Drug Development and Industrial Pharmacy, 24(8), 737–746 (1998)

RESEARCH PAPER



# Bead Compacts. I. Effect of Compression on Maintenance of Polymer Coat Integrity in Multilayered Bead Formulations

Syed A. Altaf,* Stephen W. Hoag,**,*** and James W. Ayres

*College of Pharmacy, Oregon State University, Corvallis, Oregon 97331-3507.*

## ABSTRACT

*Little information is available on the compactability of beads for oral sustained-release dosage forms. It is known that polymer-coated beads may fuse together to produce a non-disintegrating controlled-release matrix tablet when compressed. This study evaluates the effect of compression on beads with multiple layers of polymer and drug coat, and the effect of cushioning excipients and compaction pressure on drug release from compressed bead formulations. The multilayered beads consist of several alternating layers of acetaminophen (APAP) and polymer coats (Aquacoat®) with an outer layer of mannitol as a cushioning excipient. Percent drug release versus time profiles showed that the release of drug decreases from noncompacted beads as the amount and number of coatings increases, with only 43% of drug released in 24 hr for coated beads with 10 layers. It was shown that the compacted multilayered beads will disintegrate in gastrointestinal fluids, providing a useful drug release pattern. It was shown that beads of drug prepared by any method can be spray-layered with excipients such as Avicel and mannitol. Spray-layering of the cushioning excipient onto beads can provide an effective way to circumvent segregation issues associated with mixing of the polymer-coated beads and powdered or spherical/nonspherical cushioning excipients. Spray layering of the cushioning excipient can also provide excellent flow properties of the final formulation as visually observed in our experiments. Triple-layered caplets*

*Present address: GILEAD Sciences, 333 Lakeside Drive, Foster City, CA 94404.
**Present address: School of Pharmacy, University of Maryland at Baltimore, 20 N. Pine Street, Baltimore, MD 21201.
***To whom correspondence should be addressed.

*(TLC) were also prepared with outer layers of Avicel PH-101 or polyethylene oxide (PEO), and a center layer of polymer-coated beads. For TLC, the polymer coating on the beads fractured, and nondisintegrating matrix formulations were obtained with both caplet formulations.*



## INTRODUCTION

Compression of polymer-coated beads into tablets raises concerns regarding the loss of integrity of the polymer coat following compression, because coat integrity is necessary to serve as a diffusion barrier to delay drug release from these compressed tablets. The polymer coat must have the right combination of strength, ductility, and thickness to withstand the forces generated during compaction without rupturing. The need to develop such a dosage form arises from product tampering, high cost of capsule production, and the difficulties associated with esophageal transport of capsules. A review of the limited information available in the literature on multiparticulate compaction is given by Celik (1).

Juslin et al. (2) reported an increase in drug release when acrylic-coated phenazone spheres were compacted at low pressure; however, at higher compaction pressure a decrease in drug release was observed. This slower drug release at higher compaction pressures may have been due to fusion of the polymer coat which forms a matrix. Chang and Rudnic (3) evaluated the effect of compaction on solvent-based and latex-based polymer coatings. They found that the latex/pseudolatex films fractured upon compaction of the coated KCl crystals, and the solvent-based coatings had an insignificant increase in release rate compared to the noncompacted coated crystals. Béchard and Leroux (4) studied the effect of particle size and the use of various excipients in maintaining polymer coat integrity. They showed a loss of sustained release properties upon compaction of polymer-coated beads. Similar results were found by Maganti and Celik (5), who concluded that regardless of the amount of coating applied, sustained release properties of the compacted coated beads were lost.

In addition to the above concerns, another major concern that has not been stressed in the literature is segregation of polymer-coated beads from cushioning excipients during normal production. The use of Avicel PH-101 as a cushioning agent in powder form (4,6,7), granulations (8), and in the form of spheres (9) has been investigated for prevention of polymer coat fracture. It was thought that mixing placebo spheres of the same size as that of polymer-coated spheres would solve the segregation problem. However, as investigated by Aulton et al. (10), the use of placebo spheres requires additional consideration of factors such as density and strength of the spheres. The pilot study done by Aulton et al. did not show a segregation problem, but the authors did not rule out the possibility of segregation upon scale up. Ragnarsson et al. (11) developed a rapidly disintegrating multiple-unit system comprising of polymer-coated beads mixed with tablet-forming excipients; however, there was no mention of the segregation problem that may occur during scale up. A 1:1 mixture of microcrystalline cellulose and polyethylene glycol (PEG 8000) has previously been spray-layered on polymer-coated beads (12). These beads were then compacted without any additional tableting excipients, but a nondisintegrating matrix tablet was achieved which provided sustained release properties similar to those of the noncompacted polymer-coated beads.

The purpose of this study was to evaluate the effects of compression on a new concept design, i.e., multilayered beads with alternating multiple layers of polymer and drug coat. The idea behind the concept was that when the multilayered beads are compressed into caplets the outermost layers will absorb the pressure and fracture to provide immediate release, while the innermost layers would be protected from fracture and provide sustained drug release. This study also examined the utility of spray-coating cushioning excipients onto polymer-coated beads to eliminate the segregation problem. In addition, the effect of cushioning excipient type and amount and compaction pressure on drug release from compressed multilayered beads was investigated.

## EXPERIMENTAL

### Materials

Acetaminophen (4-acetamidophenol) (APAP) and dibutyl sebacate (sebacic acid dibutyl ester) were purchased from Sigma Chemical Co., St. Louis, MO; poly(vinylpyrrolidone) K-30 (PVP) was supplied by E. M. Science, Gibbstown, NJ; hydroxypropylcellulose (HPC) Type EXF NF was supplied by Aqualon, Wilmington, DE; Aquacoat® ECD-30 and Avicel® PH-101 samples were provided by FMC Corp., Philadelphia, PA; triethyl citrate and mannitol were purchased from Morflex

Chemical Co., Inc., Greensboro, NC, and J. T. Baker Chemical Co., Phillipsburg, NJ, respectively; and Nupariel PG sugar spheres 25/30 mesh were from Crompton and Knowles Corp., Pennsauken, NJ. The pill crusher was obtained from American Medical Industry, Highland Park, IL.

### Coating Procedure

A weighed amount (100 g) of Nupariel sugar beads were placed into the coating chamber of a fluid-bed spray coater with an Aeromatic® chamber and a Wurster column insert (Labline Instruments, Inc., Melrose Park, IL). The beads were fluidized for 20 min to equilibrate the temperature (40°C). The APAP drug solution was prepared in 95% ethanol using HPC/PVP (1:2) as binders. The drug solution was then sprayed onto the beads. A 6% w/w polymer coat (Aquacoat with 30% plasticizer, i.e., dibutyl sebacate/triethyl citrate [DBS/TEC] 1:1) was applied over each drug layer. The 30% plasticizer DBS/TEC (1:1) lowers the glass transition temperature ($T_g$) of Aquacoat (27% w/w ethylcellulose dispersion) from 130 to 43°C. A 20-min cure time was allowed after each coating layer in order for the polymer coat to coalesce and form a film. Note that as multiple layers are applied to each batch of beads, layers which were 6% of previous batches become a smaller percent in the final product. This process of coating drug and polymer layers was repeated until the last layer (layer 10) of polymer coat was applied (see Fig. 1, Table 1). A 14% mannitol layer was applied under the last polymer coat. Since it was difficult to fluidize the beads in the coating chamber after the tenth layer, no further layering of the polymer coat was performed.

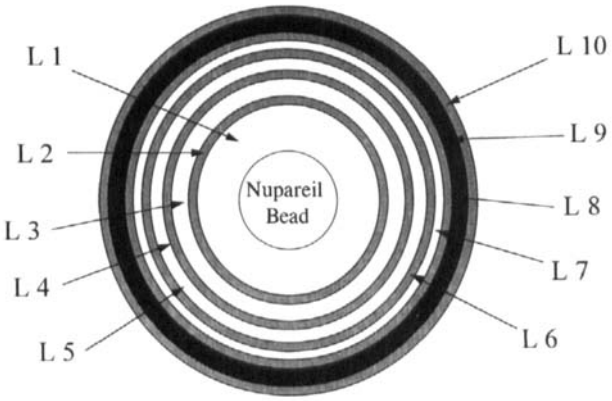



**Figure 1.** Cross-sectional view of a 10-layer multilayered bead, L = layer number.

Multilayered beads with Avicel PH-101 as the outer four layers were also prepared to study the percentage of excipient needed to protect the polymer coats from fracturing upon compression. Avicel was added as one big batch and the samples were collected after each coating layer at 20, 40, 60, and 80% Avicel w/w added onto beads as layers 7, 8, 9, and 10, respectively (Table 2).

### Bead Compaction and Dissolution Testing

Caplets (1000-mg capsule-shaped tablets) were made on a Carver hydraulic press by compressing the multi-

*Table 1*

*Formulation Compositions for the Multilayered Beads*

| Formulation Ingredient | L1 (%) | L2 (%) | L3 (%) | L4 (%) | L5 (%) | L6 (%) | L7 (%) | L8 (%) | L9 (%) | L10 (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| Beads | 56.0 | 52.6 | 43.3 | 40.9 | 34.0 | 32.0 | 26.9 | 25.3 | 21.6 | 20.3 |
| APAP 1 | 37.3 | 35.1 | 28.9 | 27.3 | 22.7 | 21.3 | 18.0 | 16.9 | 14.4 | 13.5 |
| AQ 1 | – | 6.0 | 4.9 | 4.7 | 3.9 | 3.6 | 3.1 | 2.9 | 2.5 | 2.3 |
| APAP 2 | – | – | 17.6 | 16.6 | 13.9 | 13.0 | 11.0 | 10.3 | 8.8 | 8.2 |
| AQ 2 | – | – | – | 5.7 | 4.7 | 4.4 | 3.7 | 3.5 | 3.0 | 2.8 |
| APAP 3 | – | – | – | – | 16.7 | 15.7 | 13.2 | 12.4 | 10.6 | 9.9 |
| AQ 3 | – | – | – | – | – | 6.0 | 5.1 | 4.8 | 4.0 | 3.8 |
| APAP 4 | – | – | – | – | – | – | 15.8 | 14.9 | 12.6 | 11.9 |
| AQ 4 | – | – | – | – | – | – | – | 6.0 | 5.1 | 4.8 |
| M | – | – | – | – | – | – | – | – | 14.9 | 14.0 |
| AQ 5 | – | – | – | – | – | – | – | – | – | 6.1 |

APAP = Acetaminophen, APAP solution for all layers was prepared in hydroxypropylcellulose (2.2%):poly(vinylpyrrolidone) (4.5%); M = mannitol; AQ = Aquacoat with 30% w/w plasticizer (dibutyl sebacate/triethyl citrate, 1:1); L = layer on bead.

*Table 2*

*Formulation Compositions for the Multilayered Beads with Avicel PH-101 as the Outer Layers*

| Formulation Ingredient | L1 (%) | L2 (%) | L3 (%) | L4 (%) | L5 (%) | L6 (%) | L7 (%) | L8 (%) | L9 (%) | L10 (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| Beads | 56.0 | 52.6 | 43.3 | 40.9 | 34.0 | 32.0 | 25.6 | 19.2 | 12.8 | 6.4 |
| APAP 1 | 37.3 | 35.1 | 28.9 | 27.3 | 22.7 | 21.3 | 17.0 | 12.8 | 8.5 | 4.3 |
| AQ 1 | – | 6.0 | 4.9 | 4.7 | 3.9 | 3.6 | 2.9 | 2.2 | 1.5 | 0.7 |
| APAP 2 | – | – | 17.6 | 16.6 | 13.9 | 13.0 | 10.4 | 7.8 | 5.2 | 2.6 |
| AQ 2 | – | – | – | 5.7 | 4.7 | 4.4 | 3.5 | 2.7 | 1.8 | 0.9 |
| APAP 3 | – | – | – | – | 16.7 | 15.7 | 12.6 | 9.4 | 6.3 | 3.2 |
| AQ 3 | – | – | – | – | – | 6.0 | 4.8 | 3.6 | 2.4 | 1.2 |
| AV 1 | – | – | – | – | – | – | 20.2 | 17.3 | 14.7 | 12.4 |
| AV 2 | – | – | – | – | – | – | – | 22.7 | 19.3 | 16.3 |
| AV 3 | – | – | – | – | – | – | – | – | 26.1 | 22.0 |
| AV 4 | – | – | – | – | – | – | – | – | – | 29.2 |

APAP = Acetaminophen, APAP solution for all layers was prepared in hydroxypropylcellulose (2.2%):poly(vinylpyrrolidone) (4.5%); AQ = Aquacoat with 30% w/w plasticizer (dibutyl sebacate/triethyl citrate, 1:1); AV = Avicel PH-101; L = layer on bead.



layered beads at different compaction pressures. The beads were observed to have excellent flow characteristics and were compressed without the addition of any filler material. Dissolution studies on the uncompacted and compacted beads were conducted using USP dissolution apparatus II at 50 rpm with simulated intestinal fluid (pH 7.4 ± 0.1) maintained at 37 ± 0.5°C. Samples (5-ml aliquots) were collected with replacement and after filtration and proper dilution. Samples were analyzed with a UV spectrophotometer at $\lambda$ = 244 nm. All dissolution experiments were conducted in duplicate. The maximum standard deviation observed for any batch was not more than 3%; therefore, error bars were not included in the dissolution profiles to avoid visual complexity of the several dissolution curves in individual graphs.

### Scanning Electron Microscopy (SEM)

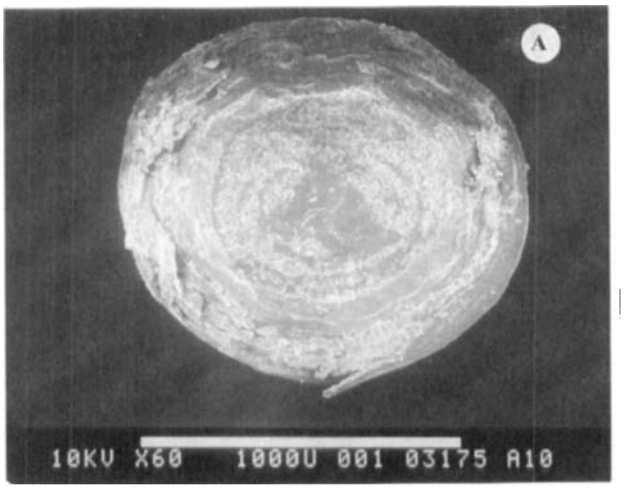
An AmRay (model 1000A) microscope at an accelerating voltage of 10 kV was used for SEM. The beads and caplets were prepared by either freezing in liquid nitrogen and then fracturing in a mortar with a pestle or by simply slicing the material with a razor blade. The samples were then coated with 60:40 gold/palladium alloy prior to microscopic examination. The samples prepared by two different techniques produced similar SEM results.

## RESULTS AND DISCUSSION

### Multilayered Beads

The multilayered beads consisted of several alternating layers of APAP and polymer coats (Aquacoat) with an outer layer of mannitol as an additional cushioning excipient (Fig. 1). As shown in Figure 2 the drug/polymer layers are distinct, a higher magnification shows the distinct layers as displayed in the artist's conception of a 10-layered bead (Fig. 1). Percent drug release versus time profiles for noncompacted multilayered beads are plotted in Fig. 3. As expected, the percent drug release rate decreases as the amount of coating increases, i.e., only 43% of the drug is released in 24 hr for the 10-layered beads. Notice that the beads with a drug outer layer release drug at a faster rate even when there is a 6% polymer coat underneath the final drug layer. This may be due to wicking action of the dissolution fluid through the APAP layer which creates channels for the dissolution fluid to diffuse through the polymer layer. On the other hand, when mannitol is the outer layer the drug release rate is not significantly greater (see profiles of layers 8 and 9 in Fig. 3).

The multilayered beads were then compressed into caplets at 500 lb pressure without the addition of any tableting excipient. Beads with layers 5–10 (Table 1) were used for compaction studies. Upon compaction, discrete beads can still be clearly distinguished within the caplet; however, significant deformation of the beads



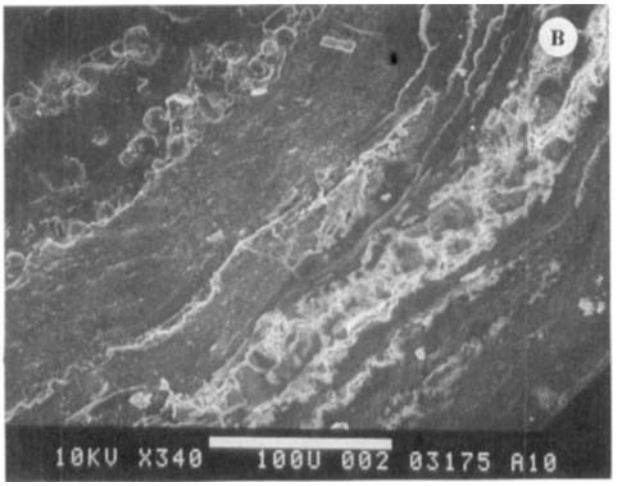




**Figure 2.** Scanning electron micrographs (SEMs) of an L 10 multilayered bead; magnification (a) = 60 and (b) = 340.

is observed (Fig. 4). Compaction of the beads into caplets also leads to densification of the drug/polymer layers; cracks in some of the layers can also be observed (Fig. 4). Figure 5 compares dissolution profiles of compacted (500 lb) and noncompacted beads for layered beads 6, 8, and 10. Layer 6 caplets disintegrated after 12 hr and layer 8 and 10 beads formed nondisintegrating matrix caplets. These three formulations contained beads with an outer layer of Aquacoat (layer 6, 8, and 10 beads). The non-disintegrating caplets in which the outer layer was a polymer coat showed sustained release properties. For disintegrating matrix caplets, release patterns in Fig. 5 show that compression caused at least some bead coatings to rupture. An increase in drug release

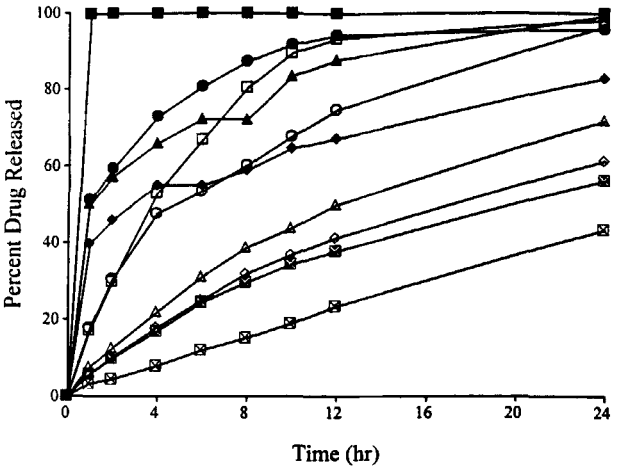



**Figure 3.** Percent drug release versus time profiles for the noncompacted multilayered beads. ■ = L1, □ = L2, ● = L3, ○ = L4, ▲ = L5, Δ = L6, ◆ = L7, ◇ = L8, ▣ = L9, ⊠ = L10.

from caplets compared to noncompacted beads was observed.

To simulate the harsh conditions these caplets could be exposed to, some of the caplets made with multilayered beads at 500 lb force were crushed with a pill crusher, and dissolution tests were conducted to compare release profiles of intact and crushed caplets (Fig. 6). Crushed caplets released drug more quickly than the original noncompacted beads, indicating that many of the polymer coatings ruptured during compression. Caplets with the drug outer layers on the beads disintegrated in 2–3 min, and those with mannitol as the outer layer disintegrated within 20 min. However, crushed or intact caplets with drug or mannitol as the outer layer released all of the drug in about 4 hr, except for the crushed caplet of the formulation with 10-layered beads. In this case 50% of the drug was released in 0.5 hr and the remaining 50% of drug was released over an 8-hr period (Fig. 6), which indicates that many of the beads withstood compaction and subsequent crushing.

Tylenol ER is marketed in the United States and is labeled with the Radebaugh U.S. patent number 4,820,522. Radebaugh et al. indicate the need for a controlled-release formulation of APAP. A primary advantage of their invention is that their nondisintegrating tablets are bioerodible. That is, no insoluble tablet-shaped device remains to be excreted or removed from the body after APAP is depleted from the tablet. Dissolution of this product in the USP paddle dissolution apparatus with 2 hr of gastric fluid followed by 2 hr of intestinal

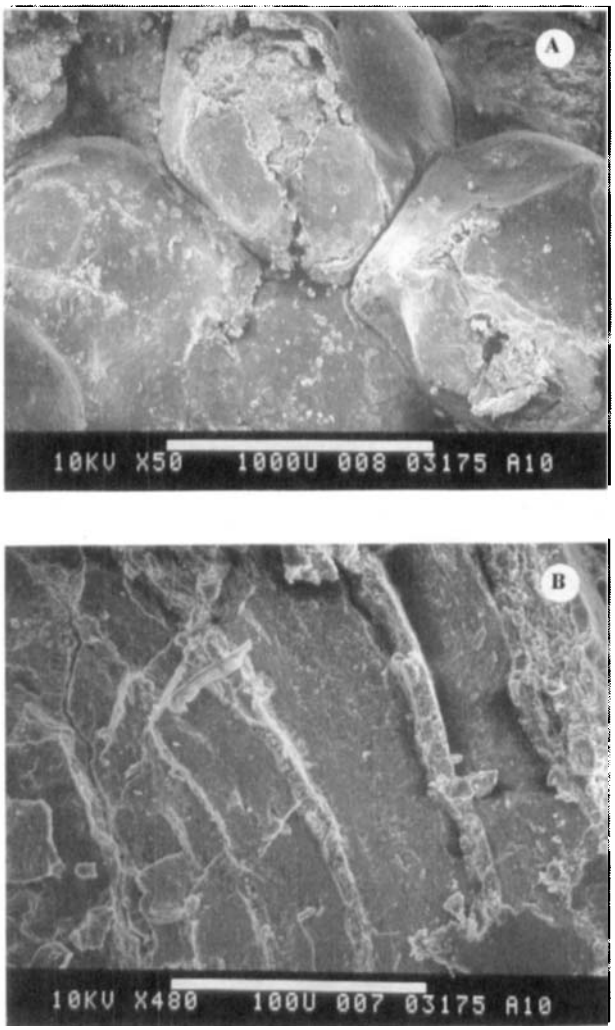



**Figure 4.** SEMs of the deformed multilayered bead upon compaction at 500 lb; magnification (a) = 50 and (b) = 480.

fluid resulted in dissolution of 50% of the dose in about 20 min, 70% dissolution in about 50 min, and more than 90% dissolution in about 1.5 hr. These results are consistent with data in Table 2a of U.S. patent 4,820,522, which show a maximum plasma concentration of APAP at 1.5 hr post dosing.

Results for the layer 9 beads, containing mannitol as the outer layer, show similar dissolution of the active ingredient (APAP) for both intact caplets and crushed caplets (Fig. 6). The intact caplet disintegrated in about 20 min in the dissolution fluid. Figure 6 shows that dissolution of APAP from the disintegrating compact was 50% in about 50 min, 70% dissolution in about 100 min, and 90% dissolution in about 10 hr. The crushed caplet for the beads with mannitol as the outer layer released

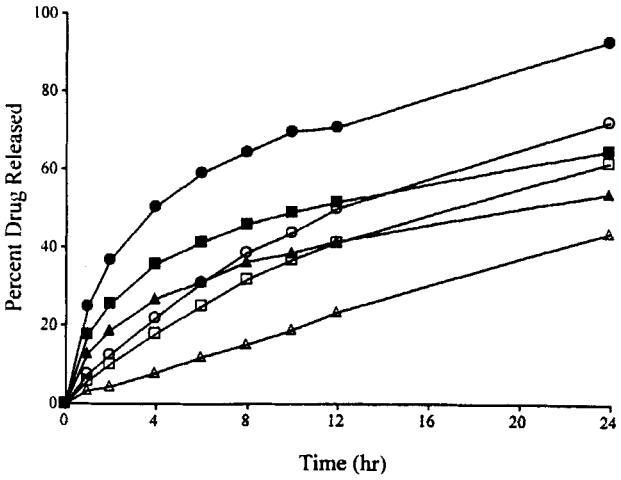



**Figure 5.** Dissolution profiles of the compacted (500 lb) versus noncompacted multilayered beads, ● = L6 (caplet), ○ = L6 (bead), ■ = L8 (caplet), □ = L8 (bead), ▲ = L10 (caplet), Δ = L10 (bead).

50% APAP in about 30 min, 70% in about 2.7 hr, and about 90% in just under 5 hr. This example therefore shows that polymer-coated drug particulates can contain one or more additional layers of drug, polymer coats, and excipients, and be directly compressed into a compact which will disintegrate in gastrointestinal fluids, providing a useful drug release pattern. This system has many advantages over the system described in U.S. patent 4,820,522. The 4,820,522 patent indicates that use

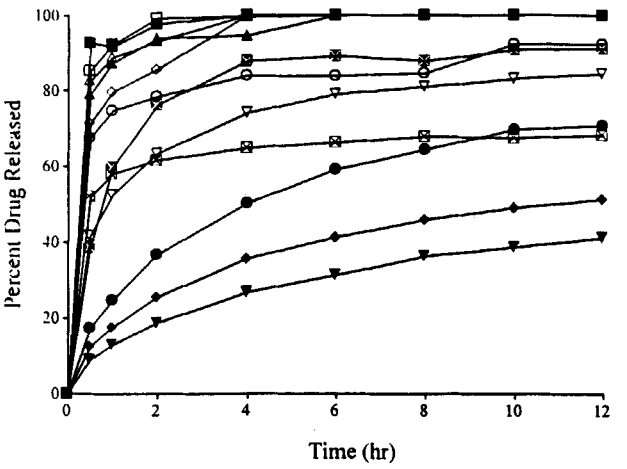



**Figure 6.** Multilayered beads compressed at 500 lb: Effect of drug release from intact (ic) and crushed caplets (cc). ■ = L5 (ic), □ = L5 (cc), ● = L6 (ic), ○ = L6 (cc), ▲ = L7 (ic), Δ = L7 (cc), ● = L8 (ic), ◇ = L8 (cc), ■ = L9 (ic), ⊠ = L9 (cc), ▼ = L10 (ic), ∇ = L10 (cc).

of a bilayer tablet containing both an immediate-release and a sustained-release layer is preferable. Multiple-layer beads are easy to produce using standard spray-coating equipment, but multiple-layer tablets require specialized tableting equipment not routinely available. Direct compression of ingredients is preferred over wet granulation in manufacturing because wet granulation requires drying, sieving, blending, and milling, which are all costly steps and errors can be introduced at each step. Particle sizes must be carefully controlled to avoid segregation during production. The current system eliminates these steps. In addition, the current system produced a product wherein APAP release from the intact compressed caplet and the crushed caplet resulted in similar drug release. This is a distinct advantage over the formulation in the 4,820,522 patent because crushing the product of the 4,820,522 patent destroys the controlled-release matrix. Tablets that are crushed prior to being swallowed are advantageous for the elderly and pediatric population, and for many others who have trouble swallowing compacts.

### Avicel-Coated Formulations

The current study also investigated the use of Avicel PH-101 as a spray-coated cushioning agent over the drug-layered, polymer-coated beads. Figure 7 shows a cross-section of the theoretical 80% (AV4 in Table 2) by

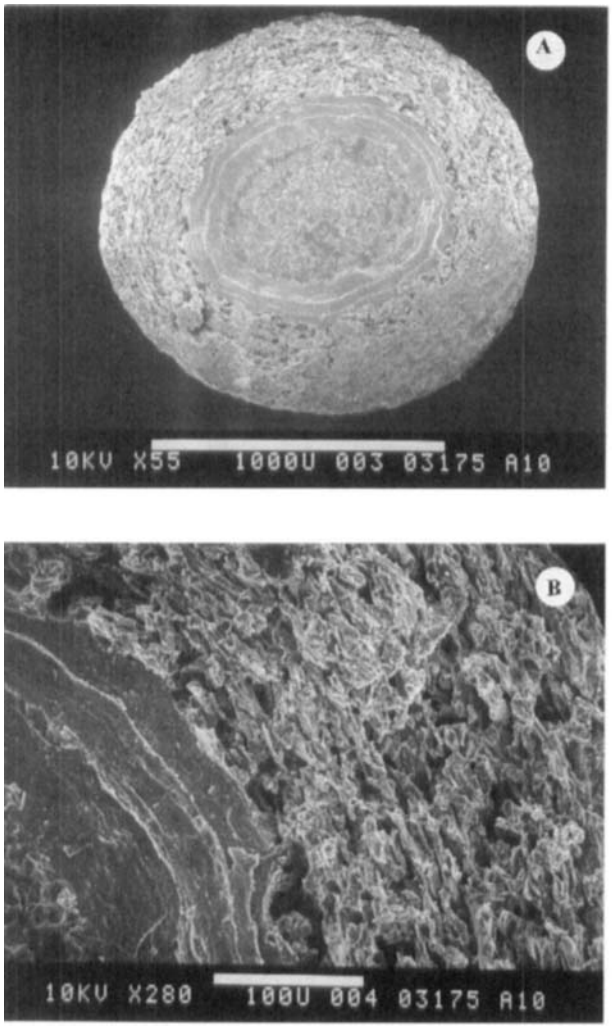



**Figure 7.** SEMs of the cross section of noncompacted Avicel PH-101 coated multilayered bead; magnification (a) = 55 and (b) = 280.

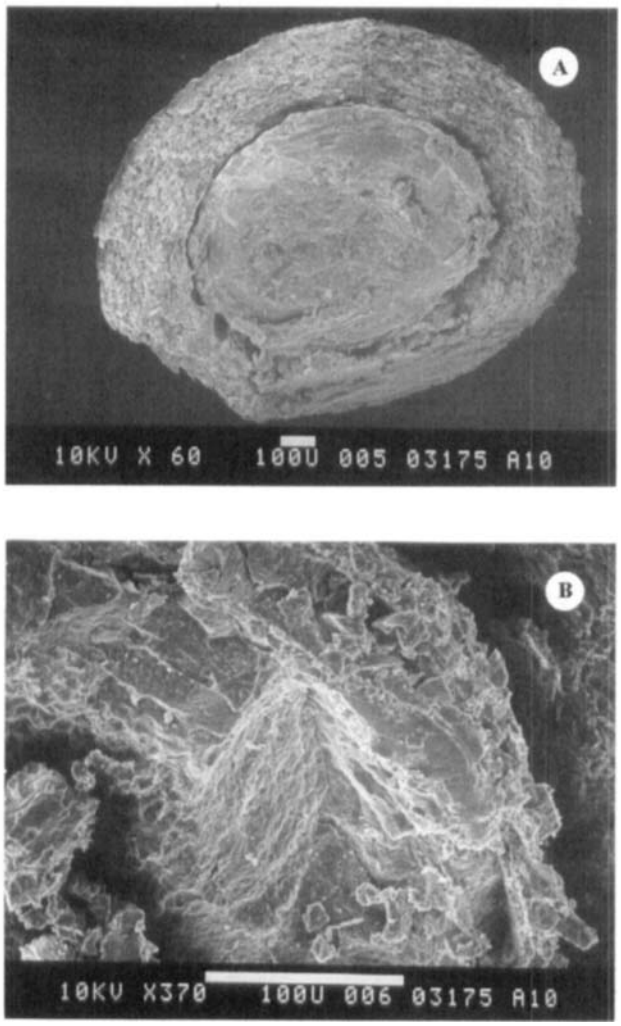



**Figure 8.** SEMs of the cross section of deformed Avicel PH-101 coated multilayered bead upon compaction at 100 lb; magnification (a) = 60 and (b) = 370.

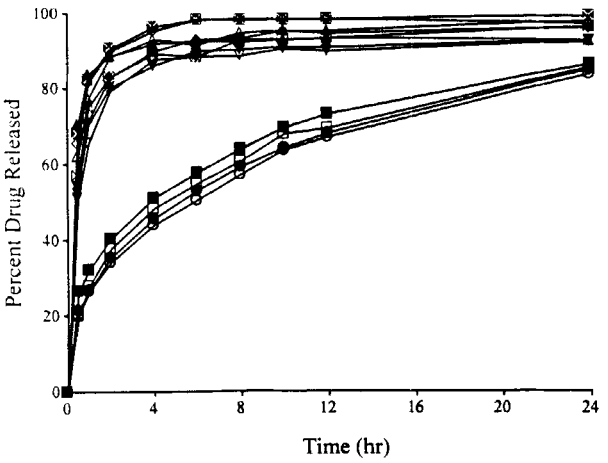



**Figure 9.** Effect of Avicel PH-101 coating as cushioning excipient on drug release from compressed multilayered beads. ■ = AV1, □ = AV2, ● = AV3, ○ = AV4, ▲ = AV1 at 100 lb, Δ = AV2 at 100 lb, ◆ = AV3 at 100 lb, ◇ = AV1 + AV2 at 100 lb, ⊠ = AV1 + AV3 at 500 lb, ⊠ = AV2 + AV3 at 100 lb, ▼ = AV2 + AV4 at 500 lb, ∇ = AV3 + AV4 at 500 lb.

weight Avicel-coated noncompacted beads. Distinct drug, polymer, and Avicel layers are observed. Upon compaction at 100 lb pressure, once again deformation of the bead and densification of the drug/polymer layers were observed (Fig. 8). Dissolution results show loss of sustained release properties upon compaction with total drug released in 4 hr (Fig. 9), indicating that all polymer coats in these multilayered beads were disrupted. However, a sufficient amount of coatings remained in place to control release of drug such that there was 70% release at about 50 min and 90% release in about 2–6 hr. These compacts readily disintegrate (less than 20 min in the dissolution test) and can be crushed prior to swallowing. Again, this is of significant value for the many elderly and pediatric patients who have difficulty swallowing.

Because of the larger size beads, i.e., 10/20 mesh, especially with 80% Avicel-coated beads as in the case of 10-layered multilayered beads, it was difficult to make physically stable caplets at lower pressures. This is possibly because of a decrease in the number of potential bonding sites among the crushed and deformed beads that occur because of the smaller surface-to-volume ratio of the larger beads (5). Thus, a mixture of different percentage Avicel-coated beads was also compacted, in which smaller beads would fill in the voids to form caplets. For some combinations of Avicel-coated beads, a pressure of 500 lb was required to produce physically stable caplets. The percentage of Avicel coating on beads did not produce any significant effect on drug release from either noncompacted or compacted beads (Fig. 9).

## Triple-Layer Caplets (TLC)

Triple-layered caplets (TLCs) were also evaluated, for which the top and bottom layers were postulated to provide the cushion effect for the polymer-coated beads in the center layer. Avicel PH-101 or polyethylene oxide (PEO) were used as cushioning excipients for the two outer layers.

The caplets made with PEO layers produced decreased drug release with an increase in pressure (Fig. 10). Formulation A beads (see Table 3) were used to make TLC with PEO. The beads were compressed into TLCs using about 16% PEO each as top and bottom layer. As shown in Fig. 10, there is a lag time of 1 hr before the drug is released from the swollen PEO layers. The PEO swelled to almost twice the size of the original caplet and formed a translucent ghost barrier for drug release. The TLC made at 50 lb pressure disintegrated into two relatively large chunks with approximately 25% of the beads separated from the translucent gel after 2 hr. This is evident from the sharp rise in the drug-release profile, with 70% drug released in 4 hr. The layers from caplets made at 100 and 250 lb pressure fell apart after 2 hr and the bottom layer stuck to the bottom of the dis-

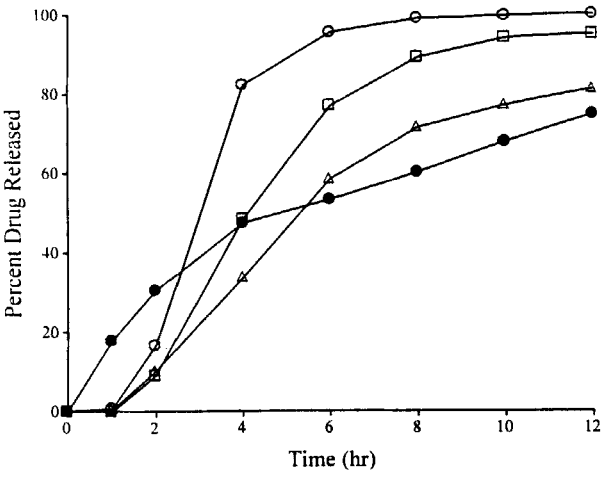



**Figure 10.** Triple-layered caplets: Effect of pressure with PEO layers (33%) on drug release from compressed beads. ● = Uncompacted beads, ○ = 50 lb, □ = 250 lb, Δ = 500 lb.

*Table 3*

*Percentage Compositions for the Various Bead Formulations for Triple-Layered Compacts*

| Formulation Ingredient | A (%) | B (%) | C (%) |
|---|---|---|---|
| Nupariel beads | 31.5 | 32.75 | 40 |
| APAP | 31.5 | 32.75 | 40 |
| Aquacoat | 9 | 14.5 | 20 |
| APAP | 19 | – | – |
| Aquacoat | 9 | – | – |
| PEG 8000 | – | 20 | – |

APAP = Acetaminophen, APAP solution for all layers was prepared in hydroxypropylcellulose (2.2%):poly(vinylpyrrolidone) (4.5%); Aquacoat dispersions were added with 30% w/w plasticizer (dibutyl sebacate/triethyl citrate, 1:1).

solution flask, while the remainder of the caplet, with the top PEO layer still attached to the center layer, swirled under the paddle. The caplets made at 500 lb pressure were intact throughout the dissolution. All PEO-based TLCs, except the one made at 500 lb, disintegrated into distinct individual beads. Drug release from PEO-based matrix tablets can therefore be controlled by swelling and diffusion of the polymer as reported by Cherng-Ju Kim (13).

TLCs were also made with 15% Avicel or 15% PEO each as top and bottom layer using formulation B beads (Table 3). Almost all of the TLC made with Avicel as

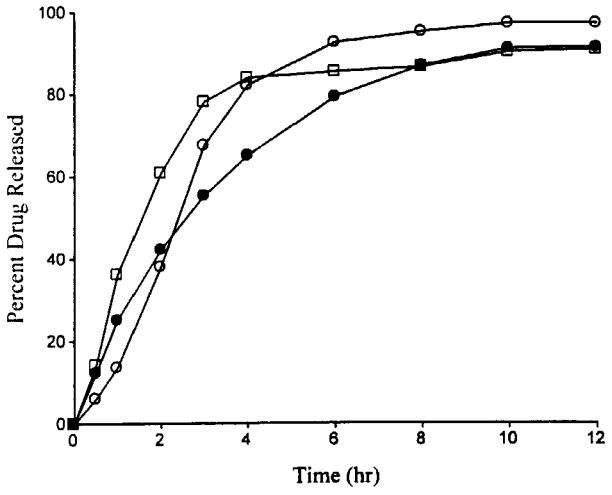



**Figure 11.** Triple-layered caplets: Effect of Avicel and PEO layers on formulation C compressed beads. ● = Uncompacted beads, ○ = Avicel 20% at 500 lb □ = PEO 20% at 500 lb.

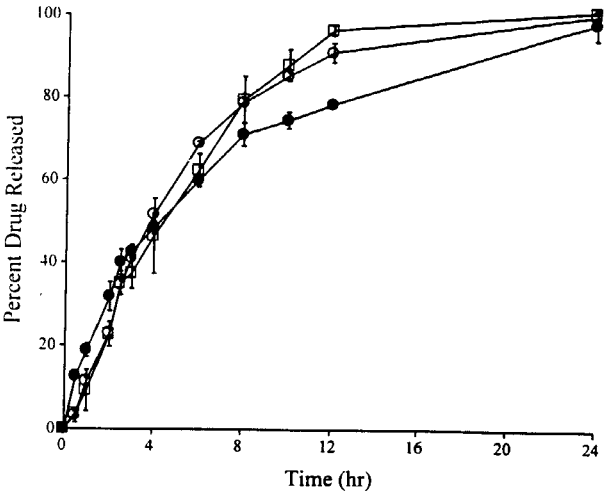



**Figure 12.** Triple-layered caplets: Effect of Avicel and PEO layers on formulation E compressed beads. ● = Uncompacted beads, ○ = Avicel 20% at 300 lb □ = PEO 20% at 300 lb.

the outer layers started to disintegrate immediately with the top and bottom Avicel layers falling apart. The center layer was intact for at least 4 hr, at which time it was completely or partially disintegrated into smaller chunks. Figure 11 shows that TLC made with Avicel released total drug in 4 hr, and for PEO-based TLC, it took about 8 hr for the total drug to be released. However, when TLCs were made using formulation C beads (Table 3), there was an insignificant difference in drug release from the beads compressed with Avicel and those with PEO layers (Fig. 12).

## CONCLUSIONS

The effect of compression on multilayered beads was investigated and it was found that the amount of polymer coating, compression pressure, bead size, number of layers, and type of cushioning excipient were important factors which affected drug release characteristics. It was also shown that polymer-coated drug particulates can contain one or more additional layers of drug, polymer coats, and excipients, and be directly compressed into a compact, which will disintegrate in gastrointestinal fluids, providing a useful drug release pattern. The present technique allows for controlling the immediate release-to-controlled release ratio of drug through selection of the layer(s) containing drug. Different amounts or ratios of active ingredients can be "buried" in the core or applied only to the surface layer if desired to obtain a pre-

ferred drug release rate. Although upon compaction, permanent deformation of the beads was observed and some polymer coats were broken, spray-coating of the cushioning excipient onto beads provided an effective way to circumvent segregation issues associated with mixing of the polymer-coated beads and powdered or spherical/nonspherical cushioning excipients. Spray-coating of the cushioning excipient also provided excellent flow properties of the final formulation as visually observed in our experiments. It is concluded that drug-coated beads can be layered with excipients such as Avicel and mannitol. TLCs can be optimized for useful sustained-release polymer-coated bead compacts.

## ACKNOWLEDGMENTS

This research forms part of the doctoral dissertation submitted by Syed A. Altaf to the Graduate School at Oregon State University. The authors wish to thank Eli Lilly and Company for partial financial support. The authors would also like to thank Al Soldner for the SEM work, and FMC Corp. and Crompton and Knowles Corp. for the generous donation of excipient samples and sugar spheres, respectively.

## REFERENCES

1. M. Juslin, L. Turakka, and P. Puumalainen, *Pharm. Ind.*, 42, 829 (1980).
2. R.-K. Chang and E. M. Rudnic, *Int. J. Pharm.*, 70, 261–270 (1991).
3. S. R. Béchard and J. C. Leroux, *Drug. Dev. Ind. Pharm.*, 18(18), 1927–1944 (1992).
4. L. Maganti and M. Celik, *Int. J. Pharm.*, 103, 55–67 (1994).
5. M. Celik, in *Multiparticulate Oral Drug Delivery*, Marcel Dekker Inc., New York, 1994, pp. 181–215.
6. R. Ruiz, A. Sakr, and O. L. Sprockel, *Drug Dev. Ind. Pharm.*, 16(11), 1829–1842 (1990).
7. H. A. M. Sayed and J. C. Price, *Drug. Dev. Ind. Pharm.*, 12(4), 577–587 (1986).
8. J. J. Torrado and L. L. Augsburger, *Int. J. Pharm.*, 106, 149–155 (1994).
9. M. Celik and L. Maganti, *Drug. Dev. Ind. Pharm.*, 20(20), 3151–3173 (1994).
10. M. E. Aulton, A. M. Dyer, and K. A. Khan, *Drug. Dev. Ind. Pharm.*, 20(20), 3069–3104 (1994).
11. G. Ragnarsson, A. Sandberg, U. E. Jonsson, and J. Sjögren, *Drug. Dev. Ind. Pharm.*, 13(9–11), 1495–1509 (1987).
12. Colorcon® Bulletin, West Point, PA, 1994.
13. C.-J. Kim, J. Pharm. Sci., 84(3), 303–306 (1995).