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Hydrophobic Aerosils as Dry Coating Agents for Sustained-Release Formulations

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ABSTRACT

An innovative and simple dry coating process for formulation of oral sustained-release dosage forms was developed. A hydrophobic aerosil (Aerosil® R972) was investigated as a dry coating agent. Aerosil® R972 particles adhered to the surface of acetaminophen particles upon dry coating. The release rate of the drug decreased with increased concentrations of aerosil. The release of acetaminophen from dry coated mixtures in capsules followed a square root of time release for the first 2 hours followed by zero-order release. A first-order relationship was found between the release rate and concentration of Aerosil® R972 in dry coated mixtures.

INTRODUCTION

Development of sustained-release drug delivery systems has long been a major research area in pharmaceutics. The oral route has been a preferred route for the administration of sustained-release dosage forms because it offers more flexibility in dosage form design and administration than other routes (1).The manufacturing processes of sustained-release dosage forms currently are highly complex. The objective of this project is to develop a simple dry coating process for sustained-release dosage forms using hydrophobic aerosils.It has been reported that hydrophobic substances like magnesium stearate and other stearic acid salts decrease the dissolution rate of drugs and thus prolong drug release (2). In spite of this possible beneficial effect for use in sustained-release products, there is a widespread concern in the use of magnesium stearate for this purpose, due to problems with lot to lot variability (3,4).It was shown that fine cohesive particles adhered to the surface of a coarser excipient. During blending of powders in a mixer, preferential adhesion and sticking of powders onto the surfaces of other powders were observed as a result of electrostatic charging, sticking, or friction of fine cohesive powders. These frictional charging and physical adhesive properties can be used to prepare

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mechanically ordered mixtures or to modify and encapsulate the surface of drug solids (5).The hydrophobic aerosil (Aerosil® R972) is chemically colloidal silicon dioxide, the silanol groups of which are silylated with dimethyldichlorosilane (6). These have extremely large specific surface areas and excellent surface coating characteristics. It was shown to sustain the release of potassium chloride from capsules (7). It was also reported that Aerosil® R972 decreased the dissolution rate of sodium valproate from suppository formulations (8).The focus of our study was to find out the effectiveness of a hydrophobic aerosil (Aerosil® R972) as a dry coating agent for the formulation of sustained-release dosage forms and to evaluate the release characteristics of the products.

MATERIALS AND METHODS

Materials

Aerosil® R972 (obtained as a gift sample from Degussa Corporation) as dry coating agent, acetaminophen (APAP), and theophylline as model drugs.

Dry Coating

Dry coating is a method involving simple mixing of drug, diluent, and dry coating agent in a twin-shell V-blender, in the required order and for the required time. The mixtures were prepared and then filled into hard gelatin capsules.

Release Test

Release tests on the capsules were carried out at 37 ± 0.5°C using a standard USP dissolution method "A" (basket method). Nine hundred milliliters of deaerated dissolution medium was placed in each vessel. Dissolution media studied were 0.1 N hydrochloric acid, distilled water, and pH 7.4 phosphate buffer. After evaluating the effect of stirring speed in the range of 50–150 rpm, it was maintained constant at 100 rpm in all the experiments. Samples (10 ml) were withdrawn at various time intervals for 8 hr and filtered through 0.45 μ membrane filters. An equivalent volume of fresh dissolution medium at the same temperature was added into the dissolution vessel immediately after each sample drawing, to maintain the original volume. Percent drug dissolved was determined by spectrophotometric analysis at 244 nm for acetaminophen and 272 nm for theophylline.

Microscopic Studies

The surface coating characteristics of Aerosil® R972 on acetaminophen in dry coated mixtures were investigated with scanning electron microscopy (SEM). Samples were mounted onto stubs using Microstik® adhesive and sputter coated with gold film for 3 minutes in a sputter coater and analyzed by a JEOL JSM-35C scanning electron microscope. The images obtained were photographed using Polaroid 665 black and white film.

RESULTS AND DISCUSSION

A dry coating method for oral sustained-release dosage forms was developed using Aerosil® R972 as the dry coating agent. Initially, acetaminophen was used as a model drug in our study. The effect of Aerosil® R972 was studied in the concentration range of 1–5% w/w. The results showed that aerosil in these concentrations decreased the dissolution rate of APAP drastically. Further study with lower concentrations of Aerosil® R972 (0.1–0.8% w/w) showed that 0.6% w/w Aerosil® R972 was an optimum concentration to prolong the release of acetaminophen, to release 80–100% of drug in 8 hr. The dissolution profiles of acetaminophen from capsules containing dry coated mixtures of acetaminophen and Aerosil® R972 in 0.1 N hydrochloric acid are shown in Figures 1 and 2. Increase in concentration of Aerosil® R972 decreased the dissolution rate of acetaminophen.

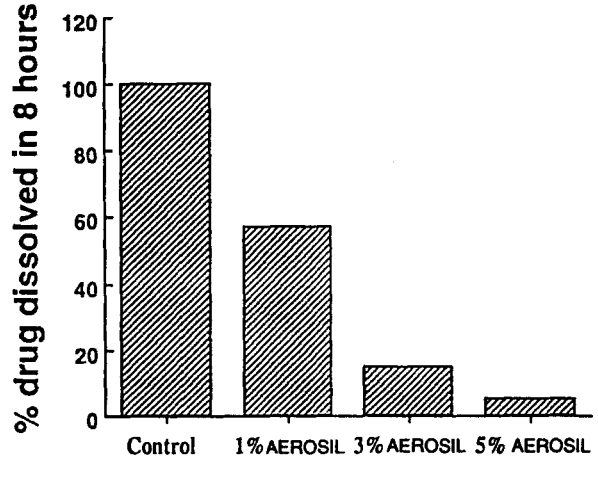

Figure 1. Percent drug dissolved in 8 hours from acetaminophen capsules containing 1%, 3%, and 5% Aerosil® R972.

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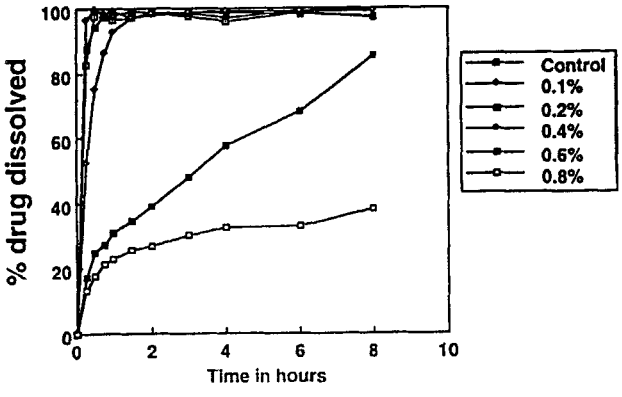

Figure 2. Dissolution profiles of acetaminophen capsules containing 0.1–0.8% Aerosil® R972.

Effect of Dissolution Conditions

The effect of stirring speed of dissolution and dissolution medium on the prolonged release effect of Aerosil® R972 was studied.

Effect of Stirring Speed

Dry coated mixtures of acetaminophen were prepared and filled in capsules and subjected to dissolution testing. Stirring speeds of 50, 100, and 150 rpm were evaluated in this study. The dissolution data was analyzed by multifactor analysis of variance using Statgraphics® software program. Stirring speed does not have any significant effect on the release of acetaminophen and prolonged release effect of aerosil (Tables 1 and 2).

Effect of Dissolution Media

In order to study the effect of dissolution medium on the release of acetaminophen from dry coated mixtures, three different dissolution media were selected: 0.1 N hydrochloric acid, water, and pH 7.4 phosphate buffer. Mixtures of acetaminophen containing 0.2–5% Aerosil® R972 were prepared by dry coating for 30 minutes and were filled into capsules. Dissolution testing was conducted on these capsules using the three dissolution media as specified above. Figure 3 shows the dissolution profiles of acetaminophen capsules containing dry coated mixtures of acetaminophen with 0.6% Aerosil® R972 in three different dissolution media. This graph indicates that there is no effect of dissolution medium on the prolonged release effect of aerosil. Analysis of variance and multiple range analysis (Tables 3 and 4) show that the dissolution medium does not have any significant effect on the release of acetaminophen and the prolonged release effect of Aerosil® R972.

Scanning Electron Microscopy

SEM studies showed that Aerosil® R972 particles adhere to the surface of acetaminophen. These mixtures can be regarded as having been encapsulated by Aerosil® R972. The surface appearance of the coated particles is more uniform for granular material (directly compressible acetaminophen) (Figures 4 and 5).

Kinetics of Drug Release

The dissolution data were analyzed according to Higuchi's equation that predicts a linear relationship be-

Table 1

Analysis of Variance for % Dissolved in 30 Minutes by Stirring Speed (Effect of Stirring Speed)

Source of Variation	Sum of Squares	Mean Square	F-Ratio	Sig. Level
Main Effects				
Stirring speed	4.0250	2.0125	1.799	0.2772
Aerosil concentration	120.2939	60.1469	53.766	0.0013
Residual	4.4747	1.1187		
Total	128.7937			

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Table 2

Multiple Range Analysis for % Dissolved in 30 Minutes by Stirring Speed (Effect of Stirring Speed)

Method: 95% Least Significant Difference (LSD)

Level	Count	Average	Homogeneous Groups
50	3	5.8663	*
150	3	7.2737	*
100	3	7.2960	*

tween the amount of drug released versus square root of time for diffusion-controlled mechanism of release. This was done following the observation of an intact matrix at the end of 8 hr of dissolution. However, only certain segments of this graph exhibited linearity. Initial deviation perhaps is due to slow wetting of aerosil by the dissolution medium. Positive deviation at the later stage of dissolution could be due to disintegration of the matrix into agglomerates. The data of capsules containing acetaminophen dry coated with 0.6–5% w/w Aerosil® R972 fitted to Higuchi's equation up to 2 hr followed by a zero-order release (Figure 6). This could be due to disintegration of matrix in 2 hr into acetaminophen particles encapsulated with Aerosil® R972 (possible mechanism shown in Figure 7).

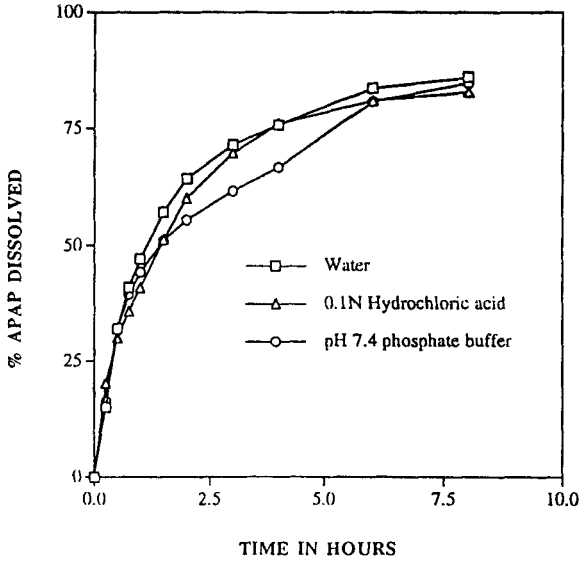

Figure 3. Effect of dissolution medium on acetaminophen dissolution from capsules containing acetaminophen + 0.6% Aerosil® R972.

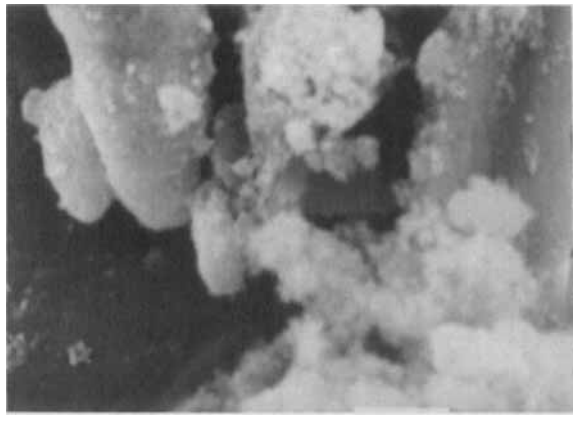

Figure 4. Scanning electron micrograph of dry coated mixture of acetaminophen with 5% Aerosil® R972.

Correlation of Release Rate Versus Concentration of Aerosil® R972

A model to correlate release rate (square root of time-release portion) versus the concentration of Aerosil® R972 was developed. The data were fitted to various equations using the software MINSQ®.A first-order relation was found between release rate of APAP and concentration of Aerosil® R972 employed (Figure 8).

Table 3

Analysis of Variance for % Dissolved in 30 Minutes by Dissolution Medium (Effect of Dissolution Medium)

Source of Variation	Sum of Squares	Mean Square	F-Ratio	Sig. Level
Main Effects				
Medium	61.4160	30.7081	1.852	0.2068
Aerosil Concentration	27342.0530	5468.4105	329.882	0.0000
Residual	165.7687	16.5769		
Total	27569.2380			

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Table 4

Multiple Range Analysis for % Dissolved in 30 Minutes by Dissolution Medium (Effect of Dissolution Medium)

Method: 95% Least Significant Difference (LSD)

Level	Count	Average	Homogeneous Groups
pH 7.4 buffer	6	39.4528	*
0.1 N HCl	6	41.8290	*
Water	6	43.9755	*

The data fit the first-order equation:

$$k = k_0 * \exp(-S * C)$$

where k is the release rate of acetaminophen from APAP capsules containing C% Aerosil® R972 ($\%/t^{0.5}$); k_0 is the release rate of acetaminophen from control APAP capsules containing no aerosil; S is the first-order rate constant ($\%^{-1}$); C is % w/w of Aerosil® R972 in capsule. The r-squared obtained was 0.9998. This provides a model to correlate the effect of concentration of Aerosil® R972 on release rate of acetaminophen from dry coated mixtures.

Effect on Theophylline

The effectiveness of Aerosil® R972 as dry coating agent for sustained release was demonstrated using an ideal sustained-release candidate, theophylline.Dry coated mixtures of theophylline were prepared by mixing theophylline with 0.1–5% w/w Aerosil® R972 for 30 min. These mixtures were filled in hard gelatin capsules

Figure 5. Scanning electron micrograph of dry coated mixture of COMPAP with 0.8% Aerosil® R972.

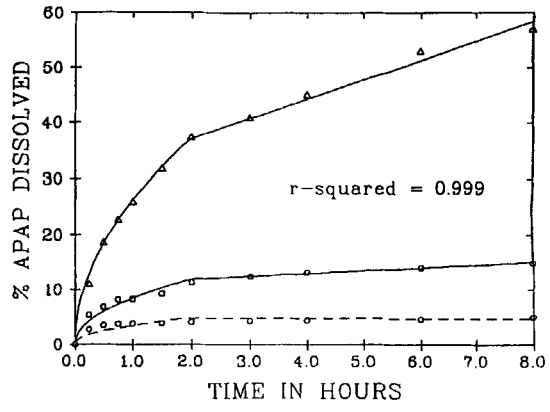

Figure 6. Data fit for acetaminophen capsules containing dry coated mixtures of acetaminophen with 1%, 3%, and 5% Aerosil® R972.

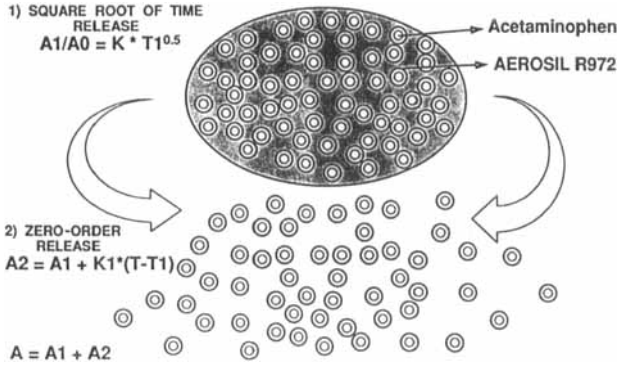

Figure 7. Mechanism of sustained release.

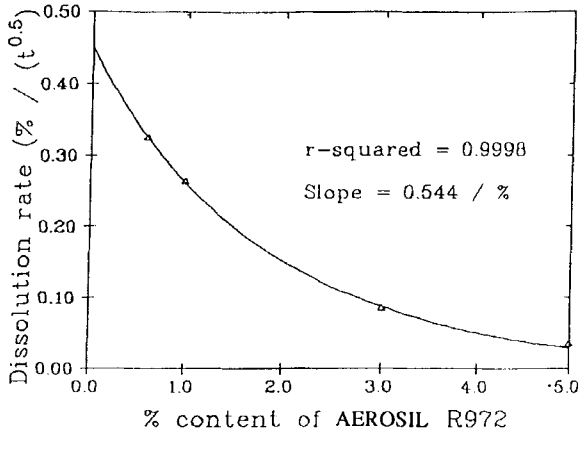

Figure 8. Correlation of dissolution rate and Aerosil® R972 concentration.

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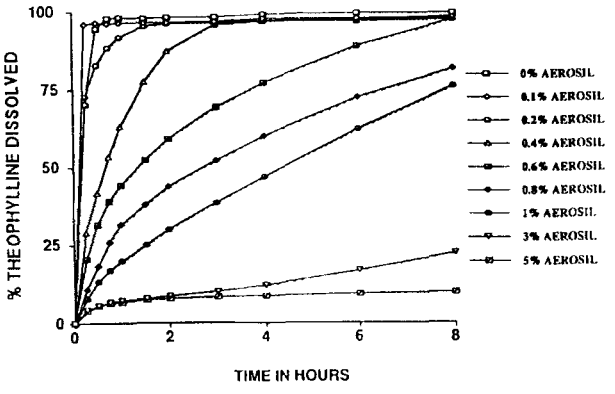

Figure 9. Percent dissolved from theophylline capsules containing 0.1–5% Aerosil® R972.

and subjected to dissolution testing. It was found that dry coating with Aerosil® R972 sustained the release of theophylline. Increase in Aerosil® R972 concentration led to a decrease in release rate and amount of theophylline (Figure 9).

CONCLUSIONS

The results from these studies show that the hydrophobic aerosil (Aerosil® R972) decreases both dissolution rate and amount of acetaminophen dissolved. This effect was further confirmed using an ideal sustained-release candidate, theophylline. The release profiles were found to fit the square root of time release equation for the first 2 hours followed by a zero-order equation. A first-order relation was found between the release rate and concentration of Aerosil® R972 employed. Our study demonstrates the effectiveness of Aerosil® R972 as a dry coating agent for sustaining the release of acetaminophen and theophylline, an entirely new application for these aerosils.

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