Bead Coating. I. Change in Release Kinetics (and Mechanism) Due to Coating Levels

Guohua Zhang,[1,2] Joseph B. Schwartz,[1,3] and Roger L. Schnaare[1]

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Beads containing 50% acetaminophen (APAP) and 50% microcrystalline cellulose (Avicel PH 101) were prepared and then coated using an aqueous ethylcellulose based dispersion (Aquacoat) to evaluate the effect of the coating level on drug release. The APAP release was shown to be dependent on levels of the coating and a change in mechanism was suggested. Drug release from incompletely coated beads at low levels of coating can be described with the square root of time model, while drug release from beads with a high level of coating appears to be best described by zero-order release. At low coating levels, the drug release rate constant based on the square root relationship seems to be linear with the coating level. At high coating levels, drug release rate in terms of a zero-order model appears to be proportional to the reciprocal of the coating level.

KEY WORDS: release mechanism; release kinetics; coating level effect; coated spheres; beads; ethylcellulose.

INTRODUCTION

Drug delivery systems with a diffusion-controlled release mechanism generally are based on two approaches. The first approach entails placement of the drug in an insoluble matrix. The eluting medium penetrates the matrix and the drug diffuses out of the matrix for ultimate absorption (1–3). The second approach involves enclosing the drug with a polymeric coat. In this case the portion of the drug which has dissolved in the polymer coat diffuses through an unstirred film into the surrounding fluid (4–6). From a mathematical modeling point of view, the former systems can possibly be described by the square root of time relationship (7–9), which takes the following form for dispersed drug in an inert porous matrix:

$$Q_t = \left[D_a \frac{\epsilon}{\tau} C_s(2A - \epsilon C_s)t \right]^{1/2} \quad (1)$$

where the cumulative amount of drug release per unit surface area, Q_t, in time, t, is related to the initial drug concentration in the matrix, A, the diffusion coefficient of the drug in the medium, D_a, and the drug solubility, C_s, as well as the porosity and the tortuosity of the matrix, ϵ and τ.

The latter systems are reportedly governed by a barrier controlled release-type zero-order model (10–12), which can be expressed by the following equation:

$$Q = \frac{D_m K_m C_s t}{L} \quad (2)$$

where D_m is the diffusion coefficient of the drug in the barrier or coating, K_m is the drug partition coefficient between the coating and the medium, and L is the barrier thickness.

It has been reported that drug release from uncoated marumerizer beads containing microcrystalline cellulose can be characterized as an inert matrix system and described by the pore controlled-release model (13,14). The present study deals with drug release from the marumerizer beads coated with an aqueous ethyl cellulose-based dispersion. Ethyl cellulose is a water-insoluble polymer widely employed in the research and production of controlled-release dosage forms. The effects of the coating level, the amount of plasticizer, and the mixing time in the plasticization on drug release have been investigated (15). The purpose of this work is to demonstrate that a change occurs in the kinetics and mechanism of drug release from low to high coating levels.

MATERIALS AND METHODS

Materials. An ethyl cellulose-based dispersion (Aquacoat), microcrystalline cellulose, USP (Avicel PH 101), and dibutyl sebacate (DBS), a plasticizer, were supplied by FMC Corp. (Philadelphia, PA). Acetaminophen, USP (APAP), was used as the model drug, and distilled water as granulating solvent.

Spheronization. Five hundred grams of acetaminophen and 500 g of Avicel PH 101 were mixed in a planetary mixer (Hobart) and were granulated by adding distilled water. The total mixing time, including 5 min for the premixing process, was 30 min. The wet mass was extruded through a screen of 1.5 mm and at 50 rpm. The extrudate was spheronized in the marumerizer, equipped with a 2-mm scored friction plate, at 1000 rpm for 1 min. The extrudate charge in the marumerizer was 500 g. The resulting spheres were dried in an oven at 40–42°C for 20 hr. Only spheres of a 16/18 mesh cut were used for coating.

Coating. The Aquacoat dispersion containing 20% DBS (based on the solid content) was gently mixed for 20 min. The coating process was performed in a fluid bed column (Strae I Model, Aeromatic AG, Towaco, NJ). The coating dispersion was supplied and atomized from the bottom of the column at a rate of 4 to 8 ml/min. The inlet air temperature was set at 70°C. The coated spheres were dried in the column for 10 min after completion of the coating process. The percentage of the coating applied to the 16/18-mesh beads, based on the weight increase the uncoated beads, was calculated in terms of the total weight of the coated spheres.

Dissolution Testing. The dissolution test was performed on the beads stored for more than 5 days after coating, using the USP/NF dissolution apparatus I with a basket rotational speed of 50 rpm. Distilled water was utilized as the dissolution medium (900 ml). The amount of APAP released in the medium as a function of time was determined by means of a UV spectrometer at 249 nm.

[1] Department of Pharmaceutics, The Philadelphia College of Pharmacy and Science, Philadelphia, Pennsylvania 19104.
[2] Permanent Address: Department of Pharmaceutics, China Pharmaceutical University, Nanjing, People's Republic of China.
[3] To whom correspondence should be addressed.

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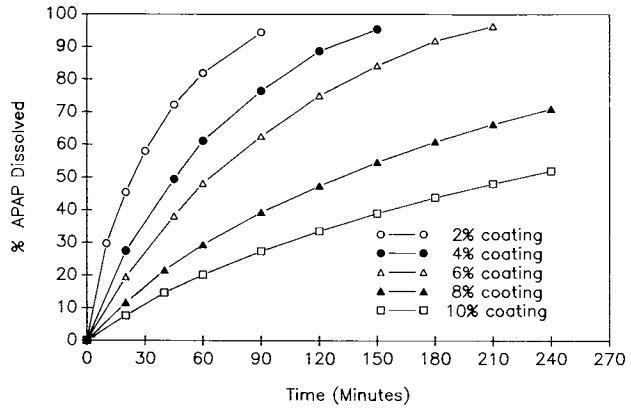

Fig. 1. Dissolution profiles for acetaminophen beads (16/18 mesh) with 2–10% aquacoat coating levels.

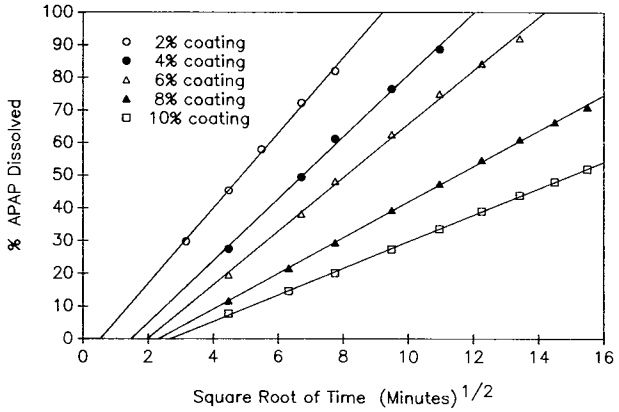

Fig. 3. Dissolution data for acetaminophen beads (16/18 mesh) with 2–10% aquacoat coating levels plotted as the percentage drug released versus the square root of time (minutes$^{1/2}$).

RESULTS AND DISCUSSION

The dissolution profiles of the coated beads are shown in Figs. 1 and 2. As expected, the drug release decreases with increasing coating levels. The curves shown in Fig. 1 represent 2 to 10% coating levels determined by the weight increase. At the higher coating levels of 12 to 20% (Fig. 2), the profiles appear more linear. This observation was the first indication of a change in release mechanism with coating level. This is further supported by the square root of time plots of the same data. The low coating levels appear to fit that model (Fig. 3); the higher coating levels do not (Fig. 4). In the literature, four mechanisms for drug release from such a system have been proposed (16–18):

(a) transport of the drug through flaws, cracks, and imperfections (or pores) within the matrix or uncoated system;
(b) transport of the drug through a network of capillaries (or pores in the coating) filled with dissolution media—applicable only if a water-soluble component of the film is leached out.
(c) transport of the drug through a hydrated swollen film—applicable if the water-soluble component is retained within the matrix; and
(d) transport of the drug through the barrier or nonporous coating, which is determined by the permeability of drug in the film.

In the present work, it appears that more than one of these is operative, depending on the coating level applied. It is proposed that transport is by the first and the second mechanisms for incompletely coated beads, while transport is by the last mechanism for beads with a complete coating.

A possible interpretation of the drug release mechanisms from coated spheres is that at low levels of coating (or incomplete coating), the coating may be porous, so that drug takes less resistant pathways for release, i.e., through the pores or channels through the coating. In Fig. 3, it can be observed that there are differences with various coating levels; specifically there are differences in (i) the dissolution rate constant based on the square root of time relationship and (ii) the pseudo-lag time based on extrapolation to the abscissa. The pseudo-lag time is defined here as the squared value of the x axis intercept based on the square root of time model. Figures 1 and 2 show that there is no real lag time in the traditional sense; only in the square root plots is the value apparent, and it is used in this study only to demonstrate changes, and not to describe release characteristics. By considering that spheres are continuously layered with additional coating material, pores through the coating should

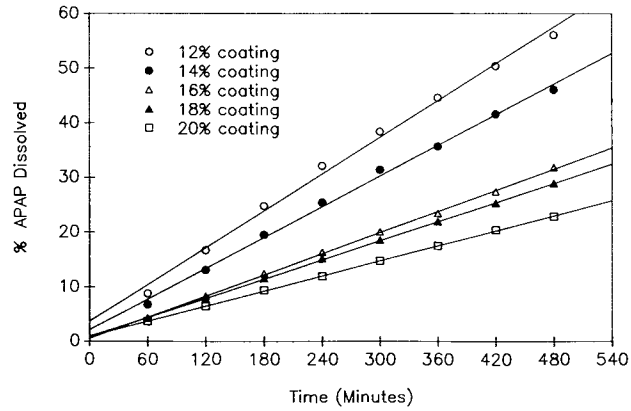

Fig. 2. Dissolution profiles for acetaminophen beads (16/18 mesh) with 12–20% aquacoat coating levels.

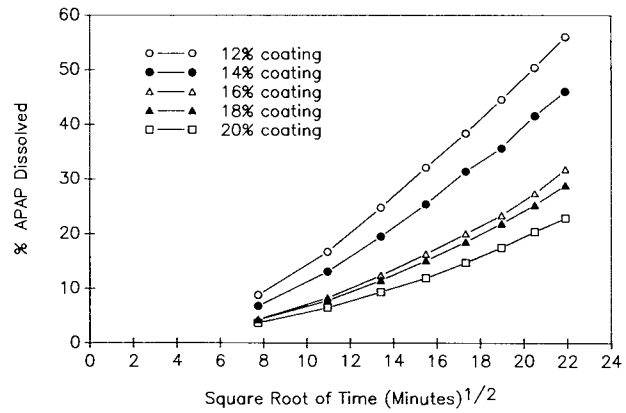

Fig. 4. Dissolution data for acetaminophen beads (16/18 mesh) with 12–20% aquacoat coating levels plotted as the percentage drug released versus the square root of time (minutes$^{1/2}$).

be gradually blocked to reduce the number and the size of channels and, hence, the dissolution rate. Therefore, the higher the coating level on the spheres, the longer the lag time and the lower the apparent drug dissolution rate constant.

At a high coating level, a film barrier predominately governs drug release because all pores are blocked. The drug must, therefore, take the pathway involving diffusion through the barrier; this can be related to drug permeability in the coating and the coating thickness. Therefore, drug release from spheres with high levels of the coating should exhibit a zero order model.

This interpretation was further supported by the scanning electronmicroscopic photographs of coated spheres with 4 and 16% coating level, respectively, as shown in Figs. 5 and 6. A 4% coating represents a low coating level resulting in a discontinuous film over the beads (Fig. 5A) and visible holes (Fig. 5B). These pores, through the full thickness of the coating, which is 6 ± 2 μm, provide the channels for drug release. At a high coating level, for example, a 16% coating applied over the beads, a continuous film can be obtained (Fig. 6A). There are some superficial pinholes in the film but they do not penetrate the full thickness of the coating, which is 26 ± 9 μm. Therefore, drug release is controlled by diffusion through the film barrier. Additional evidence of zero-order kinetics for drug release from spheres with high coating levels was obtained using extended (24-hr) dissolution testing, as shown in Fig. 7. These data were obtained after a 2-year storage period of the coated spheres.

If the slopes of the dissolution data in Figs. 1 and 2 (based on the square root of time relationship) are obtained

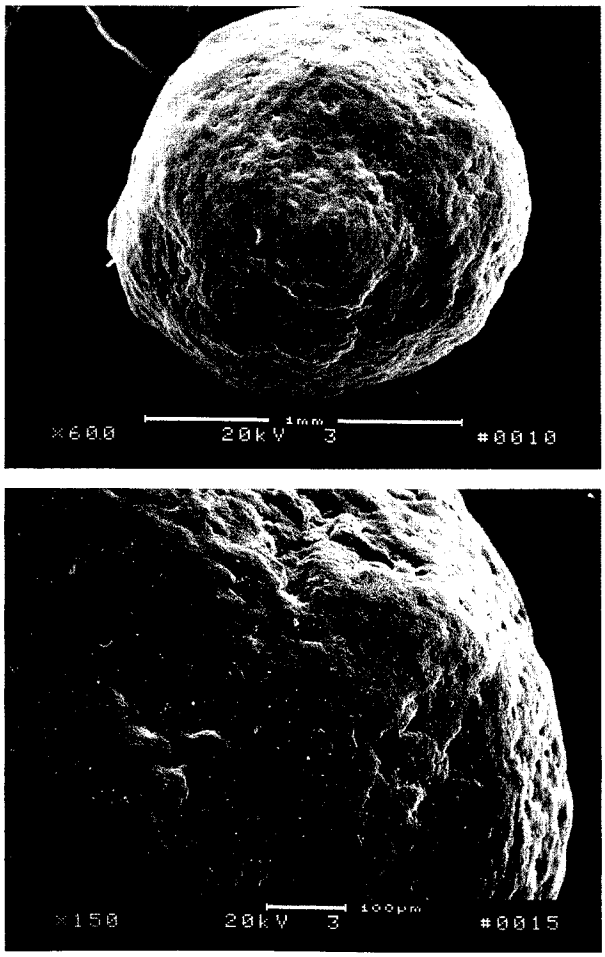

Fig. 5. Scanning electromicroscopic photograph of coated spheres with a 4% level of Aquacoat.

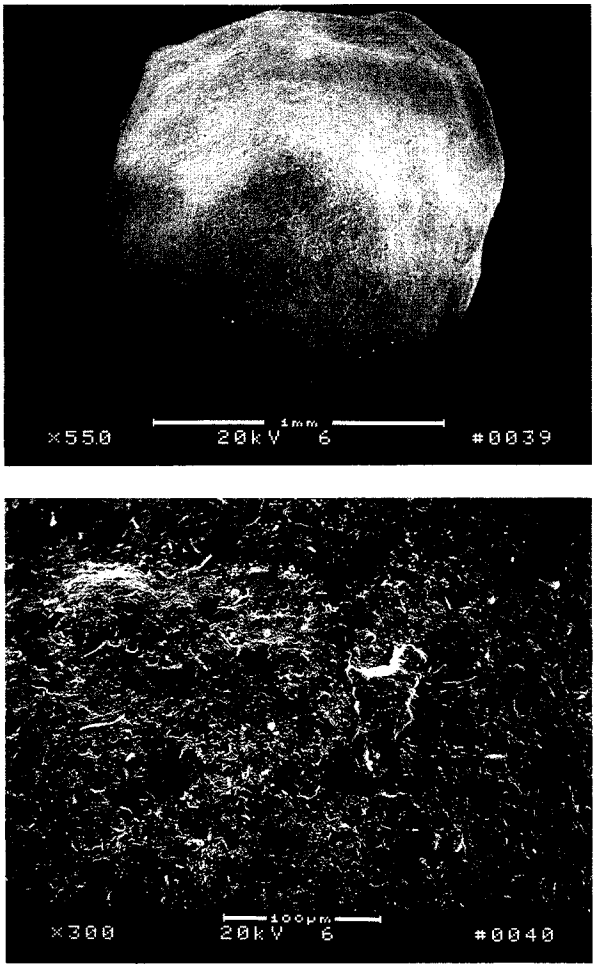

Fig. 6. Scanning electromicroscopic photograph of coated spheres with a 16% level of Aquacoat.

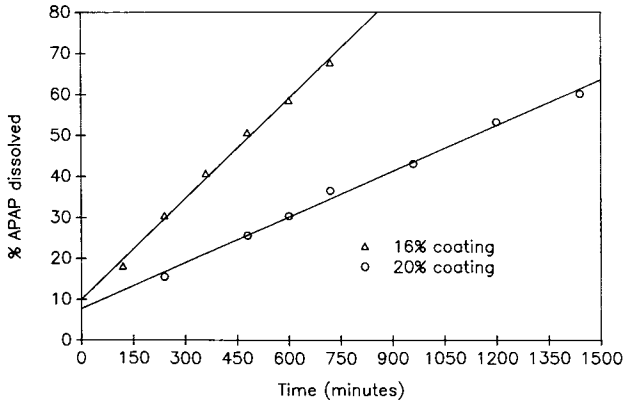

Fig. 7. Dissolution profiles for acetaminophen beads (16/18 mesh) with 16 and 20% Aquacoat coating levels.

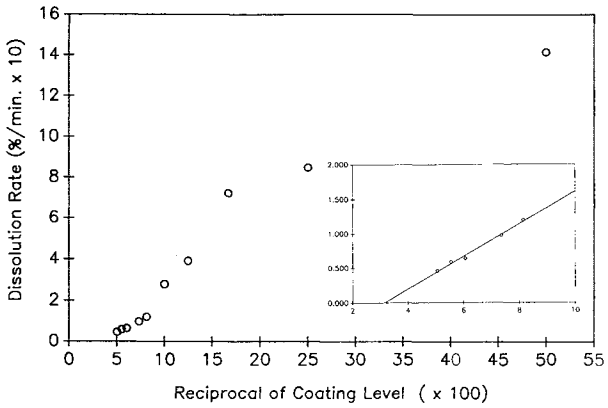

Fig. 8. Dissolution rate constant versus coating level profile for acetaminophen beads (16/18 mesh cut) coated using Aquacoat.

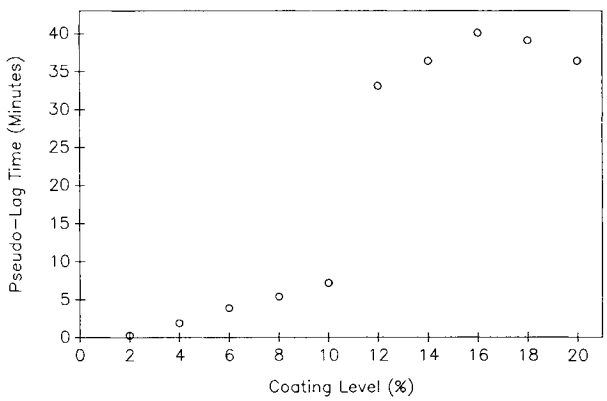

Fig. 10. Pseudo-lag time versus coating level profile for acetaminophen beads (16/18 mesh cut) coated with Aquacoat (based on the square root of time relationship).

by linear regression and plotted as a function of coating level, the results (Fig. 8) indicate an apparent change in the release mechanism. Two trends are observed in Fig. 8. In the first phase it seems that the dissolution rate constant is proportional to the coating level up to 10%, and the relationship appears to be linear. At coating levels greater than 10%, the drug release mechanism is different. Moreover, if the linear portion is extrapolated to the x axis, the intercept is approximately 14% coating, and this could indicate a complete coating level.

It is reasonable that at the intermediate levels of the coating, both mechanisms of drug release are operative. Therefore, the drug release mechanism should be a combination of pore and barrier controls. Other authors (19,20), attempting to describe drug release from a coated system, have combined pore release and barrier release by incorporating porosity and tortuosity terms into the barrier equation as follows:

$$Q_t = \frac{D\epsilon K_m C_s t}{\tau L} \tag{3}$$

The present authors believe that different terms must be used to account for the two types of release. (A separate communication will describe the derivation of an appropriate equation.)

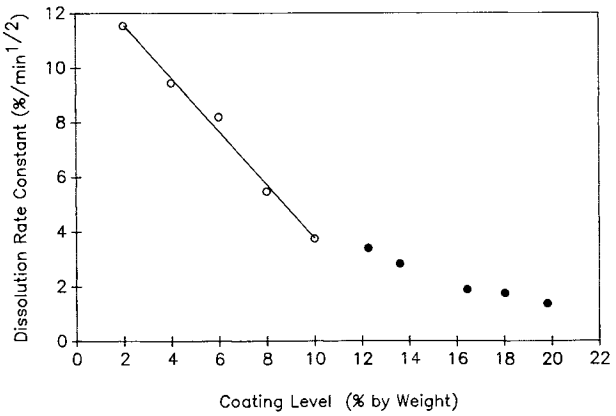

Fig. 9. Dissolution rate versus coating level profile for acetaminophen beads (16/18 mesh cut) coated with Aquacoat.

From Eq. (2), the drug dissolution rate should be proportional to the reciprocal of the coating level if drug release follows the zero-order model. Figure 9 represents such a plot based on a zero-order dissolution rate and the initial dissolution data for all coating levels, but two different trends are observed. At the higher coating levels, the appropriate relationship exists, i.e., the dissolution rate is linearly related to the reciprocal of the coating level. At the lower coating levels this is not true. A change of release mechanism is suggested.

Further support for the change in mechanism is obtained by looking again at the square root plots and the pseudo lag time. If these values are plotted as a function of the coating level (as shown in Fig. 10), one can observe a break in the curve, indicating a mechanism change. The explanation for this break is that longer times are required for water to penetrate a complete film and comparatively short times are needed for water to enter via pores an incomplete coating. It is interesting to note that the break point in Fig. 10 is close to the complete coating level obtained in Fig. 8 (14%).

CONCLUSION

These results show that at low levels of coating, drug release data can be described by a square root of time relationship; and at high levels of coating, by a zero-order relationship. These changes and kinetics, therefore, suggest a change in the mechanism of drug release. The physical model explaining this change will be presented in a separate manuscript (14).

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