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Tableting of controlled release multiparticulates, the effect of millisphere size and protective overcoating

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Abstract

Controlled release enalapril millispheres of different diameters were prepared and tableted with excipients in a 1:1 ratio on a Carver press. Drug release rate profiles showed that the microporous coating on the millispheres was severely damaged during the compression process. Overcoating of the microporous coating with hydroxypropyl methylcellulose E5 (HPMC E5) protects the microporous coating during compression by absorbing and dissipating the compressional forces. This protection becomes more pronounced as the size of the millispheres is reduced. A novel investigation of individual millisphere strength was conducted to identify the most favorable coating and size combination which would preserve the controlled release properties of the millispheres. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Millispheres; Multiparticulates; Tableting of multiparticulates; Enalapril; Controlled release; Coating of multiparticulates; Millisphere crushing

1. Introduction

Controlled release drug delivery systems are being developed to provide once-a-day dosing for the convenience of the patient. Controlled drug delivery can also be used to eliminate high or spiking blood levels of drug, which can be associated with adverse reactions. The Spansule technology using millisphere dosage forms for controlled drug release has been in use for years. Other controlled release millisphere dosage forms employing different release mechanisms are also

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being used, e.g. Cardizem SR® and Cardizem CD® (Hoechst Marion Roussel). These two products are sold as hard gelatin capsules containing the millispheres. Another product, Seloken® ZOC (AB Astra), is a tablet containing controlled release millispheres of metoprolol succinate. The main advantage of tableting millispheres is that divided doses can easily be offered with a scored tablet. Tablets also have an advantage over capsules in being more tamper resistant.

Porter and Ghebre-Sellassie (1994) have reviewed the preparation of modified-release multiparticulates by film coating, aqueous polymer dispersions, and hot melts. Dressman et al. (1994) have reviewed the mechanisms of drug release from coated multiparticulates.

The compaction of multiparticulates, whether coated or not, has led to a variety of results. The formation of millispheres using microcrystalline cellulose by the extrusion/marumerization process can lead to a material which does not compress well when compared to tablets prepared from the non-spheronized material and different drug release profiles can be obtained by changing the core materials and/or hardness of the compact (Bechard and Leroux, 1992; Maganti and Celik, 1993; Aulton et al., 1994; Schwartz et al., 1994). Bansal et al. (1993) showed that coated niacin millispheres showed faster drug release profiles after tableting compared with the uncompressed millispheres and Maganti and Celik (1994) also found that coated pellets lost their sustained release characteristics on compaction. It has been reported that very small controlled release microspheres (i.e. spheres with diameters less than 500 μm) can be tableted with little change in drug release rates following tableting (Sayed and Price, 1986). The properties of the millisphere cores and the type and size of the excipients used to tablet them have also been shown to play a role in protecting them during tableting (Aulton, 1994; Dyer et al., 1994; Torrado and Augsburger, 1994).

This paper reports the effect of millisphere size and the use of a protective overcoating of hydroxypropyl methylcellulose on the tableting of controlled release enalapril millispheres prepared by the extrusion/marumerization process and coated with a microporous cellulose acetate butyrate coating.

Enalapril maleate is an angiotensin converting enzyme inhibitor (ACE inhibitor) used for the treatment of hypertension. It has a molecular weight of 492.5, is a white to off white powder of melting point 143–144.5°C and has a solubility in water of 25 mg/ml (Ip and Brenner, 1987).

2. Materials and methods

Enalapril maleate was from Merck, Avicel PH101 and PH200 from FMC, STA-Rx 1500 starch from Staley, fast flow lactose No. 316 from Foremost, lactose EP grade D10 (large particle size) from Meggle, magnesium stearate and sucrose from Spectrum, cellulose acetate butyrate from Eastman, hydroxypropyl methylcellulose E5 from Dow and triethyl citrate from Sigma; acetone and 95% ethanol were standard reagent grade.

3. Preparation of millispheres

The 0.5- and 0.7-mm millispheres were prepared by combining five 1-kg batches. The 1.0-mm millispheres were prepared in one large batch. Table 1 summarizes the materials and equipment used to prepare the millispheres.

Table 1
Materials and equipment used to prepare millispheres

Formulation	1-kg batch (0.5- and 0.7-mm Spheres) (g)	22-kg batch (1.0-mm Spheres) (g)
Enalapril maleate	33.6	739.2
Sodium bicarbonate	17.5	385
Avicel PH-101	210	4620
Corn starch	70	1540
Lactose	195	4290
Water	300	6600
Equipment		
High shear mixer	Fukae LFS-GS-2J	60L fielder
Extruder	Luwa EXKS-1	Luwa twin screw
Marumerizer	Luwa AJ230	Luwa M230
Fluid bed dryer	Scientific products	Glatt WSG-15

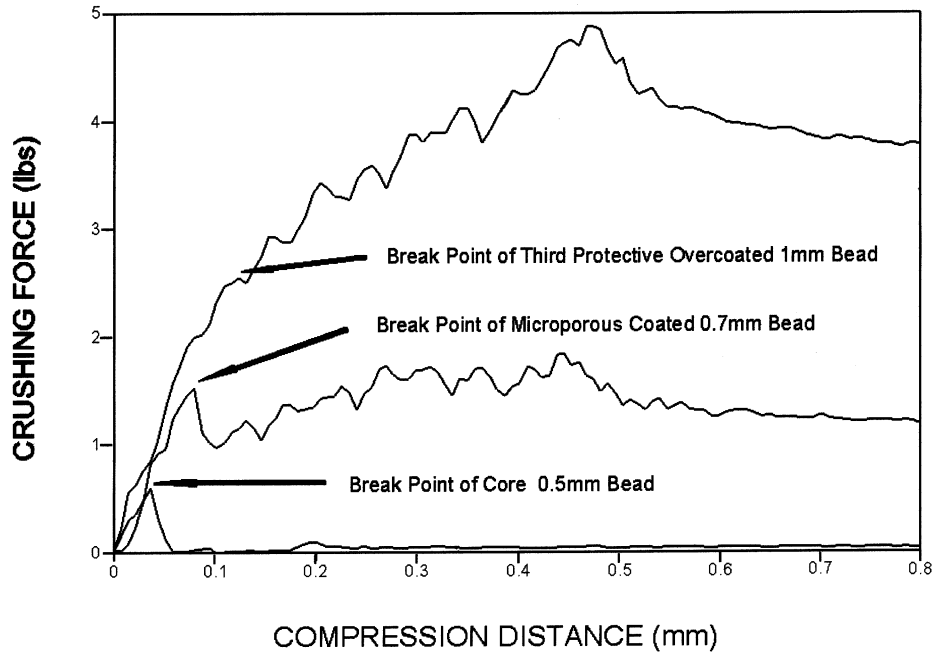

Fig. 1. Representative force profiles for core, microporous-coated, and HPMC-overcoated millispheres.

The granulating solution for the small batches was prepared by suspending the enalapril maleate in the water in a 2-L beaker and adding the sodium bicarbonate in 2-g aliquots with stirring; subsequent aliquots were added when the foaming receded. This process was repeated until all the bicarbonate had been added. The remaining powders were placed in the high shear mixer and mixed for 2 min with the agitator at 250 rpm. The granulating solution was added over a 4-min interval with the agitator speed increased to 500 rpm and the chopper speed held at 1000 rpm.

Granulation continued for an additional 2 min at these conditions. Two batches were combined and extruded with a screw speed of 31 rpm and a screen size of 0.5 or 0.7 depending on the desired bead size. The material was marumerized at 1000 rpm plate speed for 4 min. The resulting beads were dried using an inlet air temperature of 80°C until the outlet temperature reached 70°C at which time the inlet temperature was lowered to 70°C. The beads were dried until the loss on drying (LOD, Max50, Arizona, oven temperature set at 105°C) was less than 1%. The beads were sieved through standard sieves in order to eliminate any large or small beads.

The 1-mm beads were prepared using the same ingredients and the same procedure; however, the batch size was 22 times larger, requiring larger equipment to process this batch. The granulation solution was prepared by adding aliquots of sodium bicarbonate to the suspended drug in a 15-l stainless steel pot with overhead stirring. Approximately 600 g of the extrudate were marumerized for 3 min in the marumerizer. Following the spheronization process the beads were dried to an LOD of less than 1% moisture.

4. Coating of millispheres

All the millispheres were coated using 2.5-kg batches in a Glatt GPCG-3 column coater. The coating solution consisted of the following: cellulose acetate butyrate (381-20, 360 g), sucrose (126 g), triethyl citrate (108 g), acetone (10 L), ethanol (2 L) and water (2 L). The coating conditions were: inlet air temperature, 50°C; outlet air tem-

Table 2
Average size and percentage of drug loading in the various millispheres

Designation of bead size	Actual average size (mm)	Standard sieve sizes used to retained beads	Percentage of drug by weight[a]
0.5	0.590	25, 30, 35, 40	5.46
0.7	0.702	20, 25, 30, 35	5.99
1.0	1.019	16, 18, 20, 25	6.31

[a] Determined spectrophotometrically at 210 nm in 0.05 M phosphate buffer at pH 7.5 using an extinction coefficient of 0.0426 l/mg cm. The beads were crushed and sonicated prior to analysis.

perature, 31–34°C; atomization air pressure, 2.2 bar; fluidizing air flow, 90–110 m^3/h; and coating rate, 40–45 g/min. The amount of coating applied to each size of bead was adjusted to achieve similar drug release rates. The amount of coating solution applied to the beads was 6033, 8180, and 13075 g for the 1-, 0.7- and 0.5-mm millispheres respectively. These values are within 10% of the theoretical amounts based on surface area differences needed to achieve the same coating thickness on the same initial weight of beads.

Overcoating of the microporous millispheres with hydroxypropyl methylcellulose E5 was done in a UniGlatt fluidized bed coater. The coating solution consisted of 160 g of hydroxypropyl methylcellulose E5 premium and 1 g of sodium lauryl sulfate in 4 L of water. About 3 L of water was heated to 80–90°C, and the hydroxypropyl methylcellulose E5 was added with stirring. Ice was added to lower the temperature, and more water was added to dilute to volume. An 800-g batch of millispheres was coated in the UniGlatt with an inlet temperature of 72–82°C, outlet temperature of 50°C, atomization air pressure of 1.4 bar, and an application rate of 10 ml/min. Static electricity on the millispheres provided some impediment to the even flow around the plexiglas windows, and there was some formation of doublets and triplets, especially with the smaller millispheres.

Table 3
Least-squares regression results from breaking force vs bead cross-sectional area plots

Designated size of millisphere (mm)	Coating type	Fitted line (N/mm^2)	Fitting coefficient
0.5	Core beads (none)	3.6	0.51
0.5	Microporous	4.1	0.13
0.5	1st HPMC overcoat	4.7	0.65
0.5	2nd HPMC overcoat	4.8	0.70
0.5	3rd HPMC overcoat	5.0	0.40
0.7	Core beads (none)	3.6	0.68
0.7	Microporous	3.6	0.79
0.7	1st HPMC overcoat	3.7	0.78
0.7	2nd HPMC overcoat	3.9	0.48
0.7	3rd HPMC overcoat	4.6	0.65
1	Core beads (none)	2.1	0.51
1	Microporous	2.2	0.70
1	1st HPMC overcoat	2.2	0.35
1	2nd HPMC overcoat	2.4	0.11
1	3rd HPMC overcoat	3.2	0.65

5. Measuring of drug release rates

Drug release profiles were measured using the standard USP dissolution apparatus set-up number 2 with a temperature of 37°C and 50 rpm paddle rotation. The release of drug was determined spectrophotometrically at 210 nm. The spectrum of enalapril maleate is pH dependent; therefore the dissolution media was buffered using 0.05 M phosphate buffer at pH 7.5. The buffer has some absorbance at 210 nm (~0.1), which remains constant throughout the run. The interference of all other excipients at this wavelength was determined and was shown to contribute less than 2% to the total absorbance. A peristaltic pump was used to circulate the dissolution media through the flow cells in the spectrophotometer at about 7 ml/min through a 5-μm, 25-mm diameter disposable syringe filter. Absorption readings were taken every 5 min over the 20-h run. Drug release percentages were calculated by dividing the absorbance at each time point by the absorbance of the sample when all the drug was released and multiplying by 100. Two dissolution samples were run for each millisphere or tablet and the average of the two runs is reported in the figures. The maximum deviation of any of the same two runs was 10% and for most runs less than 5%.

6. Millisphere crushing procedure

For each general breaking pressure test a sample of at least nine variously sized beads was selected so as to span the size range of the particular bead type. Beads of somewhat regular shape (i.e. no flattened, jagged, or double beads) were chosen so that the measurable minimum bead diameter would be representative of a bead's actual surface area and volume.

After selection, the minimum diameter of each bead was measured using a digital micrometer. The bead was then placed on the load sensor of the bead compression mechanism (see Section 7) and compressed to a depth appropriate to the bead's size. In the later tests of HPMC-overcoated beads, the final thickness of the bead was also measured, and the compressed bead was examined under a microscope, after dissolution of the HPMC overcoat, for breaks in the microporous coating.

The compression ram descended at a rate of 3.65 mm/s, which corresponded to a step rate of 920 Hz. As the ram compressed a bead, a profile of the force transmitted to the load sensor by the bead was produced. The load sensor sent a signal in millivolts to a SNAPSHOT Storage Scope (HEM Data), a digital oscilloscope and data storage hardware and software package, at a sample rate of 500 Hz—a rate that, by being half the step rate of the stepper motor, eliminated the signal noise caused by the motor's movement. SNAPSHOT displayed the results, which were analyzed on-screen, as a plot of volts versus scope sweep time. The load sensor's voltage output was later converted into units of force (pounds or Newtons) using the calibration data provided by the manufacturer. As a reference, at least one representative data set was saved to disk for each type of bead.

Using SNAPSHOT, the specific forces experienced by a bead were obtained by moving the cursor to the desired points in its force profile. A sudden drop in the force profile was taken as conclusive evidence that a bead had cracked. The core beads and microporous-coated beads usually shattered completely at their first failure point, leaving an obvious peak. In contrast, the HPMC-overcoated beads maintained their integrity and merely flattened as their inner microporous coatings and bead cores cracked and crumbled. As a result, the first failure point was much less dramatic, and the force profile quickly resumed its irregular rise. However, microscopic studies of overcoated bead appearance at various compression depths revealed that the first perceptible drop in the force profile provides an accurate indication of the first failure of the microporous coating. Therefore, first failure point was recorded along with the pre-compression baseline reading of the load sensor, and the difference between the two was considered the breaking force for the bead. Fig. 1 displays sample force profiles for core beads, microporous-coated, and HPMC-overcoated beads.

7. Description of crushing equipment

The bead compression equipment consisted of a cylindrical steel ram aligned vertically with a circular load sensor (PCB Piezotronics, Model # 200B01, Serial # 2507, calibration range: 0–10 lbs sensitive to 0.0002 lb). The load sensor served as the platform on which the beads were placed for compression; it was mounted on the horizontal base of an L-shaped heavy steel frame. The ram was driven by a stepper motor (Minebea, Astrosyn Miniangle Stepper Motor, Type 23LM-C304-15, 1.8°/step), which was mounted on the vertical part of the steel frame. The face of the ram and the face of the load sensor were the same size and shape, accurately aligned, and parallel and thus compressed the beads only in the direction of the ram movement.

The stepper motor was controlled by a software package (Arrick Robotics, MD-2 Dual Stepper Motor System). As mentioned above, data acquisition from the load sensor was also performed by software (HEM Data, SNAPSHOT Storage Scope, Version 2.61-8m).

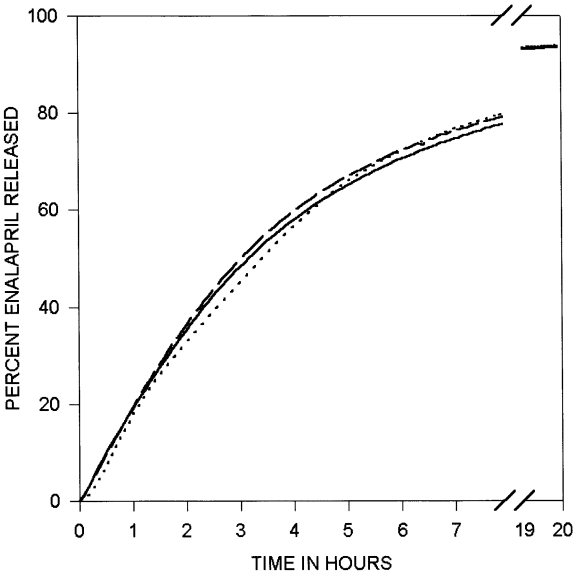

Fig. 2. Drug release profiles for three different sizes of millispheres coated with a microporous cellulose acetate butyrate coating. 0.5 mm (· · ·), 0.7 mm (– – –), 1 mm (——).

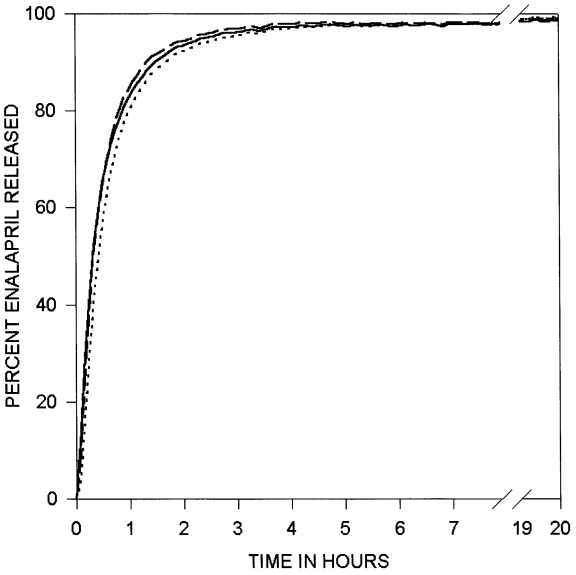

Fig. 3. Drug release profiles for tablets prepared from the three different sizes of microporous-coated millispheres. 0.5 mm (· · ·), 0.7 mm (– – –), 1 mm (——).

8. Results and discussion

The millispheres were sieved following the application of the microporous membrane. A 100-g aliquot was sieved through a series of standard mesh screens and the smallest and largest fractions were eliminated in order to achieve a tighter range of bead sizes. The discarded fractions represented less than 10% of the batch. Table 2 gives the average size for each group of beads. This value was determined by summing the fraction of beads retained on each of the sieves shown in the table multiplied by the average size of the opening (hole size of the next larger sieve minus the hole size of the sieve with the retained sample divided by two).

9. Crushing results

To determine a general strength parameter for a given type of bead (a necessity for comparing different coating and size groupings), the breaking force results for the sample were plotted against the bead cross-sectional areas. The slope of this

Table 4
Amount of overcoating applied percent weight increase

Designation of bead size (mm)	First HPMC overcoating (%)	Second HPMC overcoating (%)	Third HPMC overcoating (%)
0.5	10.9	17.4	27.7
0.7	13.1	20.5	28.1
1.0	10.2	18.0	25.7

type of plot is proportional to the pressure required to break the represented bead type. To ensure the comparability of the pressure-slope values, the lines were forced through the origin of the force versus area plots. This decision was based on overwhelming evidence, observed during early studies of core beads, that the 'breaking pressure' line consistently extrapolated near or at the origin. The microporous-coated beads also showed agreement with this trend, but the HPMC-overcoated beads tended to deviate towards a positive intercept. This positive intercept was taken as evidence of the protective ability of the overcoating. In any case, the common intercept allowed the slope to serve as a single parameter representing bead strength.

The individual bead compression tests produced encouragingly consistent results. The smaller beads showed significantly greater strength, relative to their size, than the largest (1 mm) beads. This relationship is displayed in Table 3 by the slope values, which are analogous to hypothetical breaking pressures. The smallest bead group (0.5 mm) was the strongest for its size, and all three bead types benefitted appreciably from overcoating. Based on these independent tests, overcoated 0.5 mm beads showed the greatest promise for surviving the tableting process intact.

10. Drug release results

Fig. 2 shows the untableted drug release profiles for each of the three sizes of beads coated with the microporous coating. All three sizes of beads had similar profiles (Average of two runs for each bead; maximum difference in the two release profiles was less than 5%).

The millispheres were tableted individually. The tablets were prepared by mixing equal amounts of beads with the excipient mixture taking precautions to prevent segregation and then compressing the mixture on a Carver Press to 1 metric ton using 3/8″ standard concave punches and die. The pressure was applied for approximately 3 s and then released. The tablets were prepared to contain the same amount of drug regardless of bead size. The amounts of beads used were: 279, 255 and 242 mg for the 0.5-, 0.7- and 1.0-mm beads, respectively. The excipient mix consisted of Avicel PH101, 36.7%; STA-Rx 1500 starch, 15.4%; lactose, 45.9% and magnesium stearate, 2%. The drug release profiles were determined for these tablets

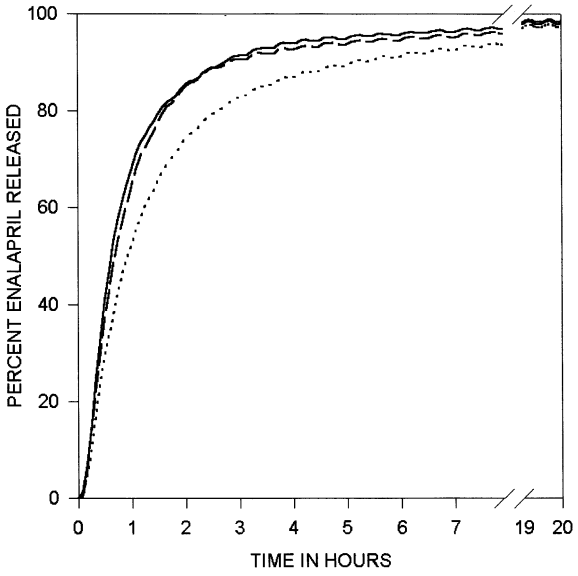

Fig. 4. Drug release profiles for tablets prepared from the three different sizes of millispheres and having the first protective overcoating of HPMC. 0.5 mm (· · ·), 0.7 mm (– – –), 1 mm (——).

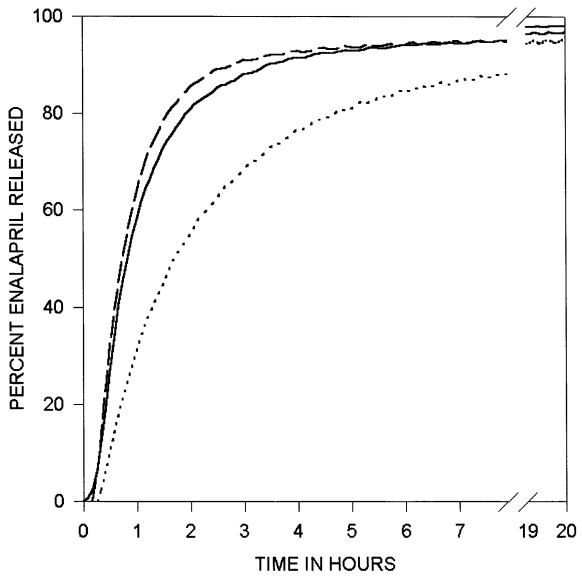

Fig. 5. Drug release profiles for tablets prepared from the three different sizes of millispheres and having the second protective overcoating of HPMC. 0.5 mm (· · ·), 0.7 mm (– – –), 1 mm (——).

as described in the methods section with the addition of a filter (Acrodisc, 5 μm) that was attached to the ends of the teflon tubes leading from the dissolution vessels. The filters were employed to remove any insoluble excipients before they reached the spectrophotometer cells. Fig. 3 shows that the microporous coating on the beads was greatly compromised by the tableting procedure with no differences between bead sizes. Tablets were also prepared and compressed at 1/4 metric ton, but the drug release profiles were almost the same as those for tablets compressed at 1 metric ton.

Overcoating of the microporous coated beads with a soft protective coating was introduced as a means of protecting the rate-determining coating during compression. A water soluble polymer which would dissolve from the beads rapidly and not interfere with the drug release properties of the microporous coating was investigated. Hydroxypropyl methylcellulose E5 was selected because it is water soluble, the coating is soft and pliable, and it is a common coating polymer. The microporous beads were coated at three different levels of coating in the UniGlatt coater as shown in Table 4. The amount of coating applied was calculated by comparing the drug contents of equal weights of the overcoated beads and the microporous beads. The drug contents were determined spectrophotometrically by crushing the beads and dissolving in phosphate buffer.

Figs. 4–6 show the release profiles of tablets prepared with the first, second and third overcoatings of HPMC. Tablets were prepared using equal weights of beads and excipient mix and were compressed to 1 metric ton. The larger the amount of overcoating, the less the microporous coating was compromised. Also, the smaller overcoated beads are less affected by the compression process than the large beads. These results correspond directly to the bead strengths indicated by the individual bead compression test results. Fig. 7 shows the release of drug from tablets prepared with the 1-mm millispheres at the three different protective overcoatings of HPMC for comparison. Each overcoating imparts a greater protection to the 1-mm millispheres.

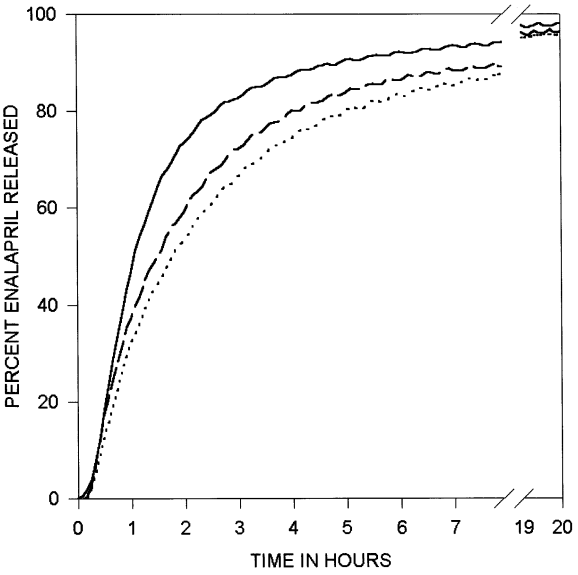

Fig. 6. Drug release profiles for tablets prepared from the three different sizes of millispheres and having the third protective overcoating of HPMC. 0.5 mm (· · ·), 0.7 mm (– – –), 1 mm (——).

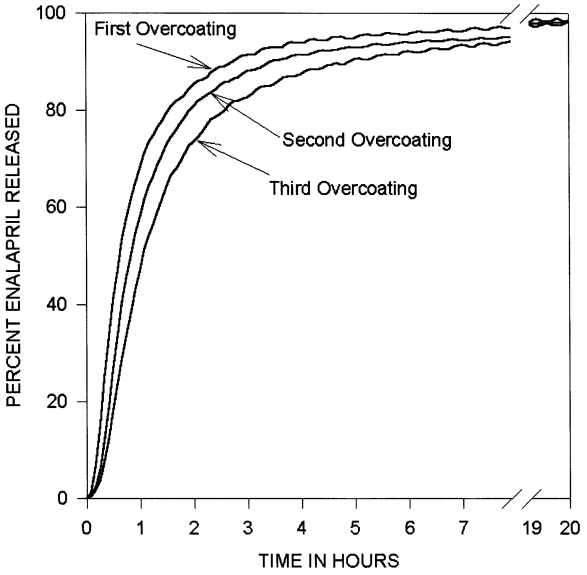

Fig. 7. Drug release profiles of tablets prepared with the 1-mm millispheres and coated with the first, second and third protective overcoating of HPMC.

It was reported by Aulton (1994) that controlled release millispheres were afforded more protection during tableting by large excipients. Avicel PH200 (FMC) and Meggle lactose EP, grade D10, are larger excipients and they were shown to be effective in reducing the effects of compression on controlled release millispheres. Avicel PH200 is a grade comprising relatively large particles (60 mesh NLT 10%, 100 mesh NLT 50%) compared to Avicel PH101 (60 mesh NMT 1%, 200 mesh NMT 30%) and Meggle lactose EP, grade D10 is a coarse-crystalline material (100% LT 20 mesh, 12–35% LT 40 mesh, 70 mesh NLT 25%, mean size about 500 μm) compared with Formost lactose 316 (60 mesh, 0–0.5%; 140 mesh, 25–50%; 200 mesh, 55–75%) These materials were substituted for their corresponding ingredients in the excipient mix, and tablets were prepared as described previously. The drug release profiles for these tablets are shown in Fig. 8 and demonstrate that the use of the larger excipients reduce the compression effects on the overcoated beads. The smallest beads continued to be the least affected by the tableting process and, in fact, their drug release profiles were similar to the profiles of the untableted beads.

11. Conclusions

This study has shown that a microporous coating consisting of cellulose acetate butyrate, sucrose and triethyl citrate does not survive the compression process with an excipient mix at 50% bead loading, presumably because the coating is brittle and fractures even at relatively low compression pressures. Application of an overcoating of HPMC to these beads does provide protection of the microporous coating. The results show that larger amounts of overcoating, especially on smaller beads, provide the best protection. This overcoating is quite soft and pliable and, from the crushing experiments, appears to protect the microporous coating through viscous deformation during the compression process.

Additional improvement can be achieved by tableting the beads with larger particle-size excipients. This apparently results in increased excipient–excipient interaction, which produces an environment in which the compression forces impact the beads less directly.

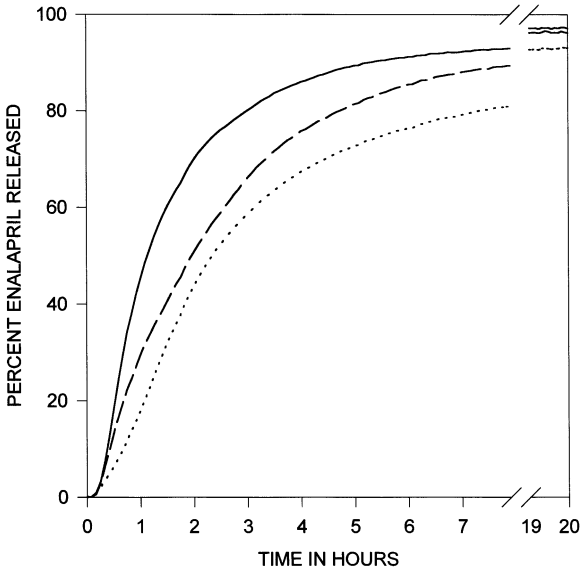

Fig. 8. Drug release profiles for tablets prepared from the three different sizes of millispheres and having the third protective overcoating of HPMC and tableted with the larger excipients (Avicel PH200 and Meggle lactose EP, grade D10). 0.5 mm (· · ·), 0.7 mm (– – –), 1 mm (——).

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