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RESEARCH PAPER

Bead Compacts. II. Evaluation of Rapidly Disintegrating Nonsegregating Compressed Bead Formulations

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ABSTRACT

In this study, three techniques for the prevention or mitigation of polymer coat fracture on compaction of sustained-release beads into tablets were investigated. All techniques in this paper were evaluated without the addition of any cushioning excipients, but rather by spray coating these excipients to avoid segregation during product manufacturing. First, it was shown that use of swellable polymers such as polyethylene oxide (PEO) serves a unique and effective role in preventing polymer coat rupture. PEO was spray coated between the ethylcellulose (EC) and microcrystalline cellulose (MCC) coats to evaluate its cushioning effect. The compacted PEO layered beads, on dissolution, disintegrated into individual beads with sustained drug release of up to 8 hr. It is postulated that the PEO was hydrated and formed a gel that acts as a sealant for the cracks formed in the ruptured polymer coating (sealant-effect compacts). Second, EC-coated drug-layered beads were also overcoated with cushioning excipients such as polyethylene glycol (PEG) and MCC with an additional coating of a disintegrant. These beads were compressed at pressures of 125, 500, and 1000 pounds into caplets and, on dissolution testing, disintegrated into individual beads when the dissolution medium was switched from simulated gastric to intestinal fluid. The dissolution profiles show that the polymer coat was partly disrupted on compaction, leading to a total drug release in 8–10 hr. Third, EC-coated beads were also granulated with cushioning excipient and compressed.

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This approach also resulted in a ruptured polymer coat on the beads, but at higher compaction pressure produced a partially disintegrating matrix caplet that showed a nearly zero-order sustained drug release for 24 hr. The effect of bead size and polymer coat thickness was also investigated.

INTRODUCTION

Different techniques have been employed to develop dispersible sustained-release compressed bead formulations (1,2). In the case of a dispersed system, polymer coat integrity, as well as rapid disintegration of the compressed beads, is required. The rapid disintegration of a compressed bead formulation into its individual units has the advantages of preventing dose dumping and product tampering, lower production cost than capsules, and ease of esophageal transport associated with capsules. These systems include the compaction of polymer-coated beads into tablets (3–10), use of an emulsion-solvent evaporation technique to produce microcapsules (11–13), use of extrusion/marumerization technology for bead manufacture (14,15), coated-particle compacts (16), use of melt granulation technique for individual dose units (17), and use of microencapsulation technique (18–20). Most of the above methods require the use of cushioning agents that are mixed with the polymer-coated beads or particles before compression, which allows for rapid disintegration into individual beads. One possible disadvantage of this method that has not been stressed or investigated in the literature is that of segregation of polymer-coated beads or granules from cushioning excipients during normal production. This problem could arise during the scale-up of the process, for which segregation of the two different particle size materials is well documented (21,22).

The use of microcrystalline cellulose (MCC) as a cushioning agent in powder form (5,8,9), in the form of spheres (11), and as granules (16) has been investigated for the 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, Dyer, and Khan (4), the use of placebo spheres requires additional consideration of factors such as sphere density and strength. 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 on scale-up. Ragnarsson et al. (3) were able to develop a rapidly disintegrating multiple-unit system comprised 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 MCC and polyethylene glycol (PEG 8000) has previously been spray coated on polymer-coated beads (8). These beads were then compacted without any additional tableting excipients, however, a nondisintegrating matrix tablet was achieved that provided sustained-release properties similar to those of the noncompacted polymer-coated beads.

The present study is an extension of an earlier study done by the authors (23) on the effects of compression on multilayered beads with alternating multiple layers of drug and polymer coats. This study proposes and evaluates three new design concepts for the compression of polymer-coated beads, they are (*a*) cushioning excipient effect, (*b*) sealant effect, and (*c*) granulated bead compacts; each of these design concepts is nonsegregating. The effects of cushioning excipient type, compaction pressure, polymer coat thickness, and bead size on drug release from the compressed bead formulations were investigated.

EXPERIMENTAL

Materials

Acetaminophen (APAP; 4-acetamidophenol) and dibutyl sebacate (DBS; sebacic acid dibutyl ester) were purchased from Sigma Chemical Company (St. Louis, MO). Polyvinylpyrrolidone (PVP) K-30 was supplied by E. M. Science (Gibbstown, NJ). Hydroxypropyl cellulose (HPC) type EXF NF was supplied by Aqualon (Wilmington, DE). Aquacoat® ECD-30 (ethylcellulose dispersion) and Avicel® PH-101 (MCC) samples were provided by FMC Corporation (Philadelphia, PA). Triethyl citrate (TEC) was purchased from Morflex Chemical Company Incorporated (Greensboro, NC). Polyethylene glycol (PEG 8000) and polyethylene oxide (PEO; Polyox N-3000) were supplied by Union Carbide Corporation (Danbury, CT). Sodium starch glycolate (Explotab) was supplied by Edward Mendell Company (Paterson, NJ). Nu-Pariel PG sugar spheres 25/30 and 45/60 mesh came from Crompton and Knowles Corporation (Pennsauken, NJ).

Coating Procedure

A weighed amount (100 g) of Nu-Pariel sugar beads were placed into the Aeromatic® (Niro, Columbia, MD)

Table 1

Weight Percentage Compositions for the Various Bead Formulations

Ingredient	Formulation, %						
	A	B	C	D	E	F	G
Nu-Pariel beads	42.75	32.75	40	30	27.5	22.5	28
APAP	42.75	32.75	40	30	27.5	22.5	28
Ethylcellulose (Aquacoat)	14.5	14.5	20	20	20	20	19
Polyethylene glycol (PEG 8000)	—	20	—	20	20	20	—
Polyethylene oxide (Polyox N3000)	—	—	—	—	—	—	10
Microcrystalline cellulose (Avicel PH-101)	—	—	—	—	—	10	10
Sodium starch glycolate (Explotab)	—	—	—	—	5	5	5

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

chamber of a fluid-bed spray coater with a Wurster column insert and fluidized for 20 min to equilibrate to the temperature (40°C) used in the coating process. The drug-binder solution was prepared by dissolving PVP and HPC (2 : 1) in ethanol (95%) followed by acetaminophen (final drug concentration 15%); this solution was then sprayed onto the beads. The drug-layered beads were then spray coated with different percentages by weight of the solids content of Aquacoat (with 30% plasticizer, DBS : TEC 1 : 1). The same process of coating drug, different polymer layers, cushioning excipients, and disintegrant was used for all the formulations studied (Table 1).

Bead Compaction and Dissolution Study

Caplets (1000 mg capsule-shaped tablets) were made on a Carver hydraulic press (Summit, NJ). Formulation G beads were also made using a single-punch press. The beads were compressed without the addition of any other filler material. Empirical observation showed these polymer-coated beads to have excellent flow characteristics, as observed by Connie and Hadley (24). Dissolution studies of the uncompacted and compacted beads were conducted using USP 23 dissolution apparatus II at 50 rpm with simulated gastric (pH 1.4 ± 0.1) and intestinal fluid (pH 7.4 ± 0.1) maintained at 37°C ± 0.5°C. Samples (5 ml aliquot) were collected with replacement and, after filtration and proper dilution, were analyzed with a UV spectrophotometer at $\lambda = 244$ nm.

RESULTS AND DISCUSSION

Effect of Coat Thickness

The effect of polymer coat thickness on drug release from different size beads compacted at different pressures was investigated. The following equation was used to predict the coating thickness for the two different size beads (25):

$$t = (W_W/W - W_W)\,(P/P_w)\,(d/6) \quad (1)$$

where

t = wall thickness
W_w = weight of wall (coating) material recovered
W = weight of coated particles taken
P_w = density of the encapsulated (core drug bead particles)
P = density of coating material
d = diameter of the uncoated particle

Using Eq. 1, a theoretical coat thickness of about 8 μm was obtained for a 6% polymer coat applied on drug-layered 25/30-mesh beads (bead size averaged). When the same 6% coating was used for the 40- and 60-mesh beads, Eq. 1 predicted polymer coat thicknesses of 5.17 μm and 3.04 μm, respectively. Based on Eq. 1, it was found that polymer coats of 9% and 14.5% were needed to achieve a coating thickness of around 8 μm on the 30/40- and 40/60-mesh beads, respectively. Because of smaller bead size, there is an increase in specific surface area; if the proper coating thickness is not applied, an increase in dissolution rate will be observed. Using larger beads means less polymer coat and therefore lesser control of release because the larger beads have a smaller specific surface area. Thus, to account for the bead size, Eq. 1 was used to calculate the amount of polymer needed to achieve the required polymer coat thickness.

Effect of Cushioning Excipients

To study the ability of cushioning excipients to minimize polymer coat fracture, various excipients, such as

PEG and MCC alone or in combination, were tested. A 20% PEG 8000 (formulation B) was spray coated over the 14.5% diffusional barrier coat (formulation A). PEG is a readily deformable material and was used to minimize the risk of polymer coat fracture. The glass transition temperature T_g of pure EC is 130°C, and with 30% plasticizer (DBS:TEC 1:1), it is 43°C when determined by differential scanning calorimetry (DSC). The PEG 8000 was spray coated below 43°C to prevent the beads from sticking to each other and to the Wurster column and Aeromatic chamber. The dissolution results are shown in Fig. 1, which shows that, for noncompacted beads, over 90% of the drug was released in 10 hr. However, the beads on compaction at 800 pounds produced a nondisintegrating matrix caplet that had a constant drug release for 12 hr of up to 80%, and the remaining 20% was released in the next 12-hr period.

Since the sustained-release property was lost, the diffusional release barrier EC was then coated at a 20% level (formulation C). These beads were then spray coated with 20% PEG 8000 as a cushioning agent to minimize fracture (formulation D). The beads were compacted at 300-pounds pressure, and as seen from Fig. 2, the release of drug was sustained for 6 hr, with 40% of the drug released in 6 hr, followed by the remaining 60% of the drug in the next 6 hr. The caplets disintegrated into individual beads after 4 hr. The same formulation, when compacted at 3150 pounds of force, produced nondisintegrating matrix formulations, and drug release was approximately zero order from 2 hr onward, with less than 20% drug release in the first 2 hr. The drug release from the noncompacted beads and caplets made at 3150 pounds pressure were very similar. This may be due to fusion of the polymer film at higher pressure, forming a nondisintegrating matrix caplet, thereby slowing the drug release.

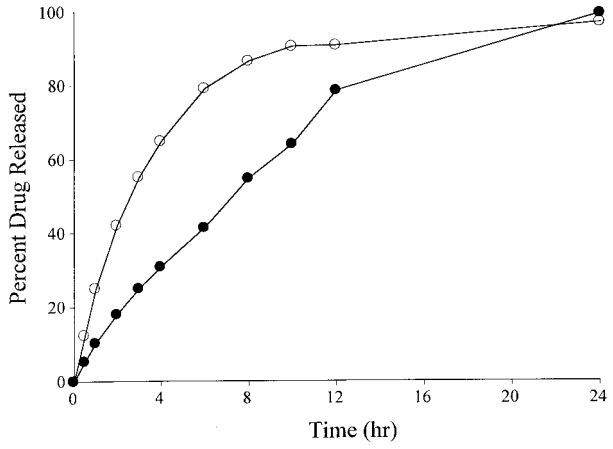

Figure 1. Effect of polyethylene glycol coat as a cushioning agent on drug release from compressed beads at different compaction pressures. ○ = Uncompacted beads, ● = compacted at 800 pounds.

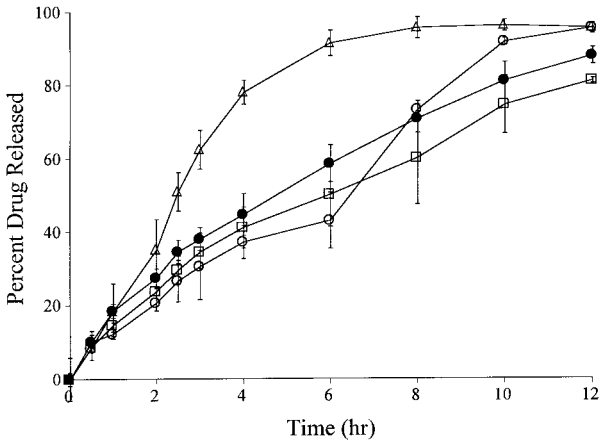

Figure 2. Effect of compaction pressure on drug release from formulation D and E compressed beads. ● = uncompacted beads, ○ = caplet at 300 pounds, □ = caplet at 3150 pounds, △ = formulation E at 200 pounds.

Formulation D had good sustained-release properties; however, the caplets did not disintegrate into individual beads. Hence, formulation E was prepared with a 5% superdisintegrant (Explotab [sodium starch glycolate]) hand mixed with the coated beads. A visual observation indicated some segregation of the superdisintegrant from the coated beads. The beads were compacted at 200 pounds of pressure. These compacts began to disintegrate within 0.5 hr and completely disintegrated into individual beads within 2 hr; however, about 80% of the drug was released at 4 hr (Fig. 2). The faster drug release may be attributed to the fact that, on compaction of beads, some of the powdered disintegrant may have entered the coating cracks, therefore allowing dissolution fluid to go in for rapid disintegration and drug dissolution.

To provide extra cushioning, a 10% MCC coat was spray layered, followed by the spray layering of a 5% disintegrant (formulation F). These beads were then compressed without the addition of any excipients into caplets at 125 to 1000 pounds of force. Figure 3 shows scanning electron micrographs (SEMs) of the formulation F noncompacted beads (Fig. 3a) and the beads compressed at 125 pounds of pressure (Fig. 3b). It is apparent from this figure that some of the beads remained intact on compaction, thereby maintaining the sustained-release

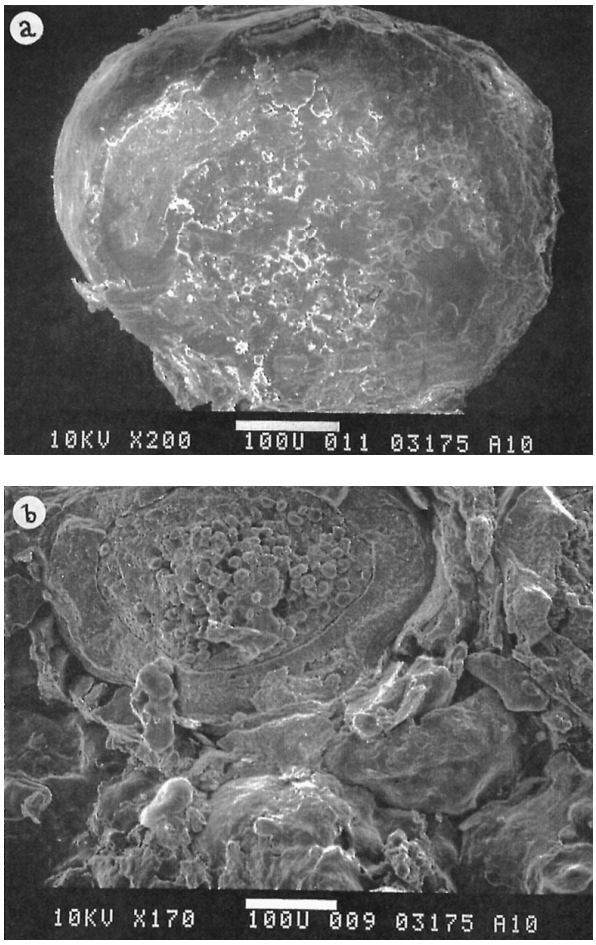

Figure 3. Scanning electron micographs of formulation F: (a) uncompacted beads and (b) beads compacted at 125 lb. pressure.

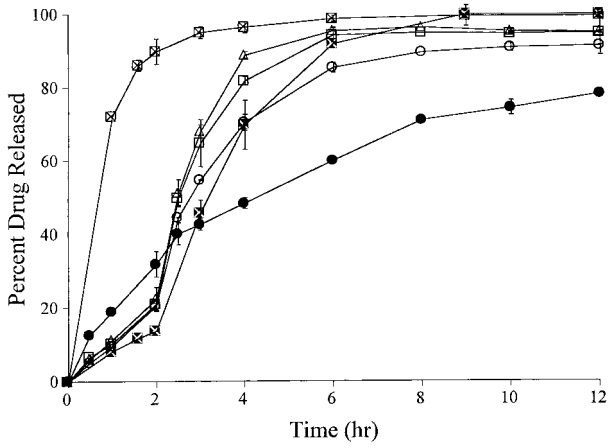

Figure 4. Effect of excipient/disintegrant coating on drug release from compressed formulation beads at different compaction pressures. ● = uncompacted beads, ○ = 125 pounds, □ = 500 pounds, △ = 1000 pounds, ⊠ = 5 kg hardness tablets, ⊠ = crushed tablets.

characteristics for a certain time period. The compacts disintegrated immediately on transfer from gastric fluid into intestinal fluid, demonstrating an immediate release and a controlled-release portion of drug, with total drug dissolved in 6–8 hours (Fig. 4). Formulation F was also compressed into a tablet on a single-punch press, which resulted in a hardness of 5 kg. The dissolution curve (Fig. 4) shows a delay in drug release for 2 hr and more than 90% of the drug released at 9 hr. All caplets disintegrated into individual beads at 2 hr when the simulated gastric fluid was replaced with simulated intestinal fluid, as can be seen from the sharp rise in drug release independent of compaction pressure. The tablets made at 5 kg hardness were crushed with a pill crusher and, on dissolution testing, showed rapid release of drug (Fig. 4), which indicates the polymer coat on the beads was ruptured during the crushing.

Thus, the results provided in Fig. 4 show that PEG provides very little advantage in protection against polymer coat rupture during compaction. PEG also has the disadvantage of producing a nondisintegrating matrix tablet. Nondisintegrating matrix tablet formulations cannot provide a readily flexible or adjustable ratio of immediate release portion of drug to sustained-release portion of drug. Application of the current method through addition of a layer of superdisintegrant or MCC, however, results in a disintegrating compact with a desirable drug release profile.

Sealant-Effect Compacts

Based on the dissolution profiles and SEMs in Figs. 1–4, it was realized that an excipient is needed that has some swelling properties, that is, a material like PEO, which will compress, but swell on contact with the dissolution fluid, thereby sealing the pores that may have been created due to fracture of the diffusional release barrier. Therefore, formulation G was prepared with 10% PEO underneath the MCC and disintegrant layer. Figure 5 shows the dissolution profile of spray-coated PEO beads and caplets. As evident from the dissolution profiles shown in Fig. 5, drug release from caplets is slower than from uncompacted beads for the first 2 hr; when the dissolution medium is changed from simulated gastric to in-

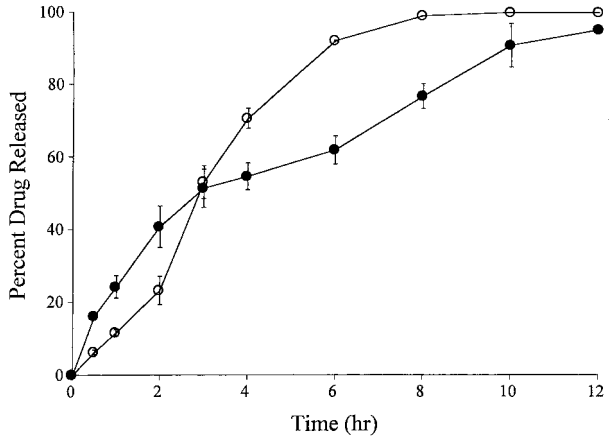

Figure 5. Effect of spray coated PEO on drug release from compressed beads. ● = uncompacted beads, ○ = 1000 pounds.

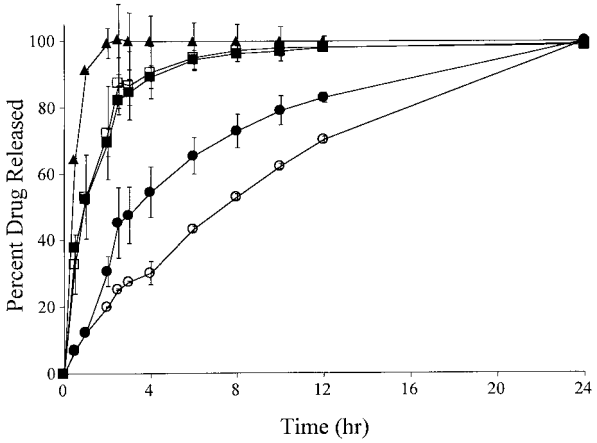

Figure 6. Granulated bead compacts: Effect of compression of Avicel-granulated polymer-coated beads on drug release. ● = Avicel-granulated formulation D beads at 250 pounds, ○ = Avicel-granulated formulation D beads at 500 pounds, ■ = Avicel granules + formulation C at 250 pounds, □ = Avicel granules + formulation D at 250 pounds, ▲ = Avicel-granulated formulation C at 250 pounds.

testinal fluid, an increase in the release rate from disintegrated caplets is observed, with total drug released in about 8 hr. All caplets disintegrated into individual beads within 20 min of dissolution testing. The PEO serves a unique and previously unknown function in maintaining controlled drug release from compacted beads, even though a nondisintegrating matrix tablet is not formed and the caplet formed does disintegrate rapidly in dissolution media. While the exact mechanism is unknown, it is postulated that PEO is hydrated and forms a gel that acts as a sealant for the cracks that form in the ruptured polymer coating.

Granulated Bead Compacts

Granulation of the polymer-coated beads with cushioning agent was also studied in an effort to avoid segregation and prevent fracture. The concept was that the granulating agent acts as a cushion between the beads and thus prevents polymer coat fracture on compression. The formulation C beads were wet granulated with 30% w/w MCC (26). The granulation was sieved and dried in a vacuum oven overnight. The screening of the dried granules produced less than 5% fines, and the granules obtained were physically stable. MCC granules alone were also made by hand mixing with the polymer-coated beads before compaction.

Figure 6 shows the dissolution profiles of MCC granulated bead compacts and hand-mixed MCC granules with formulation B and C bead compacts. As can be seen from Fig. 6, hand-mixed MCC granules with formulations B or C beads did not protect the polymer coat from fracture under low pressure; total drug was released in 4 hr. Also, when the formulation B beads were granulated with MCC, total drug was released in 2 hr. However, when formulation C beads were granulated with MCC, only 57% drug was released in 4 hr when compacted at a low pressure of 250 pounds. The same granulation, when compacted at 500 pounds of pressure, released only about 32% drug in 4 hr and produced an almost zero-order sustained-release profile for 24 hr. In both cases of MCC granulated beads, the caplets partially disintegrated into individual beads.

SUMMARY

Ragnarsson et al. (3) report that the stress induced when compacting coated pellets into tablets may disrupt the coating membrane, and an increase in particle size tends to give more rupture during tableting. However, with an EC coating of APAP beads, the coating ruptures when compacting beads of an initial size of about 45/60 mesh. All findings indicate that some of the EC coating was ruptured in this study. The small amount of MCC is an excellent binder when applied as an overcoat on the beads, allows direct compression of the beads without the use of large amounts of diluents, and avoids segregation problems, which can occur when different particle size and density materials are combined. In this case, only the final beads, and no additional powders, are needed for

compression. Larger-size drug beads can be used, which means a much larger amount of drug loading. In some cases, over 90% drug loading has been produced on sugar beads.

Application of the current method through addition of a layer of MCC and a superdisintegrant results in a disintegrating compact with a desirable drug release profile. The method of applying overcoats of tableting excipients can be applied to spheres that do not contain polymer coats. That is, drug-containing spheres without polymer coats are often produced by marumerization and are useful for immediate release of drug, but these spheres often do not form acceptable compacts (14). Thus, the formulation process presented herein of overcoating with a direct compression binder, a disintegrant, or both is useful for compacting spheres for rapid disintegration and the immediate and complete release of drug with no controlled-release component. This may be particularly useful for highly potent drugs, for which uniform mixing of small amounts of drug with large amounts of powders is problematic; by spray layering of accurately prepared solutions, precise control can be achieved. This technique may also be especially useful to maximize drug loading for large-dose drugs. Also, better flow properties can be achieved using only the coated beads alone without additional excipient during tablet compaction. The compact may be formulated and used in a manner in which the compact disintegrates either relatively rapidly or relatively slowly so that disintegration occurs during use or the compact may be crushed prior to use.

CONCLUSIONS

Segregation of polymer-coated beads in mixtures with cushioning excipients can be avoided by spray coating the cushioning excipients onto polymer-coated beads. The techniques evaluated in this study also allow for controlling the ratio of immediate release of drug relative to controlled release of drug through selection of the layer(s) containing the 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 preferred drug release rate.

It was shown that use of swellable polymers such as PEO is a unique and effective way to prevent polymer coat rupture; they act by hydrating on contact with the dissolution fluid and thereby seal the cracks formed during compaction. It was shown that the level of polymer coating, compression pressure, bead size, and type of cushioning excipient affect the drug release characteristics. The effect of polymer coat thickness when spray coating different size beads should be considered. Smaller-size beads compress to better producing, better quality caplets. Granulated bead compacts also lead to a useful nondisintegrating constant zero-order release matrix.

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