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OPTIMIZATION OF SLOW-RELEASE TABLET FORMULATIONS CONTAINING MONTMORILLONITE III. MECHANISM OF RELEASE

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ABSTRACT

The release of sodium sulfathiazole from slow-release tablet dosage forms containing 30% colloidal aluminum silicate and 20% drug, appears to follow first-order kinetics. Analysis of the data however, suggests that several mechanisms including hydration of the clay, diffusion of drug through a hydrated gelatinous barrier and attrition of the gel layer may contribute to the dissolution of sodium sulfathiazole from the tablet matrix. The influence of tablet shape and size on the dissolution properties of drug from the dosage forms was also examined.

INTRODUCTION

Previous reports by the authors have addressed the various parameters that influence the dissolution of the model drug, sodium sulfathiazole from controlled-release matrix tablets containing the montmorillonite clay, magnesium aluminum silicate (1, 2). A number of variables including pH of the dissolution media;

particle size of both drug and clay; presence of electrolytes; and the degree of agitation during the dissolution tests have all been found to influence the dissolution rate of the drug. The release rate however, was not affected by tablet hardness or the surface tension of the dissolution media.

When exposed to an aqueous environment, the tablets were found to swell and form a viscous gel layer at the tablet surface. This hydrated gelatinous layer served as a barrier between the dissolution media and the unwetted core of the tablet. Controlled-release tablets utilizing cellulose derivatives or various gum materials as the matrix material have been described in the literature (3-7). This paper describes studies concerned with the mechanism of drug release from montmorillonite containing tablets.

When drug release from a dosage form follows a diffusion-controlled matrix model, the quantity of drug released per unit exposed area is proportional to the square root of time (8, 9). Some of the constraints of this model (known as the Higuchi model) are not obeyed with the present system containing the montmorillonite clay since the surface area of the tablets does not remain constant during the dissolution tests and drug release from the entire tablet surface is occurring. Cobby, et al., (10, 11) have derived equations for fitting release data for whole tablets. However, these expressions also require a constant surface area over the test period.

EXPERIMENTAL

Tablets of various shapes and total weights were prepared using materials and techniques described previously (1, 2).

Capsule, oval and cylindrical shaped tablets were compressed[1] from the same batch of granulation. Cylindrical shaped tablets of three different weights were also prepared. These tablets were subjected to dissolution[2], hardness[3], and friability[4] tests.

Cylindrical tablets with a mean weight of 898 mg were used to evaluate the penetration of dissolution media through the gel layer. The method of Bamba et al., (7) was employed for these studies. Tablets were exposed to dissolution media under the usual test conditions for certain periods of time and then removed. The gelatinous layer surrounding the tablet was mechanically removed and the unwetted portion of the tablet was assayed for drug content. The dissolution media was sampled for drug content at the same time intervals. The drug content was analyzed by ultraviolet spectroscopy at the wavelength for maximum absorption in each dissolution medium[5].

RESULTS AND DISCUSSION

The influence of tablet weight on the in vitro release profiles is shown in Fig. 1. As the weight of the tablets increased the rate of drug release decreased. It has previously been shown (1) that the degree of agitation during the dissolution test will

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1. Stokes Model F, Single punch tablet machine
2. Hanson six spindle apparatus
3. Heberlein hardness tester
4. Roche Friabilator
5. Beckman model 25 spectrophotometer

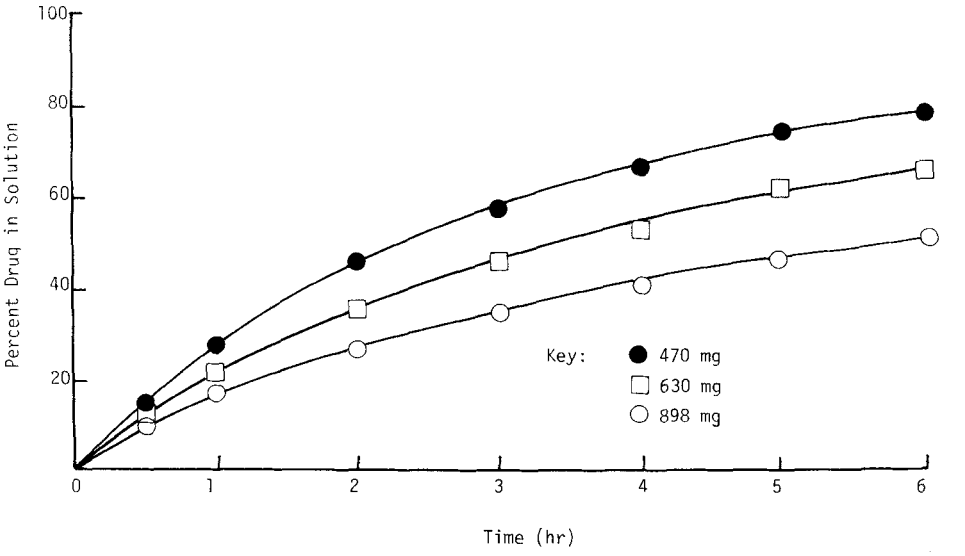

Figure 1 Influence of tablet weight on the dissolution rate of sodium sulfathiazole from slow-release tablets in 0.1N HCL at 50 RPM and 37°.

influence the release rate of drug from the dosage forms. At faster stirring speeds, friction between the dissolution basket and the tablet rapidly removed the hydrated boundary layer. Erosion of this gelatinous layer was a significant factor in controlling or altering the observed rate of drug release. The slower release, shown in Fig. 1 for the larger tablets is possibly due to their larger surface areas which result in longer periods of time for the larger tablets to hydrate and for the gelatinous layer around the tablet to erode from the dosage form.

The properties of tablets of various weights and shapes are shown in Table 1. The friability of the cylindrical tablets increased as the weight of the tablets increased. Several of the

TABLE 1

Properties of Slow-Release Tablets

Tablet Shape	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)
Cylindrical	470.39 ± 3.20	8.00 ± 0.00	0.07	95.35 ± 1.17
Cylindrical	629.81 ± 4.69	8.42 ± 0.41	0.34	126.33 ± 1.93
Cylindrical	898.39 ± 13.00	7.04 ± 0.25	2.14	172.60 ± 6.83
Oval	657.13 ± 44.25	12.29 ± 2.95	0.17	143.12 ± 9.79
Capsule-Form	593.41 ± 14.21	5.25 ± 1.02	**	121.24 ± 4.98

*Herberlein hardness tester

**Several tablets were broken during the test

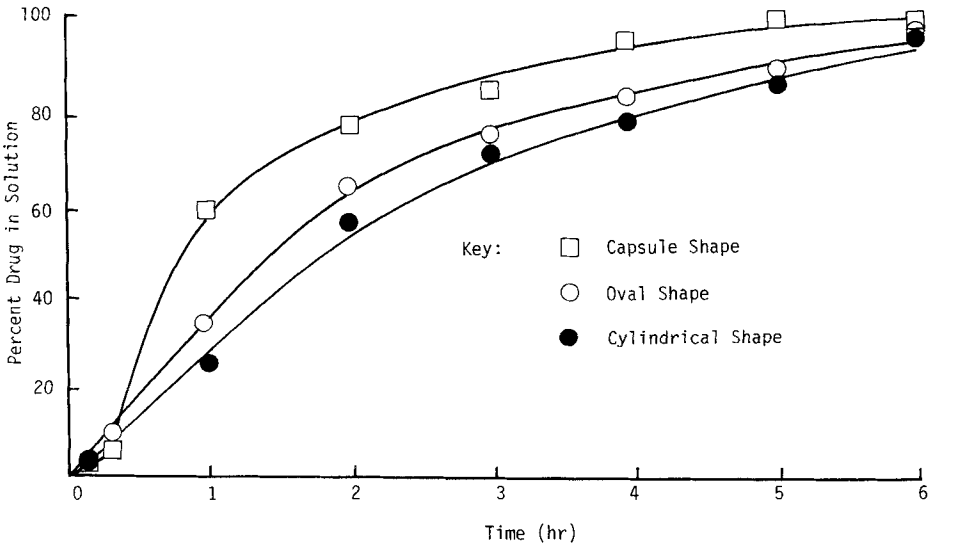

Figure 2 Influence of tablet shape on the dissolution rate of sodium sulfathiazole from slow-release tablets in deionized water at 50 RPM and 37°.

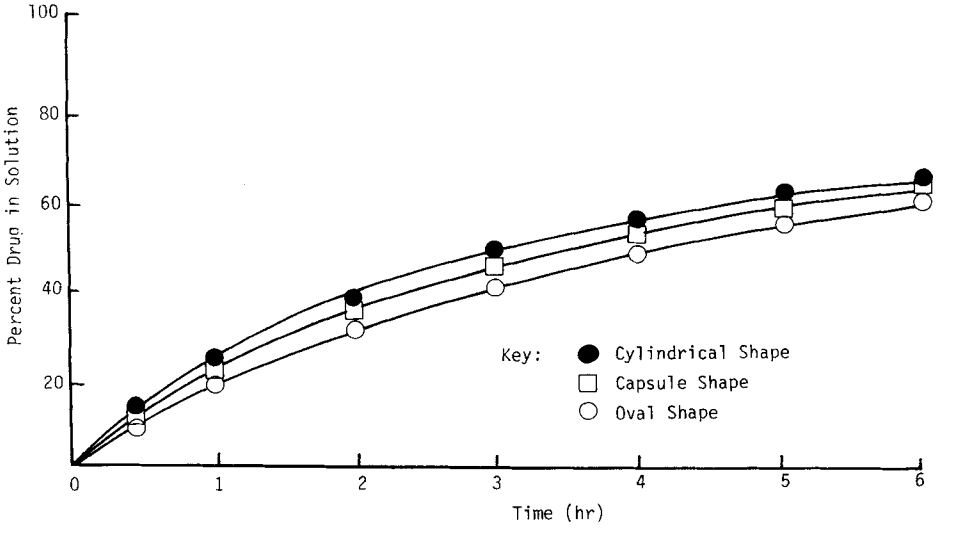

Figure 3 Influence of tablet shape on the dissolution rate of sodium sulfathiazole from slow-release tablets in 0.1N HCL at 50 RPM and 37°.

capsule shaped tablets were broken during the friability test, thus negating the results of this test for these tablets. An examination of the data in Table 1 suggests that the cylindrical tablets with a mean weight of 470 mg displayed the most uniform properties as well as the lowest friability values. Since all tablets were prepared from the same granulation, it would appear that formula modifications of the remaining dosage forms may be necessary to optimize tablet properties such as weight uniformity, hardness, drug content uniformity and friability.

The dissolution profiles in Figs. 2 and 3 compare the release of drug from capsule, oval and cylindrical tablets in deionized water and dilute hydrochloric acid respectively. The mean weight of the cylindrical tablets was 630 mg. The release profiles for the capsule shaped tablets were slightly faster than the oval and cylindrical tablets in deionized water. Insignificant differences were seen in dilute hydrochloric acid. These results indicate that the shape of the tablet does not have a significant influence on the dissolution rate of the drug from the dosage form.

A semilog plot (Fig. 4) of percent drug remaining in the tablet as a function of time for the 630 mg and 470 mg cylindrical tablets showed reasonable linearity. Regression analysis resulted in correlation coefficients of -0.996 and -0.997 respectively. Data for the 898 mg tablet gave similar results but were left out for clarity. When this same data was plotted as percent drug in solution as a function of the square root of time, profiles with two linear phases resulted as seen in Fig. 5. There was an initial

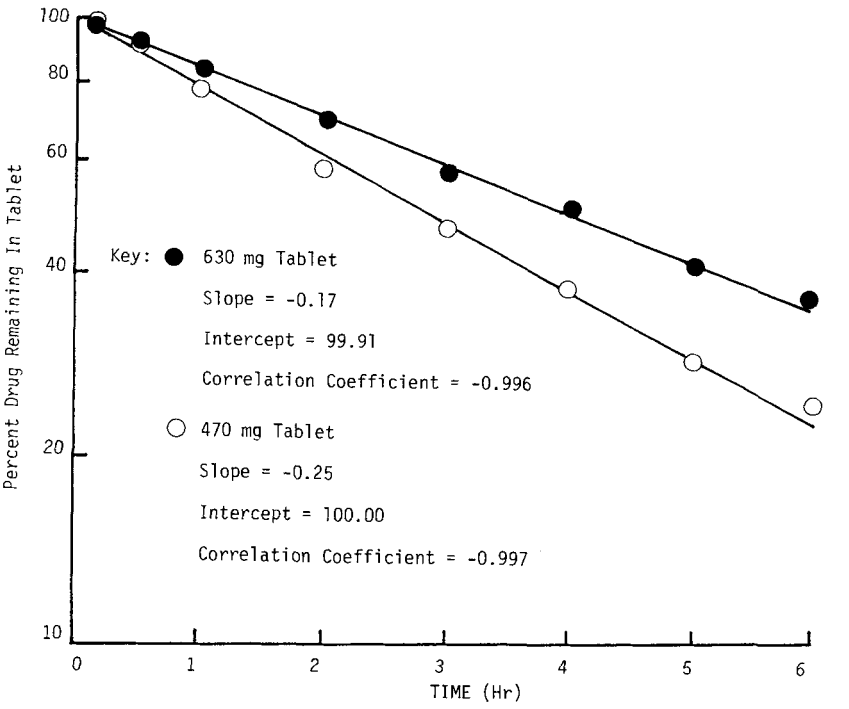

Figure 4 Semi-log plots of percent drug remaining in slow-release tablets as a function of time, in 0.1N HCL at 50 RPM and 37°.

linear phase for early time points. A break in the curve occurred at 30 minutes where a second linear phase with a more positive slope describes the data for the remainder of the study.

The initial linear portion of the biphasic response was probably due to dissolution of drug from the surface of the tablet, in addition to the drug released during the formation of the hydrated gelatinous layer surrounding the tablet. As the tablet swelled, the matrix decreased in size and the diffused drug from the tablet matrix and the gelatinous layer resulted in the second

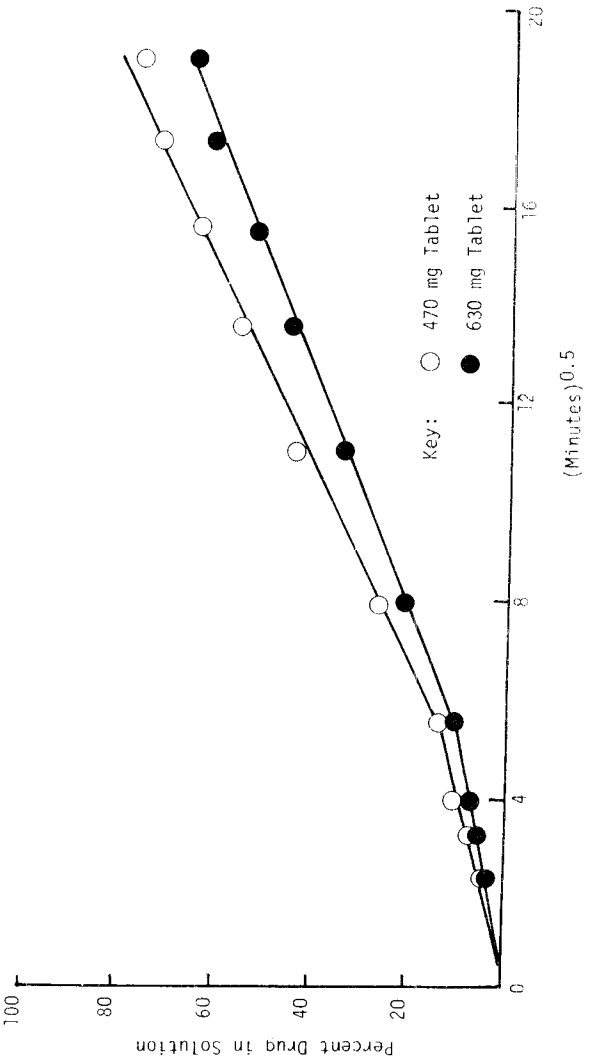

Figure 5 Percent drug in solution as a function of the square root of time for slow-release tablets in 0.1N HCL at 50 RPM and 37°.

linear phase as seen in Fig. 5. It should be pointed out that since the rate of drug release was determined from tablets where the surface areas was constantly changing, the profiles in Fig. 5 do not represent a rigid application of the Higuchi model (8, 9).

Schwartz and co-workers (12) reported that the true mechanism of release of drug from controlled-release preparations could be determined by plotting release rates at various times, versus the reciprocal of the amount released, or the amount of drug released. The rates were obtained from a Cartesian plot of amount released versus time. These authors suggested that if the mechanism was first order, then the plot of release rate versus amount released should be linear. However, if the mechanism was diffusion controlled, then the plot of rate as a function of the reciprocal of the amount of drug released would be linear. It was assumed that the surface area of the tablets would remain constant for the entire study. Treatment of the data for the montmorillonite tablets according to the methods of Schwartz and co-workers (12) yielded the profiles shown in Figs. 6 and 7. The non-linear profile in Fig. 6 and the linear profile in Fig. 7 suggested that the mechanism of drug release was truly first order. However, due to the observed swelling of the tablets and formation of a gelatinous layer, diffusion of drug through this barrier is an important parameter to be considered.

The plots of percent drug released in 0.1N HCl and deionized water, as a function of the percent drug in the unwetted core are shown in Figs. 8 and 9, respectively. If the gelatinous hydrated layer surrounding the tablet matrix was completely void of drug,

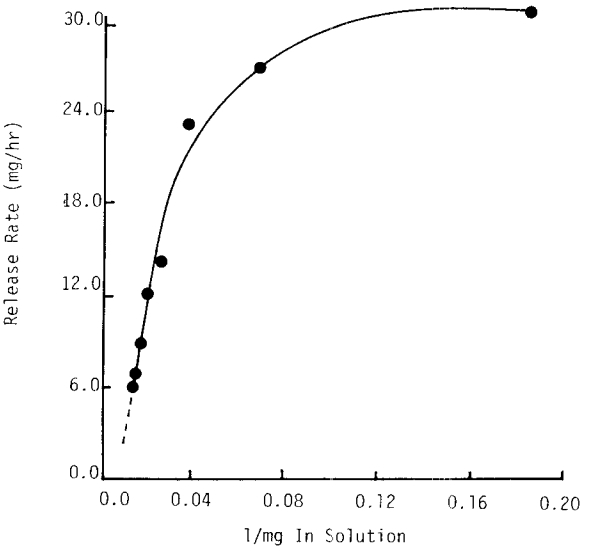

Figure 6 Profile of dissolution rate vs. the reciprocal of the amount of drug in solution for slow-release tablets (630 mg) in 0.1N HCL.

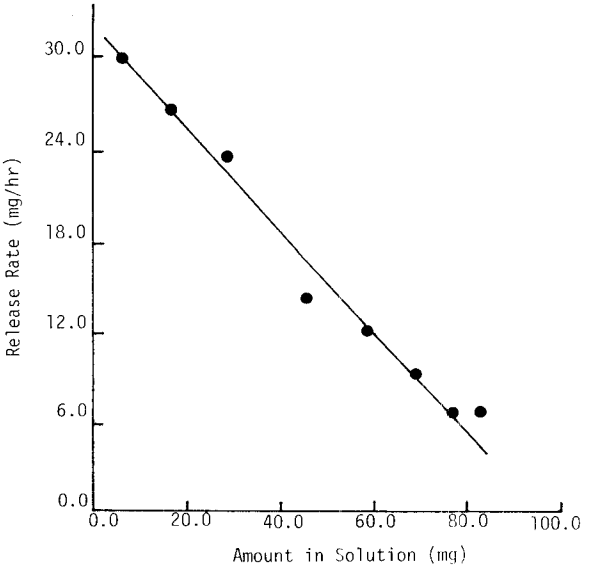

Figure 7 Profile of dissolution rate vs. the amount of drug in solution for slow-release tablets (630 mg) in 0.1N HCL.

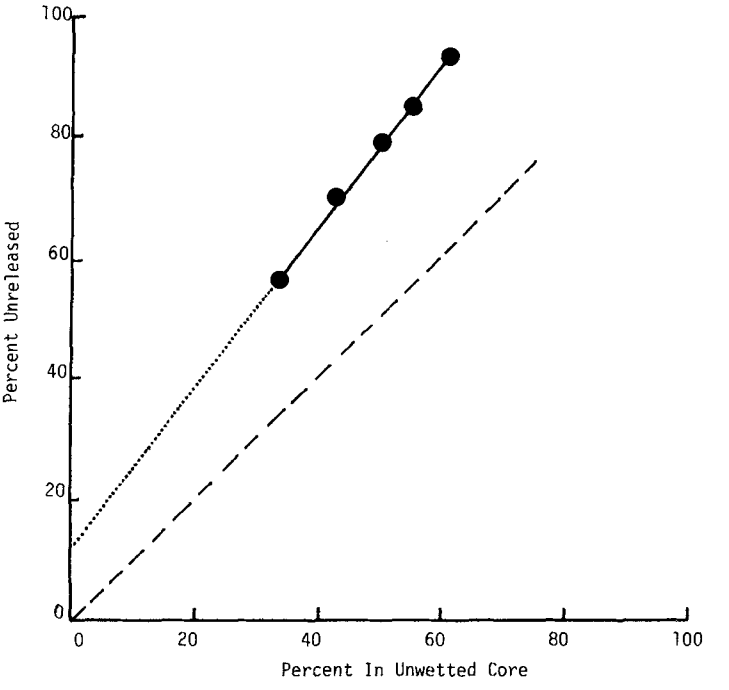

Figure 8 Profile of the percent drug unreleased from slow-released tablets (630 mg) vs. the percent drug in the unwetted core in 0.1N HCL at 37°. Key: ● experimental data; – – – theoretical line.

then a linear profile with a slope of unity and zero intercept should be obtained. These profiles in Figs. 8 and 9 are represented by the broken lines. The data for both 0.1N HCl and deionized water do not coincide with the broken lines indicating that drug was present in the hydrated layer surrounding the tablet matrix. From the distance between the lines for both media, it is possible to calculate the concentration of drug in the hydrated layer at the various times. (Data points were calculated at 0.25, 0.5, 1.0, 2.0, and 3.0 hr.) The profile in acid appears to be linear

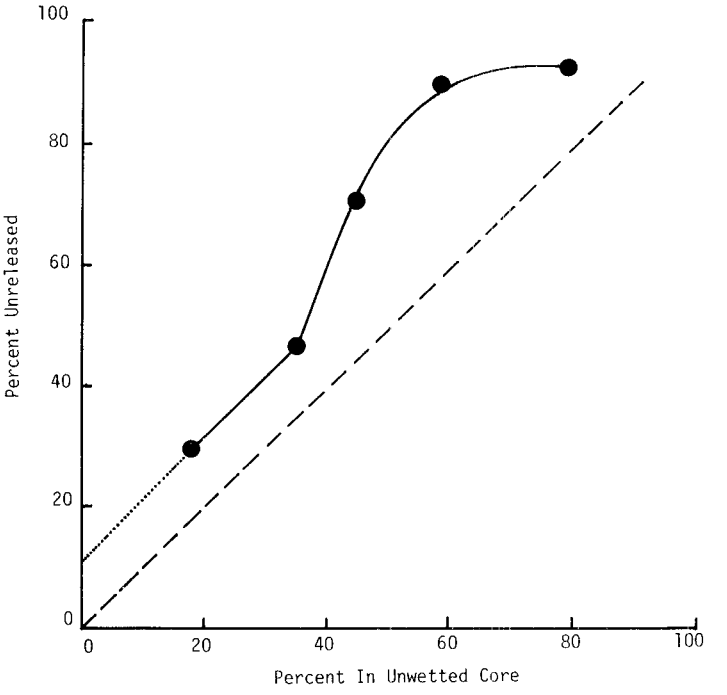

Figure 9 Profile of the percent drug unreleased from slow-released tablets (630 mg) vs. the percent drug in the unwetted core in deionized water at 37°. Key: ● experimental data; ---theoretical line.

with a positive slope of 1.33 and a positive intercept of 12.6. The intercept indicates that approximately 12.6 percent of the drug remains in the tablet when the matrix has been completed hydrated. The linearity in this case was in agreement with the dissolution results in dilute acid, where the release of drug during the time period of 0.25 to 3 hr. approached linearity (1). The results in deionized water as shown in Fig. 9 produced a non-linear relationship which also agreed with the release profiles previously observed in this medium (1). It can be seen from the profile in Fig. 9

that after 0.5 hr., approximately 10% of the drug had been released into the dissolution medium. However, only 55% of the drug remained in the unwetted core or matrix of the tablet, which indicated that 35% of the drug in the dosage form was trapped in the hydrated layer surrounding the matrix. After 3 hr., the drug that was trapped in the hydrated layer decreased to approximately 12.6%. The profiles in Figs. 8 and 9 help support previously reported data which showed that as the stirring rate increased, the dissolution rate of the drug also increased (1). Friction generated from the elevated stirring conditions resulted in a faster hydration rate of the tablet matrix and rapid removal of the hydrated layer surrounding the matrix. Drug trapped in the hydrated layer passed more rapidly into solution as the gelatinous layer was removed from the tablet matrix.

In summary, it has been shown that many variables affect the observed release rates of a soluble drug from tablet formulations containing montmorillonite. The release data indicate that a number of factors influence drug release including hydration of the clay, diffusion of drug through the gel barrier and attrition of the gel layer.

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