DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 17(6), 817-830 (1991)

BEAD COATING: II. EFFECT OF SPHERONIZATION TECHNIQUE ON DRUG RELEASE FROM COATED SPHERES

Guohua Zhang[1,2], Joseph B. Schwartz[1], Roger L. Schnaare[1]
Rodney J. Wigent[1] and Edwin T. Sugita[1]
[1] Department of Pharmaceutics
Philadelphia College of Pharmacy and Science, Philadelphia, PA 19104
[2] Present address: Formulation Research
Schering-Plough Inc., Kenilworth, NJ 07033

ABSTRACT

The effect of spheronization method on drug release from coated spheres may be evaluated by determining the drug release rate, the critical coating level and the release mechanism. Drug release is faster from pan beads than from marumerizer beads at the same coating level. An equation is proposed which indicates that the critical coating level is inversely proportional to sphere size and sphere density, which in turn results from the different spheronization techniques. From the calculation, the critical coating levels for 14/16 mesh cuts of marumerizer beads and pan beads are 12% and 18%, respectively. Disintegration, pore-control

and barrier control are involved in the release mechanisms of drugs from coated pan beads.

INTRODUCTION

Several techniques have been reported in the literature for spheronization. These techniques involved extrusion/marumerization, pan method, air fluidization, and granulation in specific granulators.[1-5] Spheronization processing variables and materials on resultant beads have been investigated.[6-7] The effect of spheronization method on drug release from uncoated spheres has been evaluated previously. Spheres made in a coating pan disintegrate during dissolution testing, while spheres made via the extruder/marumerizer remain intact, behaving like an inert matrix system.[8] The drug release mechanisms from spheres, made in an extruder/marumerizer and coated with an aqueous ethylcellulose based dispersion, have also been investigated. The drug release rate and the mechanisms were found to depend on the coating level. At a low coating level the pore control mechanism predominates, while at a high coating level drug release is mainly membrane or barrier controlled.[9]

The current work deals with drug release from coated spheres, prepared using two different spheronization methods: (1) the pan method and (2) the extruder/marumerizer method. The emphasis in this study is

on the evaluation of spheronization method on drug release from spheres coated using an ethylcellulose aqueous based dispersion.

MATERIALS AND METHODS

Materials - Microcrystalline cellulose (Avicel^R PH 101), an aqueous ethyl cellulose based dispersion (Aquacoat^R) and dibutyl sebacate (DBS) were provided by FMC Corporation (Philadelphia, PA). Acetaminophen (APAP), USP, was used as a model drug and distilled water as the granulating solvent.

Bead Preparation - Beads containing 50% acetaminophen and 50% Avicel^R PH 101 were prepared using both the pan and extruder/marumerizer techniques, described in a previous publication.[8]

Coating - The Aquacoat^R was plasticized using 20% DBS (based on the solids content in the dispersion). The coating processes were performed in an Aeromatic fluid bed column with the "Wurster insert". The coating dispersion was applied from the bottom of the column at a rate ranging from 4 mL/min to 8 mL/min. The coating level was calculated in terms of the weight difference between the uncoated and the coated spheres after drying.

Measurement of Sphere Density - One hundred uncoated spheres from each batch, having 14/16 mesh size, were used to determine the average diameter and weight of a sphere. The sphere density was calculated in terms of the sphere volume.

Dissolution Test - Dissolution was conducted using the USP dissolution apparatus I at a basket rotational speed of 50 rpm. Distilled water was utilized as the dissolution medium (900 mL). The drug released in the medium was determined by means of UV spectrometry at 249 nm.

RESULTS AND DISCUSSION

Figure 1 demonstrates the dissolution profiles of APAP from the spheres with a 2% coating level. The drug release is faster from the pan beads than from the marumerizer beads. Figure 2 shows that drug release from pan beads does not seem to have a linear dependency based on the square root of time model. It was observed in the experimentation that coated pan spheres disintegrate during dissolution testing. It may be that the disintegration force of the pan sphere core is larger than the tensile strength of the coating at this low level, which may cause the coating to break.

When pan spheres are coated to a level, where the tensile strength of the coating is greater than the disintegrating force, drug release may be

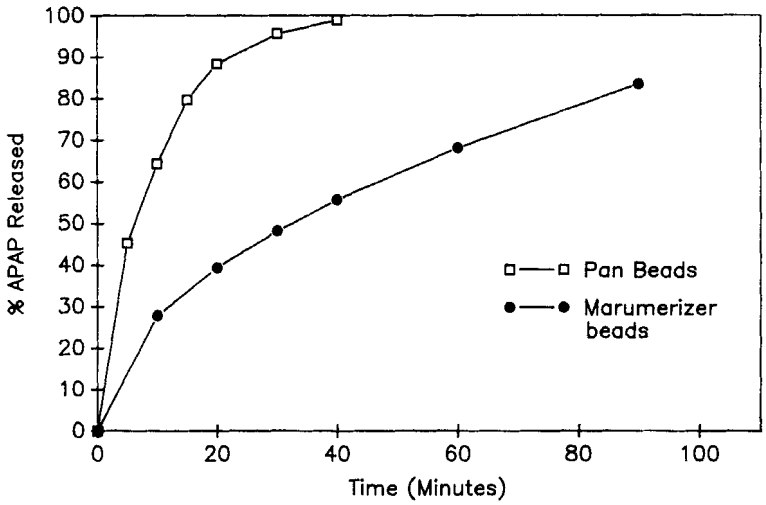

Figure 1

Dissolution of APAP from beads with 2% coating level of Aquacoat dispersion.

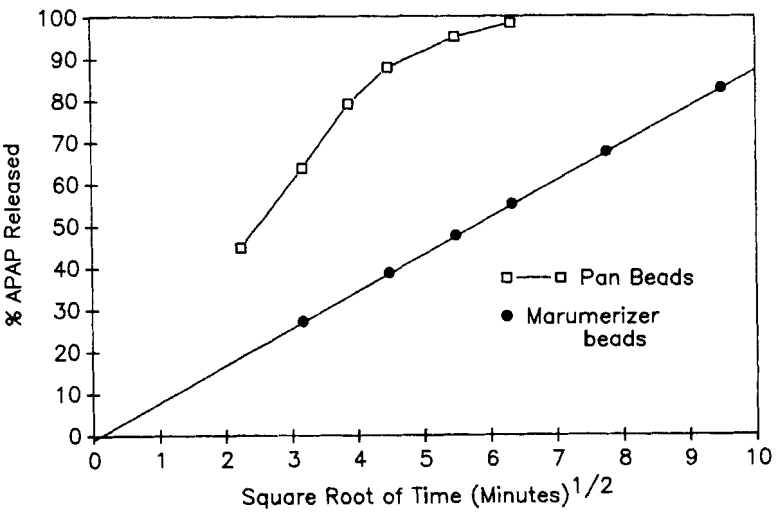

Figure 2

Dissolution of APAP beads with 2% coating of Aquacoat in terms of the square root of time model.

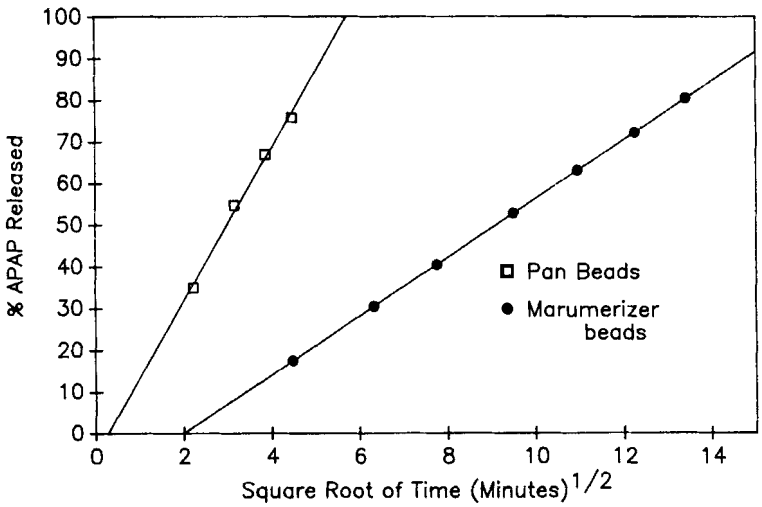

Figure 3

Dissolution of APAP beads with 4% coating of Aquacoat in terms of the square root of time model.

described by the square root of time model, thus behaving like an inert matrix system. The mechanism of drug release converts from disintegration to pore control. Plotting the release data according to the square root model yields linear profiles of acetaminophen release from both pan beads and marumerizer beads with 4% and 8% coating levels (Figures 3 and 4). This observation implies that the drug release mechanism may be identical for both pan beads and marumerizer beads with 4% or 8% coating level. At similar coating levels, drug release is faster from pan beads than from marumerizer beads because of the difference in surface area exposed to the dissolution medium and the thickness of the coating.

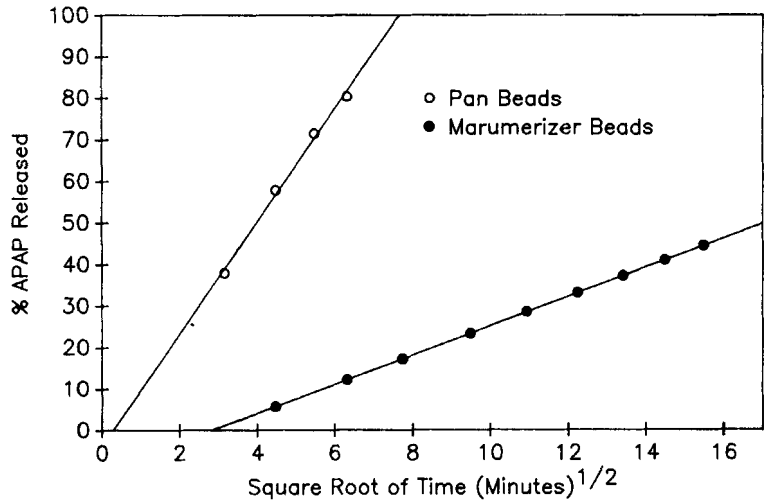

Figure 4

Dissolution of APAP beads with 8% coating of Aquacoat in terms of the square root of time model.

Usually the coating level is expressed mathematically in terms of coating thickness, but it can also be practically defined as percent weight gain. In this study, the term "coating level" is expressed as the percentage of coating weight gain based on the sphere core. The relationship between the coating level and the coating thickness can be shown in the following:

$$C=\frac{W_c}{W_b} \quad (1)$$

where C, the coating level, is the coating weight, W_c, divided by the weight of the bead core, W_b. If the bead core is spherical, Equation 1 becomes:

$$C=\frac{4\pi r^2 L\rho_c}{\frac{4}{3}\pi r^3\rho_b} \quad (2)$$

where r is the radius of the sphere; L is the coating thickness; ρ_c is the coating density and ρ_b is the bead density. Therefore, the relationship between the coating level and the coating thickness can be described in the following form:

$$L=\frac{r\rho_b C}{3\rho_c} \quad (3)$$

Equation 3 indicates that at the same coating level, the smaller the bead density, the thinner the coating thickness; hence the faster the drug release. Listed in Table 1 are sphere size and sphere density measurements. These results help explain why drug release is faster from pan beads than from marumerizer beads with an identical coating level in terms of Equation 3. As discussed previously, at a low coating level the coating may be porous, so that the drug takes less resistant pathways for release, i.e., through the pores or channels through the coating.[9] The thicker the coating the fewer the pores that are available for drug transport, which makes drug release slow, as shown for marumerizer beads.

The critical coating level has been defined as a coating level at which the drug release mechanism becomes completely barrier-controlled.[9-11] After the critical coating level, drug diffusion through a membrane barrier dominates drug release that may be described by zero

TABLE 1. Sphere Size and Sphere Density

Type Spheres	Mesh Size	Sphere Diameter mm	Sphere Density g/mL
Marumerizer Spheres	14/16	1.300	1.66 ± 0.24
Marumerizer Spheres	16/18	1.095	1.66 ± 0.26
Pan Spheres	14/16	1.300	1.12 ± 0.23

order kinetics. As previously reported, the critical coating level of marumerizer beads in 16/18 mesh using Aquacoat dispersion is 14%.[9] Based on Equation 3, the effects of sphere size and sphere density on the critical coating level can be estimated. If two different spheres are coated to the same degree (i.e, same coating thickness) with the same coating material, the relationship between the critical coating level, the sphere size and the sphere density is proposed as follows:

$$C_{c1}=\frac{\rho_{b2}r_2}{\rho_{b1}r_1}C_{c2} \quad (4)$$

where C_c is the critical coating level; subscripts 1 and 2 represent sphere 1 and sphere 2.

Equation 4 indicates that the critical coating level is a function of the sphere size and the sphere density. Interestingly, the critical coating

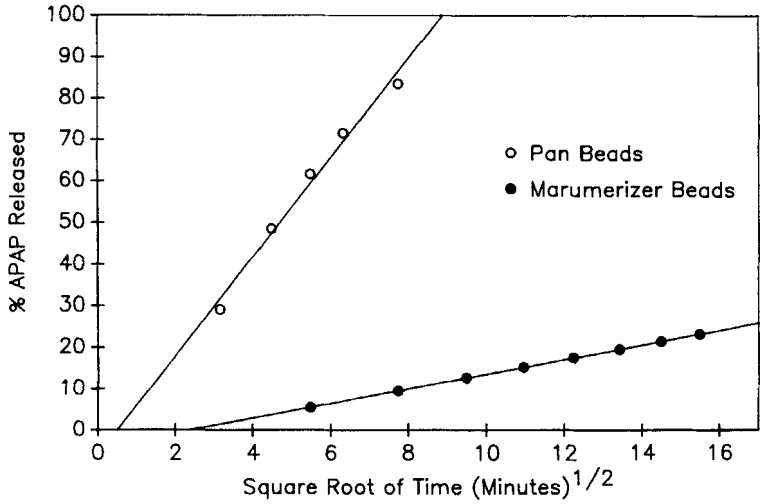

Figure 5

Dissolution of APAP beads with 10% coating of Aquacoat in terms of the square root of time model.

level of Aquacoat^{R} on marumerizer beads in 14/16 mesh can be predicted using the data in Table 1. Substituting the sphere density and sphere size as well as the critical coating level for 16/18 mesh beads, which is reportedly about 14%, the critical coating level for marumerizer beads in 14/16 mesh is approximately 12%. Therefore, at a coating level higher than 12%, drug release from marumerizer beads in 14/16 mesh size coated using Aquacoat^{R} should exhibit zero order profiles. The experimental results supported this evaluation, as shown in Figures 5 and 6. At 10% coating level, the release data for both pan and marumerizer beads still follow the square root model well, while at 12% coating level, the release

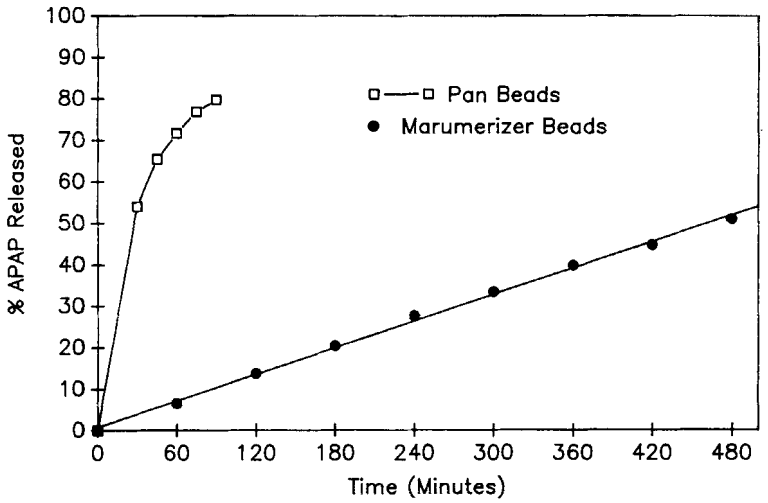

Figure 6

Dissolution of APAP from beads with 12% coating level of Aquacoat.

data can be described using zero-order kinetics only for the marumerizer beads.

Using the same principles, the critical coating level for 14/16 mesh pan made spheres should also be affected by both the sphere density and the sphere size. The smaller the sphere density, the greater the number of spheres and the larger the surface to be coated for the same mass of spheres. In terms of Equation 4, the critical coating level can be predicted based on identical critical coating thickness.

$$C_{cp}=\frac{\rho_{bm}r_m}{\rho_{bp}r_p}C_{cm}=\frac{1.66*1.095}{1.12*1.300}*14=18(\%)$$

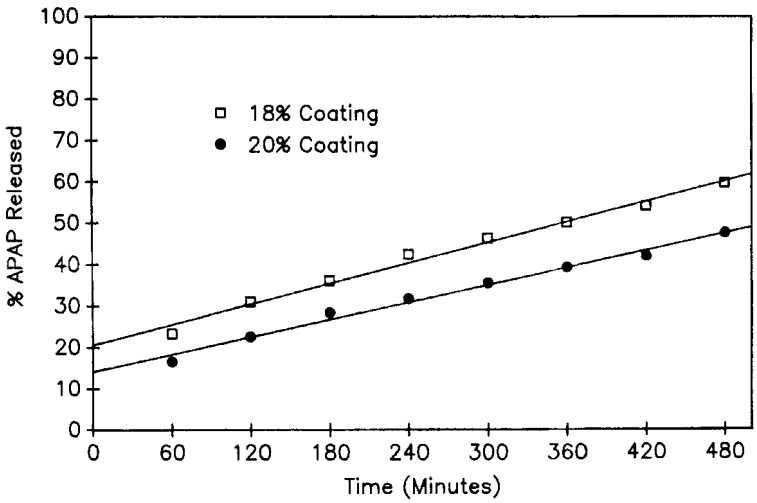

Figure 7

Dissolution of APAP from pan beads with the Aquacoat coating.

where subscripts *p* and *m* represent the pan beads and the marumerizer beads, respectively. Therefore the critical coating level of Aquacoat coating for pan spheres is higher than for marumerizer spheres if the same bead formulation is used. By increasing the coating level on pan spheres until they are essentially covered by a barrier without openings, drug release should be characterized by zero-order kinetics. Figure 7 illustrates that the pan beads with 18% and 20% coating levels can be interpreted using zero-order drug release. This evidence also supports the evaluation of the critical coating level using Equation 4.

It is clear that there are three phases in terms of the drug release mechanism of the pan spheres and these vary with the coating level. In the

first phase at the initial stage of the coating, partial disintegration takes place during dissolution testing. The second phase represents drug release with a predominately pore controlled mechanism as in a matrix system; there is a linear dependency of drug release against the square root of time. Drug release is dominated by barrier control in phase 3, after the coating of beads reaches the critical coating level.

CONCLUSIONS

Drug release from coated beads has been shown to be influenced by the spheronization technique used to form the beads. At an identical coating level, drug release is always faster from pan beads than from marumerizer beads because of the different thickness of the coating, resulting from the different sphere density due to the spheronization method. The critical coating level was found to be inversely proportional to sphere size and sphere density, which may be mathematically predictable. The drug release mechanism from the pan beads is dependent on the coating level. Disintegration, pore-controlled and barrier-controlled mechanisms are involved in drug release at the different levels of coating. Therefore, it is concluded that the different spheronization technique affects the drug release rate, the critical coating level and the drug release mechanism.

REFERENCES

1. G.H. Zhang, H.Y. Li and G.J. Liu, J. China Pharm. Univer. 16(1):28-37, 1985.
2. B. Gajdos, Drugs Made Ger., 27(1):30-34, 1984.
3. A.D. Reynolds, Mfg. Chem. Aerosol News 41(6):40, 1970.
4. G. Rothgang, Acta Pharm. Technol., 20(1):39, 1974.
5. M.J. Gamlen, Mfg. Chem., 56(6):55, 57, 59, 1985.
6. C.W. Woodruff and N.O. Nuessle, J. Pharm. Sci., 61(5):788, 1972.
7. P.J. Harrison, J.M. Newton and R.C. Rowe, J. Pharm. Pharmacol., 37:686-689, 1985.
8. G.H. Zhang, J.B. Schwartz and R.L. Schnaare, Drug Dev. Ind. Pharm. 16(7):1171-1184, 1990.
9. G.H. Zhang, J.B. Schwartz and R.L. Schnaare, Pharm. Res., in press.
10. G.H. Zhang, J.B. Schwartz and R.L. Schnaare, Proceed. Intern. Symp. Control. Rel. Bioact. Mater. 15:99-100, 1988.
11. G.H. Zhang, J.B. Schwartz and R.L. Schnaare, Proceed. Intern. Symp. Control. Rel. Bioact. Mater. 16:150-151, 1989.