DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 6(1), 35-48 (1980)

INCREASING DISSOLUTION RATES OF POORLY SOLUBLE DRUGS BY ADSORPTION TO MONTMORILLONITE

James W. McGinity and Michael R. Harris
Drug Dynamics Institute, College of Pharmacy
University of Texas, Austin, Texas 78712

ABSTRACT

The surface adsorption of griseofulvin, indomethacin and prednisone to colloidal magnesium aluminum silicate was shown to markedly improve the dissolution rates of these hydrophobic and poorly soluble drugs. 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 properties of the montmorillonite clay in aqueous media also helped to facilitate the wetting of hydrophobic drug substances. The equilibrating solvents employed in the preparation of the griseofulvin-clay adsorbates caused a significant variance in the dissolution profiles of griseofulvin. This did not occur with indomethacin. Dramatic increases in dissolution rates were seen with the prednisone adsorbates and 100 percent of the drug was present in solution from the 1:4 adsorbate after four minutes.

INTRODUCTION

Over the past decade a plethora of articles have addressed the bioavailability problems associated with poorly soluble drugs and several methods have been suggested to overcome these problems. The biological implications of *in vitro* dissolution testing was discussed by Kaplan (1) who suggested that an aqueous solubility of one percent or less be considered a guideline relative to potential solubility-limited absorption problems. Although several compounds with aqueous solubilities of less than one percent are well absorbed, this criterion should alert the investigator to a possible dissolution rate limited absorption.

In 1972 Monkhouse and Lach (2) reviewed several approaches that had been applied to improve the dissolution rates of poorly soluble or hydrophobic drugs. These methods include: complexation, salt formation, polymorph formation, micronization, solid dispersions and surface adsorption. Since 1972, further efforts to use these methods to improve solubility and dissolutions rates have been published (3-6). Essentially, the methods of surface adsorption and solid dispersion reduce a drug's particle size by increasing the surface area available to the dissolution medium. Since solid dispersions are dynamic systems, physical as well as chemical stability problems have been reported for several drug-carrier combinations (7-11). The technique of surface adsorption was first reported by Monkhouse and Lach (2) who adsorbed poorly soluble drugs on various forms of silica.

The present communication reports the adsorption of griseofulvin, indomethacin and prednisone to micronized colloidal magnesium aluminum silicate (a montmorillonite clay) and the resulting dissolution properties. This clay has a strong negative surface charge. Previous studies have shown that it interacts strongly with cationic drugs but generally not with nonionic or anionic compounds (12-14). Colloidal magnesium aluminum silicate possesses an expanding lattice structure which permits the clay to rapidly hydrate in water. These properties suggest that drugs that are weakly adsorbed to the clay could be rapidly displaced as the clay hydrated in aqueous media.

EXPERIMENTAL

Materials - The following materials were used: colloidal magnesium aluminum silicate[1], griseofulvin[2], indomethacin[3], prednisone[4], polysorbate 80[5]. All other chemicals and solvents were reagent grade and were used as received.

Preparation of Drug-Clay Adsorbates - One gram of pure drug was dissolved in 100 to 200 ml of various organic solvents. An accurately weighed amount of the micronized montmorillonite clay was suspended in the drug solution. The solvent was removed by

[1]Veegum F®, R.T. Vanderbilt, Norwalk, CT 06855
[2]Ayrest Laboratories Inc., Rouses Point, NY 12979
[3]Merck Sharp and Dohme, West Point, PA 19486
[4]The Upjohn Co., Kalamazoo, MI 49001
[5]Tween 80

the use of a rotovap at 35°, under a slight vacuum. When the solubility of the drug in the organic solvent was exceeded, drug particles were precipitated from solution and deposited onto the surface of the micronized clay. The adsorbate was removed, dried to constant weight, and passed through a 100 mesh screen. By varying the quantity of clay, 1:1, 1:4 and 1:9, drug-clay adsorbates were prepared. In all cases, samples were tested for homogeneity and drug content prior to the dissolution studies. To investigate the influence of equilibrating solvents on the dissolution properties of the griseofulvin, drug:clay adsorbates were equilibrated in chloroform, acetone, methanol and methylene chloride.

Dissolution Studies - The dissolution studies were conducted with the USP Apparatus 2 and performed on drug:clay adsorbates containing 5 mg griseofulvin, 15 mg indomethacin and 10 mg prednisone. The powdered adsorbates were added to a one liter beaker containing 900 ml of 0.02% aqueous polysorbate 80 solution which was maintained at 37° and stirred at 100 rpm. Previous studies (15) have shown that this medium more closely resembles the surface tension of GI fluids than distilled water. The presence of the surfactant prevented aggregates of pure drug from floating on the surface of the dissolution medium. Drug-clay adsorbates were found to readily wet in the absence of the surfactant. Three milliliter samples were withdrawn at various time intervals and assayed for drug content using ultraviolet spectroscopy at the maximum wavelength of the drug being studied. To maintain a con-

stant 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

The dissolution profiles in Fig. 1 are for the griseofulvin-clay adsorbates that had been equilibrated in acetone. As the percent of clay in the adsorbate was increased the dissolution

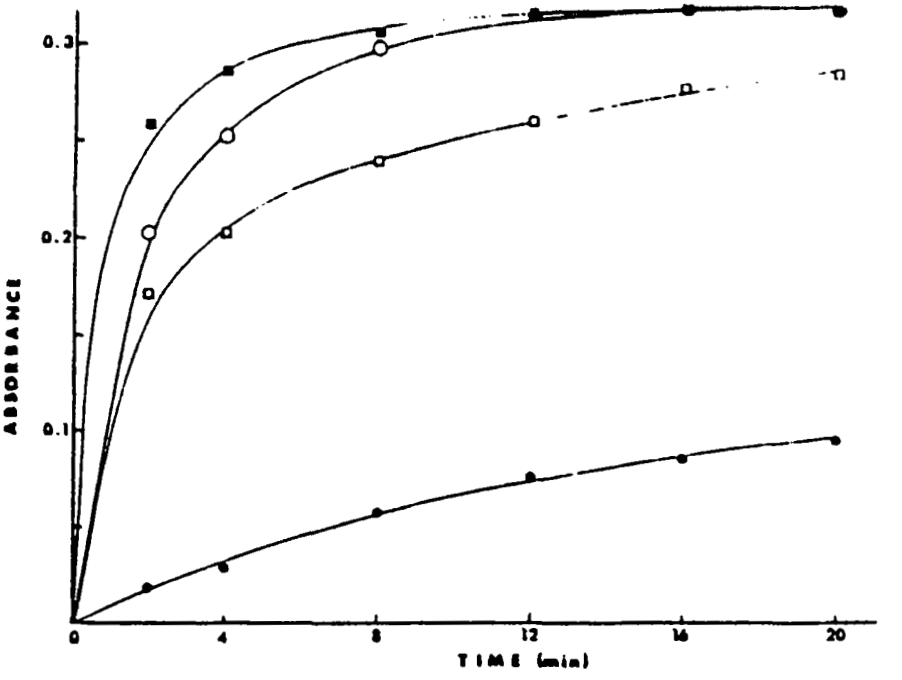

FIGURE 1

Dissolution profiles of griseofulvin:montmorillonite adsorbates (equilibrated in acetone) in aqueous polysorbate 80 solution 0.02%, at 37°. Key: ●, pure drug; □, 1:1 adsorbate; ○, 1:4 adsorbate; ■, 1:9 adsorbate.

rate was also increased. This is due to the greater surface area of clay available for adsorption. A comparison of the pure drug and the 1:1 adsorbate shows a dramatic increase in the dissolution rate for griseofulvin from the adsorbate. Nearly all the griseofulvin had passed into solution from the 1:4 and 1:9 adsorbates after approximately 10 minutes. Griseofulvin, a neutral compound, does not chemisorb to the montmorillonite clay and is held to the surface of the clay by weak van der Waal's bonds which can be easily broken. Colloidal magnesium aluminum silicate being a hydrophilic material, readily disperses, hydrates and swells in aqueous media and as a result, aggregates of the hydrophobic drug did not appear on the surface of the dissolution medium. As the micronized clay particle swelled and expanded in the aqueous medium, the griseofulvin was dislodged from the surface of the clay and rapidly passed into the solution.

The profiles in Fig. 2 represent the dissolution data from adsorbates that had been equilibrated in chloroform. Slower dissolution rates were seen when compared with the profiles in Fig. 1. The greater separation between the dissolution profiles in Fig. 2 suggested that the surface of the clay was incompletely covered with drug particles or that the equilibrating solvent had possibly influenced the physical character of the drug and the resulting dissolution behavior of drug from the adsorbates. Additional 1:1 griseofulvin-clay adsorbates were prepared by equilibration in methanol and methylene chloride and the resulting

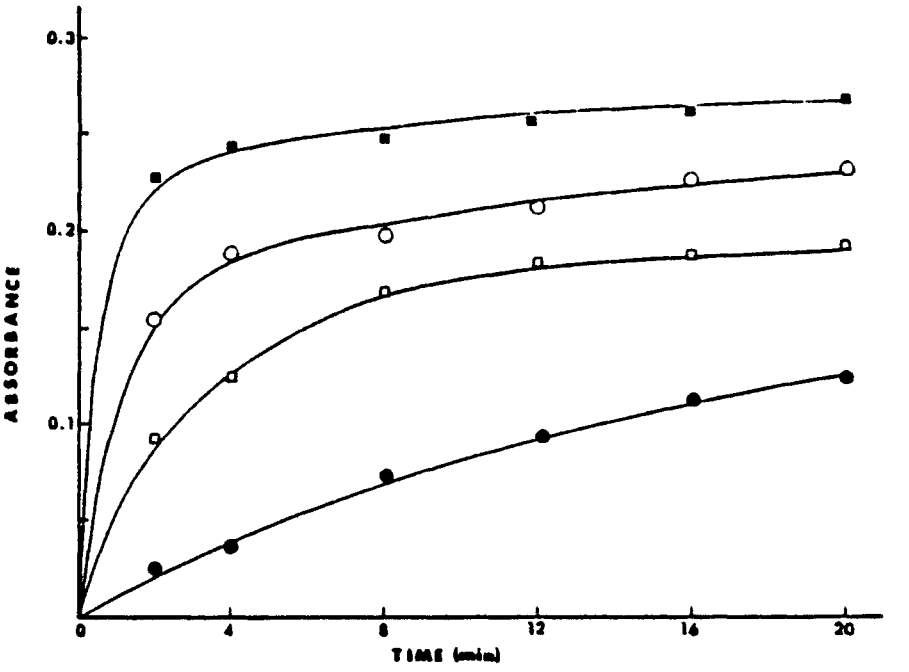

FIGURE 2

Dissolution profiles of griseofulvin:montmorillonite adsorbates (equilibrated in chloroform) in aqueous polysorbate 80 solution 0.02%, at 37°. Key: ●, pure drug; □, 1:1 adsorbate; ○, 1:4 adsorbate; ■, 1:9 adsorbate.

profiles in Fig. 3 compare the dissolution behavior of adsorbates that had been equilibrated in four organic solvents. The results suggested that two different forms of griseofulvin were present in the adsorbates. No significant differences were seen in the dissolution profiles from the pure drug that have been equilibrated in the different solvents. It would thus appear that the solvent in the presence of the clay particle may have resulted

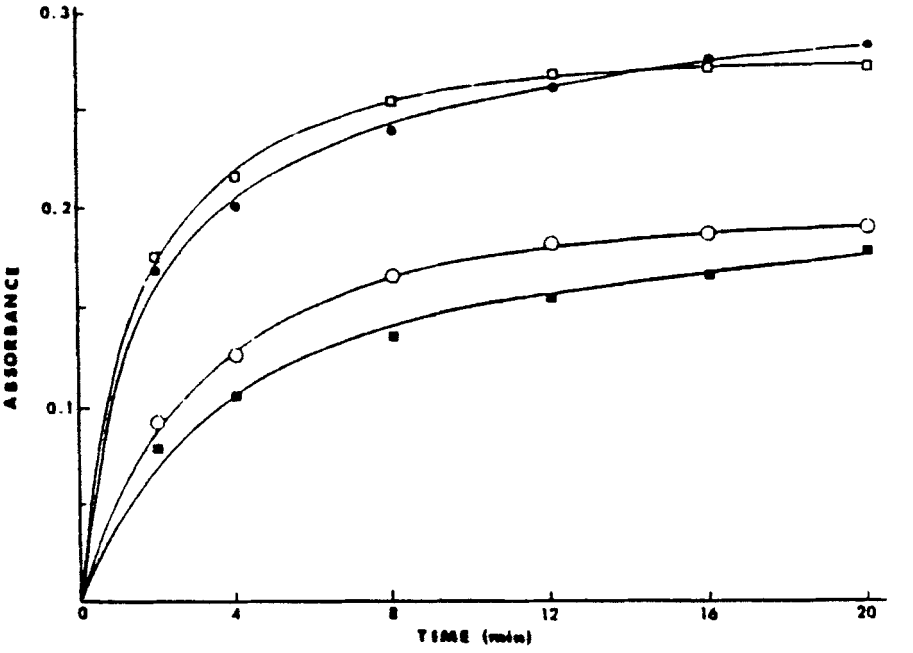

FIGURE 3

Influence of the equilibrating solvent on the dissolution profiles of 1:1 griseofulvin:montmorillonite adsorbates in aqueous polysorbate 80 solution 0.02% at 37°. Key: ■ , methanol; ○ , chloroform; ● , acetone; □ , methylene chloride.

in a change in crystalline form of the griseofulvin. Alternatively the solvents may influence the strength of the bonding of the drug to the surface of the clay or may influence the orientation of drug particles on the clay surface. These possibilities are being further investigated.

It was evident from the profiles in Fig. 4 that colloidal magnesium aluminum silicate was extremely effective in increasing the rate of dissolution of indomethacin. The hydrophobic drug

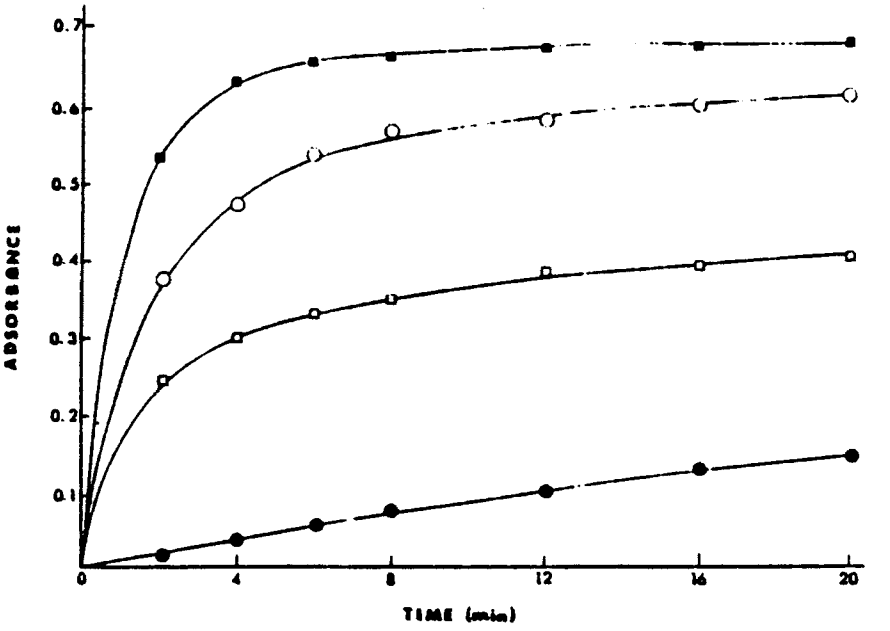

FIGURE 4

Dissolution profiles of indomethacin:montmorillonite adsorbates (equilibrated in acetone) in aqueous polysorbate 80 solution 0.02%, at 37°. Key: ● , pure drug; □ , 1:1 adsorbate; ○ , 1:4 adsorbate; ■ , 1:9 adsorbate.

substance in the absence of the clay passed into solution very slowly. As with the griseofulvin, it would appear that the hydrophilic clay material exerted two functions in producing faster drug dissolution rates; by providing a large surface area for adsorption and secondly by facilitating the wetting process of hydrophobic drug substances. Aguiar et al (16) had previously reported that the micronization of drugs will theoretically produce a larger surface area available to the dissolution medium.

However, clumping or the formation of aggregates can significantly reduce the effectiveness of this micronization.

The dissolution curves in Fig. 5 indicate that the preparation of indomethacin-clay adsorbates in chloroform, acetone, ethanol and methylene chloride did not significantly influence the dissolution behavior of indomethacin from 1:1 adsorbates. The influence of temperature on the rate of dissolution of indomethacin from 1:1 adsorbates equilibrated in ethanol is shown in Fig. 6. As the temperature of the dissolution medium increased,

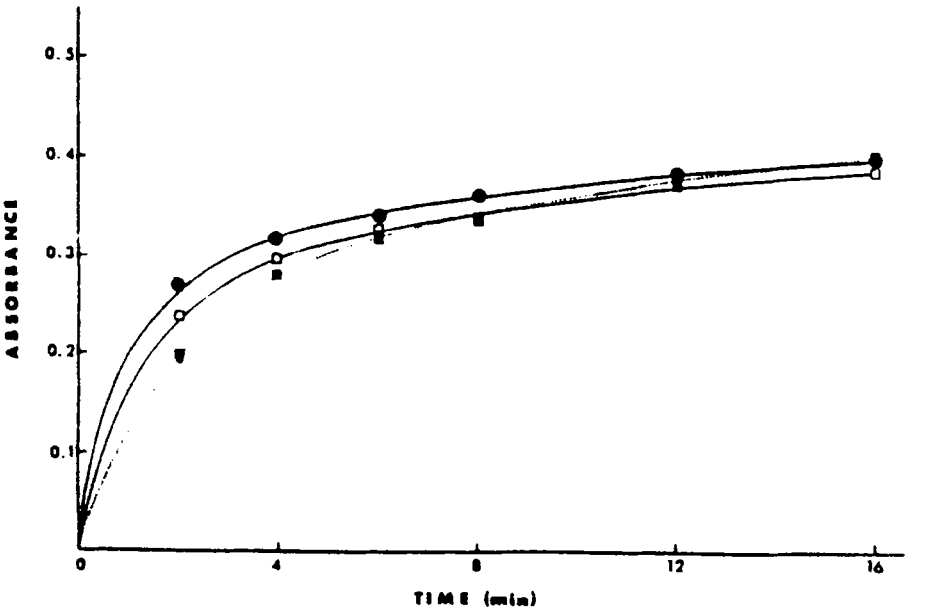

FIGURE 5

Influence of the equilibrating solvent on the dissolution profiles of 1:1 indomethacin:montmorillonite adsorbates in aqueous polysorbate 80 solution 0.02% at 37°. Key: ● , methylene chloride; ■ , chloroform; □ , acetone; ● , ethanol.

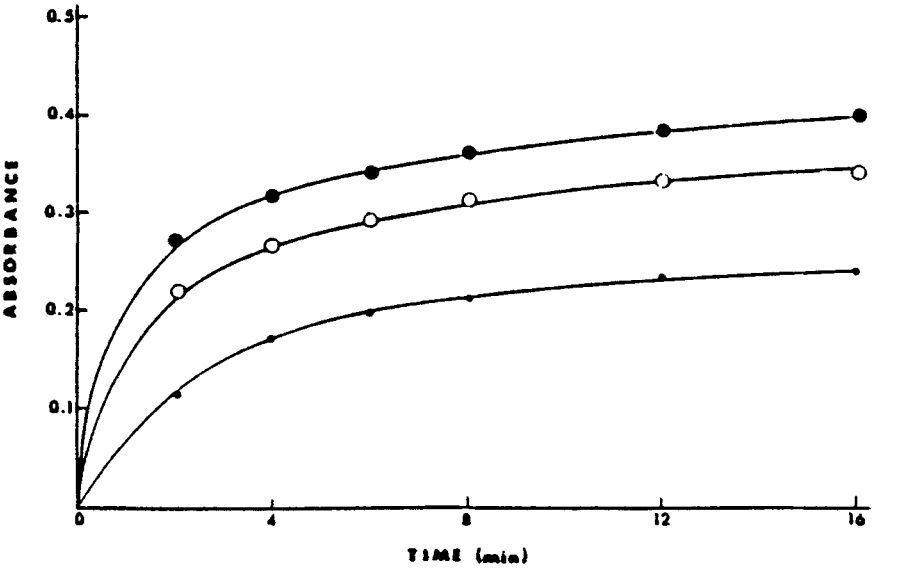

FIGURE 6

Influence of the temperature of the dissolution medium on the dissolution profiles of 1:1 indomethacin:montmorillonite adsorbates (equilibrated in ethanol) in aqueous polysorbate 80 solution 0.02% at 37°
Key: ● , 3.5° ± 1.5; ○ , 24° ± 0.5; ● , 37° ± 0.5.

so did the dissolution rate. This phenomenon was probably due to the fact that the solubility of the drug will increase as the temperature is increased and the montmorillonite clay will hydrate and swell faster in aqueous media at a higher temperature.

The dissolution profiles in Fig. 7 illustrate the dissolution behavior of prednisone from 1:1 and 1:4 adsorbates and pure micronized drug. As with the two previous drugs discussed, the montmorillonite clay was very effective in producing rapid dissolution rates for prednisone. After four minutes, 100 percent of the drug was in solution with the 1:4 adsorbate.

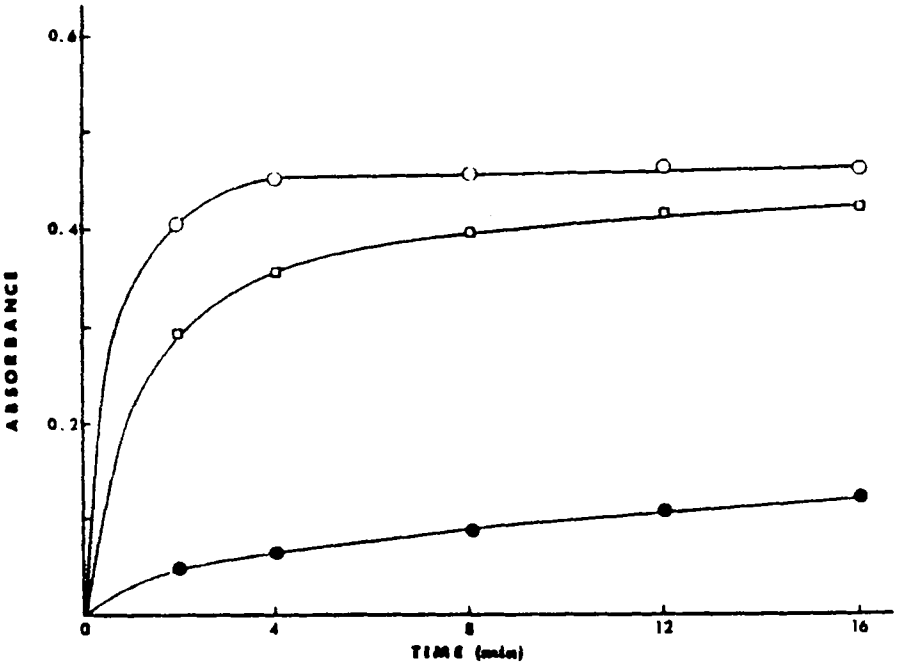

FIGURE 7

Dissolution profiles of prednisone:montmorillonite adsorbates (equilibrated in ethanol) in aqueous polysorbate 80 solution 0.02%, at 37°. Key: ●, pure drug; □, 1:1 adsorbate; ○, 1:4 adsorbate.

In conclusion, it has been shown that the surface adsorption of griseofulvin, indomethacin and prednisone to colloidal magnesium aluminum silicate can markedly improve the dissolution rates of these hydrophobic and poorly soluble drugs. The micronized clay presents an extremely large surface area (750 M^2 per g) to adsorb the drug, and the hydrophilic and swelling properties of the clay in aqueous media help facilitate the wetting of hydrophobic drug substances. It should be pointed out that although

monionic drugs in general do not interact with montmorillonite clays there are some exceptions to this rule (e.g. reserpine) where drugs chemically interact with the clay and are very difficult to displace (17). However, preliminary data presented in this report suggest that the surface adsorption of poorly soluble drugs to montomorillonite could be a viable mechanism to improve the dissolution rates and the ultimate bioavailability of the active moiety.

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