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Preparation of Controlled Release Spheronized Beads by a Simple Extrusion and Modified Spheronization Process

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Beads loaded with the water-soluble drug, phenylpropanolamine HCl (PPA), were prepared using an extruder and double arm counter-rotating roller modified from a traditional pill machine. The mean diameter of the cylindrical rod-like extrudate from the ram extruder was 3 mm; that of the uncoated bead after cutting and spheronization by the modified double arm counter-rotating roller was 3.26~3.28 mm. Although the surface of the beads was moderately rough and irregular, some exhibited hump-shaped protrusions, the sphericity was acceptable (roundness 1.15) and adequate for the subsequent coating process. An increase in mean diameter of the coated beads and improvements in friability and sphericity were observed in proportion to the amount of coating material applied (ethylcellulose or Eudragit® RS 100). It was also found that the release rate of PPA from the coated beads could be controlled by the amount and type of coating materials applied or with the incorporation of Eudragit® RS 100 into the core matrix. Further modifications to the double arm counter-rotating roller, including adjustment of the rotation speed and distance between the rollers, would yield smaller uncoated beads with improved roundness and surface roughness. In conclusion, the present method could be potentially applied to prepare controlled release drug delivery beads or pellet dosage forms.

Key words: Bead, Extrusion/spheronization, Extruder, Double arms counter-rotating roller, Pill, Controlled release

INTRODUCTION

Pills have long been part of both eastern and western cultures, but only recently have machines replaced traditional preparation methods. Herbal medicines were often pulverized, moistened, and then rubbed between the finger and palm of the hand to make a rounded pill that could be conveniently packaged, stored or administered (Hofman, 2002). Now, one form of mechanized production involves extrusion of a drug-containing wet mass, with subsequent spheronization. This type of pill machine is composed of an extruder and a pair of counter-rotating rollers, called a double arm counter-rotating roller. The extrusion and spheronization pill machines are still used for preparing herbal medicines, which are most often larger than 5 mm diameter, to form a non-crumbling, stiff and pliable mass. This is a horizontal pill forming machine widely used to manufacture small round herbal pills, such as honey pills, water and honey pills, extract powder pills and water pills (PharmaEquipment, 2001).

Extrusion followed by spheronization is a common technique for the production of pharmaceutical pellets or beads, with the process consisting of five general steps; blending, wet massing, extrusion, spheronization and drying, resulting in the formation of spherical pellets (Otsuka *et al.*, 1994). In this process, a wet mass is forced, or extruded, through die orifices and then shaped into small cylindrical particles. The size of the extrudate particles is determined as small lengths break under their own weight from the extruded mass (David *et al.*, 1997).

Extrusion devices are generally divided into the screw, roll and ram types. Screw extruders force the wet mass through the orifices by auger action. Roll extruders allow gravity to pull the wet mass into the nip area between two cylindrical rollers, and then force the wet mass through dies into hollows within these cylinders. Ram extruders are the oldest type, and feature a piston riding inside a

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cylinder or channel, which forces the wet mass through dies on the forward stroke. In the subsequent spheronization process, rounding of the extrudate particles depends on the friction generated between multiple particles and between the particles and equipment (Gandhi *et al.*, 1999). The spheronizer is thus machined to have a friction plate with a grooved surface.

Several processes have been employed for the production of drug-containing pellets, each of which has contributed to understanding the properties of the resulting pellets. Through experimental pellet production using extrusion and spheronization, pellet properties including hardness, roundness, surface smoothness, particle size distribution, and bulk and tap densities, were found to directly depend on aspects of the spheronizer, such as load, time, speed, and the type and composition of the grooved friction plate (Vervaet *et al.*, 1995; Barrau *et al.*, 1993). These same methods have been used to reveal the influences of drug and filler solubilities on the pellets physical characteristics (Sousa *et al.*, 2002). By contrast, the role of the water content of the wet mass has been investigated by comparing a twin screw extruder and a rotary ring die press (Christian *et al.*, 1998). Study of the rheological properties of the wet mass was necessary for the preparation of pellets when using extrusion and spheronization (MacRitchie *et al.*, 2002; Ramarao *et al.*, 1998). Finally, the process of hot melt extrusion and spheronization was developed for the manufacture of spherical pellets (Young *et al.*, 2002).

The present study employed a ram extruder for the initial extrusion step, and modified double arm counter-rotating rollers were then used for cutting of the rod-like extrudate and spheronization to form the beads (small pills). A cylinder of drug-containing material (150 mm long) was generated by the vertical motion of the piston of a ram extruder. Because of the strong plasticity and cohesiveness of the wet mass, gravity acting on the weight of this extrudate was not sufficient to break it into bead-sized pieces; rather, an additional mechanical force had to be applied. The double arm counter-rotating roller modified for this study had bowl-shaped furrows on the roller surfaces, such that the coming together of these half-spheres on two separate rollers would make a hollow of the desired size. This work was essentially a feasibility study for the production of beads smaller than those currently manufactured by extrusion and spheronization, with the aim of improving the controlled-release pellet drug delivery system.

MATERIALS AND METHODS

Materials and Instruments

The model drug, PPA, was obtained from Asia Chemical Company, Limited (Korea). Lactose (Pharmatose® 200 mesh) and corn starch were used as bead fillers. Ethylcellulose (49% ethoxy, 45 cps: Hayashi Pure Chemical Industry Ltd., Japan) and Eudragit® RS 100 (Rhom and Pharma Co., Germany) were used as coating materials. All other reagents were of commercial grade and used without further purification.

A laboratory-scale ram extruder (motor 2 p, 22.4 kJ/min, Changsung Industry, Korea), with a piston diameter and chamber length of 7.8 and 25 cm, respectively, was used to extrude the wet mass. The diameter and depth of the die orifices were 3 and 15 mm, respectively. A modified double arm counter-rotating roller (3" motor, 2 p, 22.4 kJ/min, Changsung Industry, Korea) was used for pelletization and spheronization. Preparation and evaluation of the beads was accomplished with a UV-1201 spectrophotometer (Shimadzu Cooperation, Japan), VK-7000 dissolution testing station, VK-750d heater and circulator (VanKel Industries Inc., NC, U.S.A.) and a laboratory pan spray coating system (Han Sung Engineering, Korea).

Pellet preparation

Two different compositions were used to prepare the core beads (Table I); (a) PPA and 2 w/w% polyvinylpyrrolidone (PVP) K-30, which were dissolved in the minimum amount of 10% ethanol solution for complete dissolution, and (b) A mixture containing PPA, 1 w/w% PVP K-30 and 1 w/w% Eudragit® RS 100, which were dissolved in the minimum amount of 50% ethanol solution.

Known proportions of lactose, corn starch and magnesium stearate were blended in a mixer (Kitchen Aid Inc., MI, U.S.A.) for 10 min, at roughly 30 rpm. The drug solutions were gradually added, and the mass mixed to homogeneity. The resultant mixtures were sealed in vials.

Approximately 50 g of the appropriate wet mass were extruded through orifices 3 mm in diameter, a 15 mm depth. The wet mass emerged from the die orifices as

Table I. Formulation conditions for the wet massing and coating solution

	S1	S2	S3	S4	S5	S6	S7
Ingredients	Quantity (w/w%) per bead						
PPA			10			10	
PVP K-30			2			1	
Lactose			82			82	
Corn starch			5			5	
Mg stearate			1			1	
Eudragit® RS 100						1	
	% Coating polymer in 95% ethanol						
Ethylcellulose (45 cps)	0	2.5	5			0	5
Eudragit® RS 100				2.5	5		

cylindrical rods, akin to spaghetti. When shark-skinned extrudate or short strands formed, the amount of 10% ethanol solution was adjusted to optimize the production of a smooth, long extrudate, which involved significant trial and error.

Schematics of the double arm counter-rotating roller and bead forming mechanism are shown in Fig. 1. The cylindrical rod-like extrudate was placed vertically in a position where the teeth of the two roller surfaces bit into each other (the two rollers had repeated semicircular pits of constant diameter, separated by protruding ridges; these hollows lay along the plane of roller, vertical to the axis of rotation). The two rollers maintained contact with each other and rotated in opposite directions. When the cylindrical strand of extrudate was put into the osculating plane of the rollers, parallel to the axis of rotation, the strand rotated in the same direction as the rollers. The optimal rpm of the two rollers was selected in a preliminary study (Jee *et al.*, 2004). The upper and lower rollers spun at 160 and 80 rpm, respectively, such that the extrudate was sliced by the protruding ridges and compressed into the semicircle pits. As a result, the cylindrical strand was transformed into beads of constant diameter.

A laboratory-scale pan spray coating system was used in this study. The coating process was initiated when the coating pan had achieved the desired temperature (50°C). This pan was rotated at 50 to 60 rpm, with the coating solution sprayed at 4 to 6 mL/min. Two concentrations of the two coating solutions were used: 2.5% and 5% ethylcellulose (45 cps)-ethanol (95%) and 2.5% and 5% Eudragit® RS 100-ethanol (95%). After coating, the beads were oven dried at 50°C for 4 h. The coating efficiency was calculated by the change in weight of the bead compared to the weight of coating solution sprayed.

Bead morphology

SEM was used to examine the surface and cross-section morphologies of the beads before and after coating. Briefly, beads were coated with a gold/palladium alloy using a sputter coater in a vacuum of 0.15 torr and at 6 to 7 mA. Samples were coated twice for 2 min to achieve continuous coverage, with an emission current of 20 mA and accretion voltage of 15 KeV.

Diameter, weight, density, friability, and roundness

The bead diameter was measured directly with calipers (estimated accuracy ± 0.05 mm). One hundred uncoated beads were weighed with an analytical balance (Denver instrument AA-160, CO, U.S.A.). The friability test was conducted by rotating 10 g of 6/7 mesh beads with 10 g of glass beads (4 mm diameter) in a PTFR-A friability tester (Pharma Test, Germany), at 25 rpm for 10 min, and then sieving the beads (Neau *et al.*, 2000). The percentage weight loss in the 6/7-mesh fraction was recorded as the friability, according to the following equation:

$$F = \frac{W_1 - W_2}{W_1} \times 100 \quad (1)$$

where F represents the percentage weight loss, W_1 and W_2 are the initial and final bead weights, respectively. The density of the beads was calculated by measuring the volume occupied by 10 g of beads in a graduated cylinder after tapping the cylinder with a 2 cm tapping-path length, 20 times. The bead roundness was calculated by computational analysis of a digital image (Scion Image, release beta 4.0.2 for Windows, Scion Corporation, MD, U.S.A.). This software computed the area and perimeter of a bead from its digital image. The roundness was then calculated from these values, according to expression (2)

$$\text{Roundness} = \frac{FP^2}{4\pi A} \quad (2)$$

where P is the perimeter of the bead image and A the area determined by the total number of pixels. The factor F corrects the perimeter for the cornering effect caused by digitization of the image. The value of F is not given by the software and thus was assumed to be unity. A roundness value of 1 corresponds to the image of a perfect sphere, with higher values corresponding to less spherical images (Rashid *et al.*, 2001).

Drug release studies

Dissolution testing of the PPA-containing beads was conducted using the USP XXV Apparatus 1 (basket method, VanKel VK7000, Cary, NC, U.S.A.) in 900 mL of pH 1.2 medium, at 37°C and 100 rpm. Samples of 5 mL were drawn at 0.5, 1, 2, 3, 4, and 5 h and filtered with a 0.45 μm PTFE filter (Whatman Inc., NJ, U.S.A.). Filtered samples were assayed by UV spectrophotometer at 257 nm.

RESULTS AND DISCUSSION

Preparation of beads

In this study, beads were prepared with a laboratory ram extruder and modified double arm counter-rotating roller (Fig. 1). A wet mass, containing known proportions of PPA, lactose, corn starch, PVP K-30 and magnesium stearate, was fed through a hopper into the ram extruder. As the wet mass passed through the die orifices, cylindrical rods, similar to strands of spaghetti, were formed. This extrudate was produced at constant force and speed. PVP K-30 was included in the mix to prevent the extrudate from breaking into short pieces. The long strands of extrudate were cut into regular sizes by the protruding ridges of the counter-rotating roller.

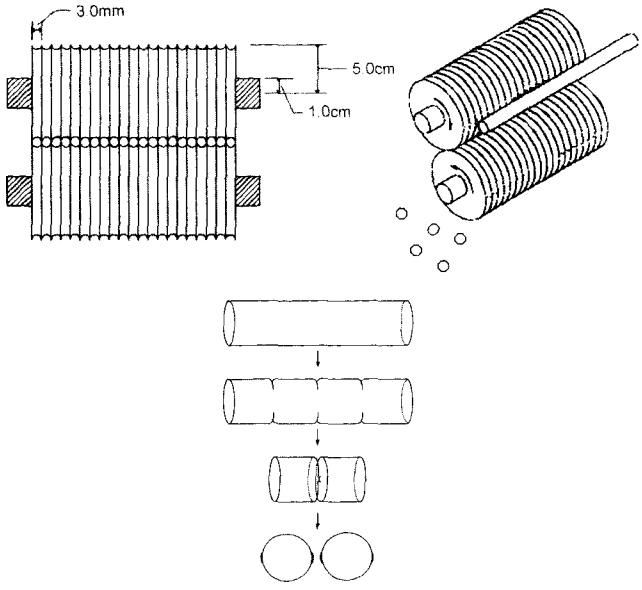

Fig. 1. Schematic of the modified double arm counter-rotating roller and bead-forming mechanism

With increasing amounts of binder (PVP K-30) in the mix, the extrudate demonstrated corresponding increasing plasticity. More importantly, this increase in plasticity provided resistance to the cutter ridges of the rollers, leaving the beads with nipple-shaped protrusions on their ends where the extrudate had not been cleanly sliced. As these short pieces of extrudate were spun in the groove between the two rollers, the protrusions became rounded and hump-shaped. Photographs of the extrudate prepared by the ram extruder, and of the beads before and after the coating process, are shown in Fig. 2. SEM micrographs of the beads are shown in Fig. 3.

Bead quality

Several physical properties of the beads prepared in this study are presented in Table II. The mean diameter of the uncoated beads was expected to be 2.9 to 3.1 mm, based on the diameter of the dies, but the particle sizes were found to be somewhat larger than this estimation. While the mean diameter of the extrudate directly from the ram extruder was approximately 3 mm, the mechanical force applied by the projecting ridges on the rollers was not completely efficient in pushing the extrudate into the adjoining hollows, but instead caused an effective reduction of the extrudate content of the beads. In the worst cases, a central cavity was formed at the mid-point of the rod cross-section, resulting in broken beads.

The size distributions of the uncoated and coated beads are shown in Fig. 4. Size measurement revealed that 15% of uncoated beads fell within the range 3.0 to 3.1 mm, while 35% fell within the range 3.3 to 3.4 mm (this represented the most common size range for uncoated beads). Overall, the size distribution of the uncoated beads was irregular, and as a result the coated beads also exhibited an irregular size distribution.

The results presented here suggest that spheronization, by cutting and rolling of a rod-like extrudate, using a

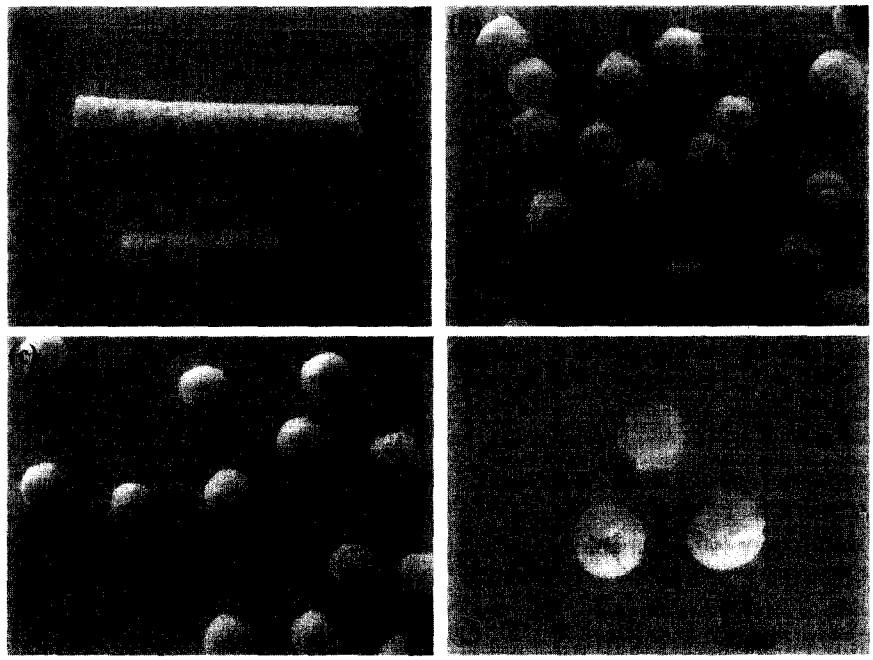

Fig. 2. Photographs of the extrudate prepared by the ram extruder, and the beads before and after the coating process; (a) extrudate, (b) uncoated beads, (c) coated beads (5% ethylcellulose) and (d) uncoated beads with protrusions or central cavities on both sides, top and lower left; broken uncoated bead, lower right

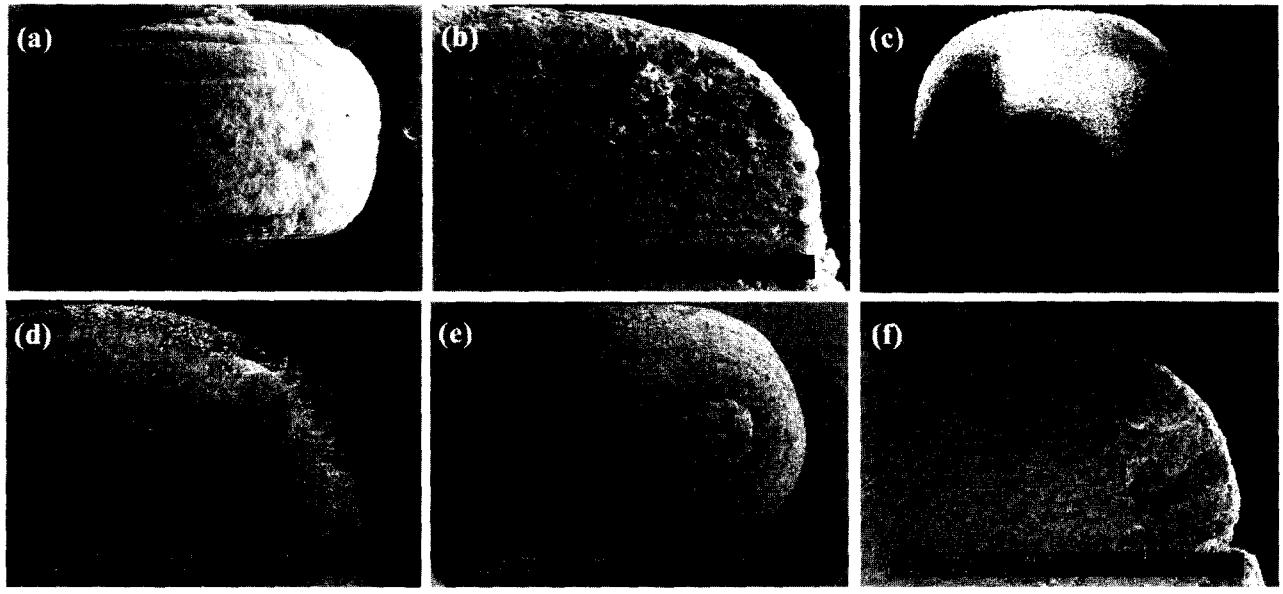

Fig. 3. SEM micrographs of the beads and their cross-sections: (a) S1, (b) S1 cross-section, (c) S3, (d) S3 cross-section, (e) S5 and (f) S5 cross-section

Table II. Properties of beads prepared by the laboratory ram extruder and double arm counter-rotating roller

Formulation	Diameter (mm)	Density (g/mL)	Friability (%)	Roundness	Coating Efficiency (%)
S1	3.28 (0.16)[a]	0.58	1.24	1.15	-
S2	3.31 (0.09)	0.55	0.09	1.14	5.5
S3	3.41 (0.10)	0.50	0	1.11	11.1
S4	3.32 (0.09)	0.54	0.78	1.13	6.5
S5	3.43 (0.11)	0.51	0.29	1.12	15.1
S6	3.26 (0.10)	0.57	0.65	1.14	-
S7	3.38 (0.09)	0.53	0.04	1.09	10.5

[a] Standard deviation (n=50)

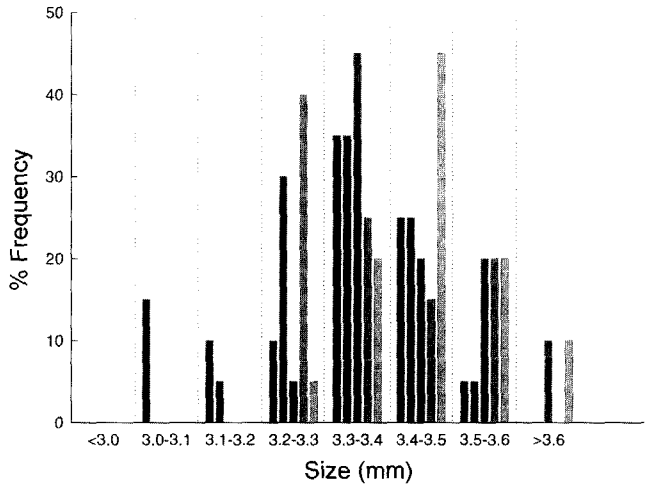

Fig. 4. Particle size distribution of the beads before and after the simple coating process; ■ S1, ■ S2, ■ S3, ■ S4, ■ S5

modified double arm counter-rotating roller, does not yield uniform beads. Indeed, humps were left on both ends of many beads. Because balling of the beads occurs instantaneously and the desired balling time cannot be dictated, the protrusions on the beads' ends can not be eliminated or reduced by balling alone.

The uncoated beads had a broad weight distribution, ranging from 17.0 to 24.5 mg (Fig. 5), although most (74%) were within the narrower range of 19.0 to 21.5 mg. The production of smaller-sized beads would constrict this weight distribution.

The physical and mechanical properties of beads are obviously quite important to their processing, and the coating process has much to do with the final properties. According to the extent of coating, the beads were found to have large diameters, low densities, low friabilities and low roundness values. Coating with ethylcellulose or Eudragit® RS 100 also gave the beads a smooth surface.

The tap density is indicative of the packing properties of beads, and depends on the diameter rather than the roundness. While the bead diameter increased with coating efficiency, the tap density decreased. In general, a decrease in the diameter and roundness would result in an increase in the density. Here however, the prepared beads were remarkably larger than ordinary pellets, and the decrease in roundness was too small to counteract this factor. The overall effect was a decrease in the bead density. Strictly speaking, coating the beads affects both their diameter and roundness, while increasing the coating efficiency has an unfavorable effect on the beads diameter and a favorable one on their roundness, a de-

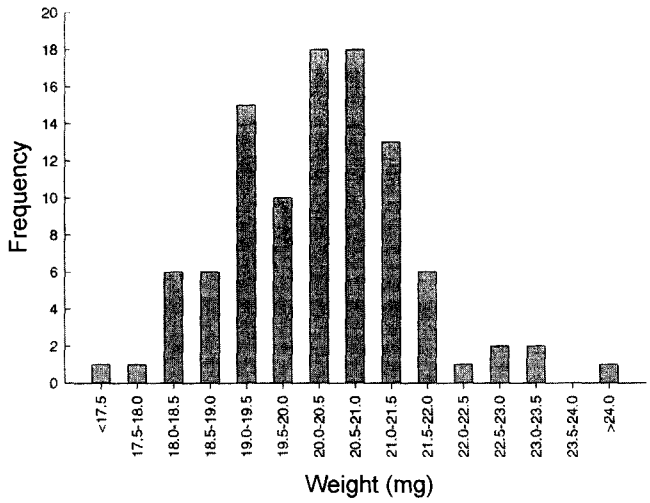

Fig. 5. Weight distribution of uncoated beads (S1) prepared using a laboratory ram extruder and double arm counter-rotating roller

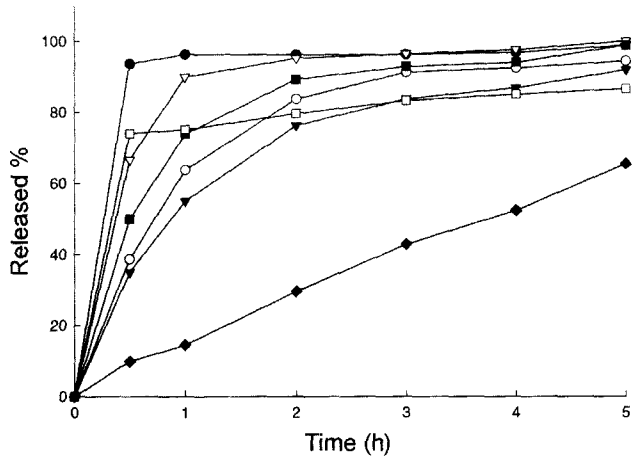

Fig. 6. Dissolution profiles of beads in simulated gastric juice: pH 1.2, 37±0.5°C and shaking at 100-rpm, using the basket method; ● S1, ○ S2, ▼ S3, ▽ S4, ■ S5, □ S6, ◆ S7.

crease in roundness is not sufficient to control the density change.

For practical purposes, the tap density of the prepared bead was insignificant, as the beads would be encapsulated in two-piece hard shell capsules. However, an obstacle does arise if the prepared beads are too large for encapsulation in these fixed volume dosage forms. Though beads can always be contained in a larger capsule, the number of beads, rather than their density, will determine the fill weight when the weight variation is not considered.

Drug release studies

PPA was expected to have a release profile influenced mostly by its high solubility (50-1000 mg/mL in water). Indeed, the excipients of formulation – lactose, corn starch, PVP K-30 and magnesium stearate – did not act as release-modifying agents. The release of PPA from uncoated beads (S1) was quite rapid, with more than 90% of the PPA released by 30 min (Fig. 6). Coating with ethylcellulose or Eudragit® RS 100, however, caused a marked decrease in drug release. Ethylcellulose and Eudragit® RS 100 exhibit low water permeability, and are frequently used to modify the release of a drug, to improve the external features of a pellet and to stabilize a formulation (Pearnchob *et al.*, 2003; Bodmeier *et al.*, 1997). As the concentration of ethylcellulose or Eudragit® RS 100 in the coating solution was increased, the coating efficiency increased almost proportionally. Conversely, the release of PPA from the uncoated beads (S6) prepared with PPA dissolved in PVP K-30 and Eudragit® RS 100 ethanol solution was slower than that from the S1 beads. The beads (S7) coated with 5% ethylcellulose showed zero order release. This release pattern might have been due to a dramatic reduction in the water permeability due to the combined effect of the Eudragit® RS 100 incorporated into the core matrix and the ethylcellulose coated membrane. The kinetics of the PPA release from other beads were not studied here, and remain to be correlated to one of the conventional models (zero order, first order, Highuchi's diffusion-controlled model). However, this study does raise the possibility of controlling the release of a water-soluble drug *via* the coating processing,

CONCLUSIONS

Beads loaded with the water-soluble drug, PPA, were prepared with a ram extruder and modified double arm counter-rotating roller. The uncoated beads prepared by this method had relatively rough surfaces and an irregular particle size distribution. Because the design of the double arm counter-rotating roller did not allow for adjustment of the rotation speed or distance between the rollers, it was difficult to obtain spherically cut pieces. The irregular shape, size and weight distributions of the uncoated beads could be corrected by improvements in the devices to control the rotation speed and distance between the rollers. Also, preparation of smaller beads would be beneficial. The present study found that beads with improved shapes and sizes could indeed be prepared. In conclusion, the present method could be potentially applied for the preparation of controlled release drug delivery beads or pellet dosage forms.

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