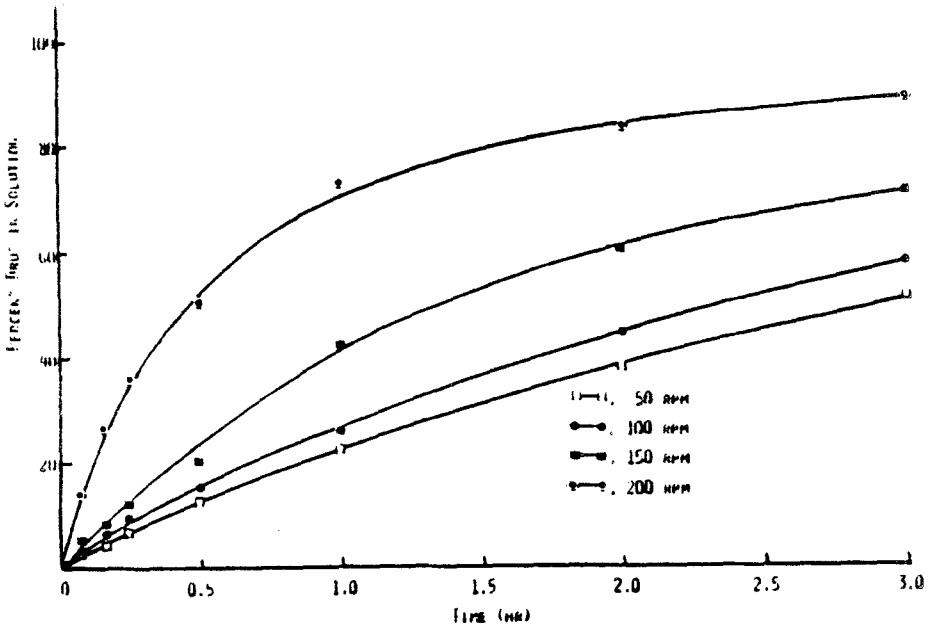

Figure 3 - Influence of stirring rate on drug release from slow release tablets (7.12 kg) in 0.1N hydrochloric acid at 37°.

hr. However, there was only a 10 to 15% difference between the profiles of samples agitated at 50 rpm and 100 rpm. As the stirring speed increased, the thickness of the hydrated gelatinous layer around the intact tablet core, was noticeably decreased, resulting in a more rapid hydration of the tablet. Similarly in deionized water (see Fig. 4), as the stirring speed of the basket containing the tablet was increased, a more rapid release was seen. The initial linear region of the dissolution profile decreased from 0.75 hr at 50 rpm, to 0.25 hr at

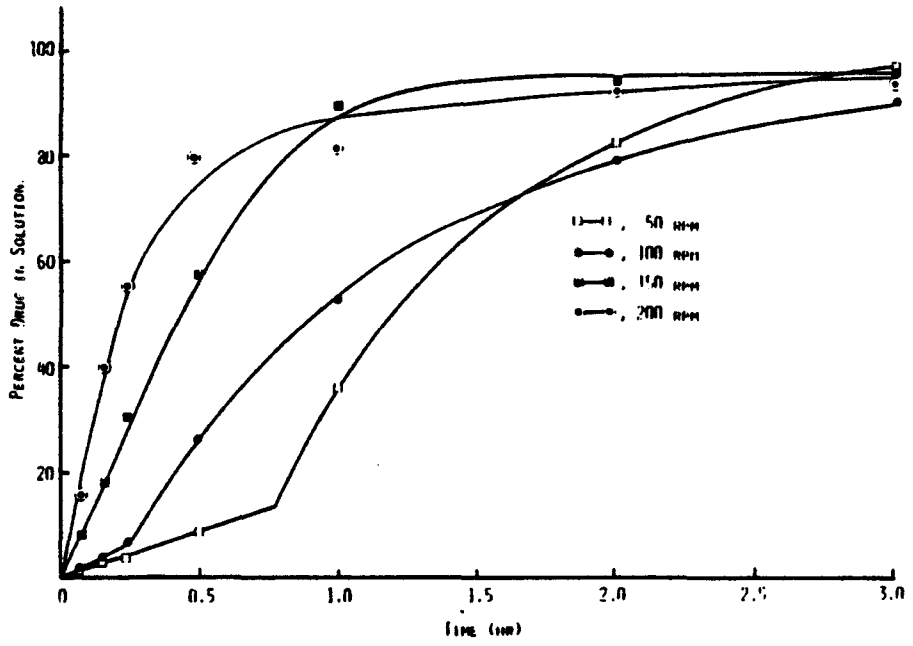

Figure 4 - Influence of stirring rate on drug release from slow release tablets (7.12 kg) in deionized water at 37°.

100 rpm. At higher speeds of agitation, the hydrated boundary region surrounding the tablet core was essentially eliminated by the friction generated under the elevated stirring conditions, leading to faster hydration rates of the tablet and elimination of the linear relationship between percent drug in solution and time.

The data in Fig. 5 show the influence of the pH of the dissolution medium on drug release from the clay containing tablets. Of the four dissolution media tested, a linear relationship between the amount of drug in solution and time for

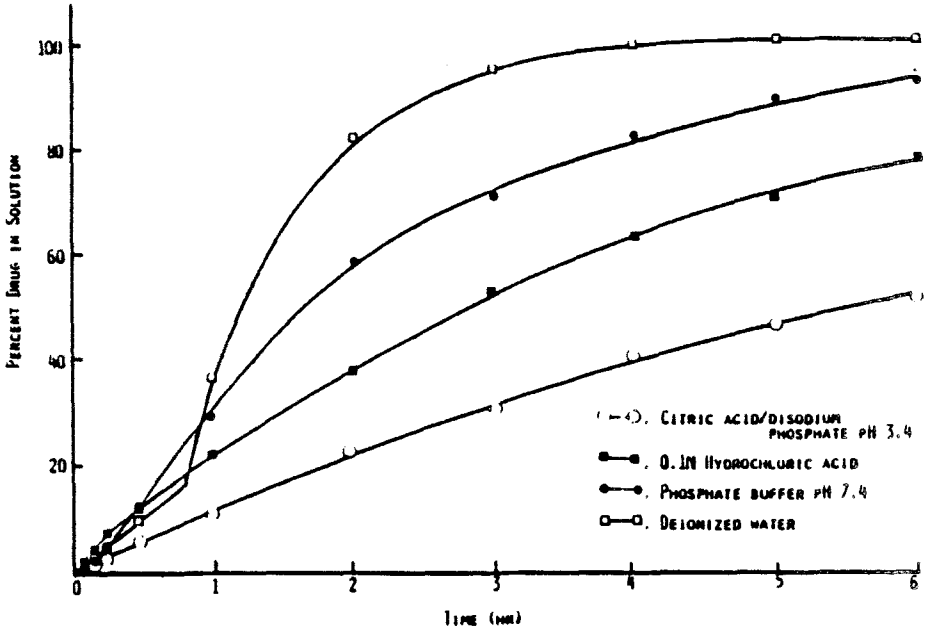

Figure 5 - Influence of pH of the dissolution medium on the release of drug from slow release tablets at 37° and stirred at 50 rpm.

the first 0.75 hr was seen only with deionized water. After 0.75 hr, the dissolution rates were found to be the fastest in deionized water, followed by phosphate buffer at pH 7.4, dilute hydrochloric acid, and citric acid-phosphate buffer at pH 3.4. At pH 3.4, approximately 50% of the sodium sulfathiazole was released into solution after 6 hr. Although the drug is less soluble at this pH than in acid and deionized water, sink conditions prevailed for all media investigated. The slower dissolution rates at pH 7.4 compared to deionized water

and at pH 3.4 compared to dilute hydrochloric acid, suggested that the ionic strength of the dissolution medium may have exerted an influence on the hydration of the montmorillonite clay and the release of drug from the tablet. This possibility is currently being investigated.

In summary, this preliminary study has shown that the inclusion of magnesium aluminum silicate at the 30% level into a directly compressed tablet containing 20% sodium sulfathiazole was successful in prolonging the release of the drug from the tablet matrix. Dissolution rates were slower in acidic media than in deionized water, however release rates increased dramatically as the degree of agitation increased. Additional studies are in progress to further characterize the system and these results will appear in future reports.

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