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Calcium pectinate gel coated pellets as an alternative carrier to calcium pectinate beads

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Abstract

A conventional method of using drug entrapped in calcium pectinate beads as sustained release drug delivery systems have long been suffering from too rapid an in-vitro release. An approach to solve this setback by the method of calcium pectinate gel (CPG) coated pellets was then initiated. The spherical theophylline pellets, which contain calcium acetate, were prepared using an extrusion-spheronization method and then coated with pectin solution, using an interfacial complexation process. An insoluble and uniform coating of CPG was formed around the pellets. The comparison was made between theophylline uncoated pellets, calcium pectinate beads and this developed method by the variation of coating time and the type of pectin. The results in simulated gastric fluid (SGF) and water showed that theophylline release from the coated pellets was slower than that from the beads. The time for 50% release of theophylline (t_{50}) from the CPG coated pellets in water and SGF are greater than the uncoated cores and the conventional beads. These results suggested that the coated pellets system were able to retard the release of theophylline to a greater extent than the conventional method. Therefore, this approach has been successfully achieved. © 1997 Elsevier Science B.V.

Keywords: Pectin; Calcium pectinate gel; Theophylline; Sustained release; Pellets; Beads

1. Introduction

Pectins are important ionic polysaccharides found in plant cell walls. They consist mainly of linearly connected α-(1→4)-D-galacturonic acid units and their methyl esters. They are industrially extracted from plant by-products and used as gelling agents in different food applications. Low methoxy pectins (with DM, degree of methoxylation (the average number of methoxy groups per galacturonic acid units), less than 50%) form gel by the action of calcium, which cross-links the galacturonic acid chains (Rolin, 1993).

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In pharmaceutical application, pectins have traditionally served as binding agent in tablet formulations (Slany et al., 1981). Recently, pectins have been investigated as matrix tablets for oral sustained release preparation (Krusteva et al., 1990; Naggar et al., 1992) and also as a carrier for colonic drug delivery (Ashford et al., 1993; Rubinstein et al., 1993). Moreover, pectin beads prepared by the ionotropic gelation method (Aydin and Akbuga, 1996) were used as sustained release drug delivery systems, the use of beads, however, has some drawback due to its rapid in vitro release.

The aim of this study is to develop and evaluate sustained release formulations of theophylline using calcium pectinate gel (CPG) coated pellets and compare with conventional calcium pectinate beads. The effect of some variables (%DM of pectin and coating time) and dissolution media on drug release were also investigated.

2. Materials and methods

2.1. Materials

GENUpectin type LM-101 (DM 36%) and LM-104 AS-FS (DM 28%) were the generous gift of Copenhagen Pectin (Denmark) and are referred to as P36 and P28, respectively. Theophylline, medium viscosity grade sodium carboxymethylcellulose, calcium acetate, calcium chloride, sodium citrate (Sigma Chemical, USA), microcrystalline cellulose (Avicel® PH101, FMC, USA), ethanol, sodium chloride, hydrochloric acid (Merck, Germany) were used as supplied and, where applicable, were AR grade.

2.2. Preparation of calcium pectinate gel coated pellets

Calcium pectinate gel (CPG) coated pellets were prepared using the diffusion controlled interfacial complexation process. One hundred grams of theophylline (40%), microcrystalline cellulose (50%), and calcium acetate (10%) was blended for 20 min in a Turbula mixer (model T2C, W. Bachofen, Switzerland). To bind the dry powder, 70 g of 1% (w/w) sodium carboxymethylcellulose was mixed in, and the plastic mass was extruded with a model 10 extruder (G.B. Caleva, UK) at 60 rpm through a 1 mm screen. The extrudate was spheronized (model 120, G.B. Caleva, UK) for 15 min at 1000 rpm and then dried in an air dryer (Zip, Australia) at 55°C for 2 h.

The 1.20–1.67 mm fraction of cores were coated by immersion into 4% (w/w) aqueous solutions of 2 types of pectin (P28 and P36) and stirring at 300–350 rpm for 10 or 20 min. The water from the aqueous solution of pectin penetrated and diffused through the pore of the core. The calcium salt in the core was then dissolved and diffused to the surface, forming a complex with the pectin and depositing as a gel of calcium

Table 1
Codes of calcium pectinate beads and CPG coated pellets

Beads	% DM of pectin	Coating time (min)	Designation
	36	20	B36
	28	20	B28
Uncoated cores	—	—	P
Coated pellets	36	10	P36/10
	36	20	P36/20
	28	10	P28/10
	28	20	P28/20

Table 2
Drug loading capacity of calcium pectinate beads and CPG coated pellets

	Drug content[a] (% ± S.D.[b])	Encapsulation efficiency[c] (% ± S.D.[b])
B36	17.23 ± 0.470	42.62 ± 1.175
B28	20.88 ± 0.162	52.14 ± 0.405
P	40.03 ± 0.223	100.06 ± 0.558
P36/10	28.59 ± 0.177	71.48 ± 0.442
P36/20	25.33 ± 0.168	63.32 ± 0.420
P28/10	27.47 ± 0.059	68.67 ± 0.146
P28/20	24.65 ± 0.842	61.61 ± 2.104

[a] The drug content was calculated based on the total weight of pellets or beads.
[b] S.D. was calculated from three repeated measurements.
[c] Encapsulation efficiency was calculated based on the initial drug loading (40%).

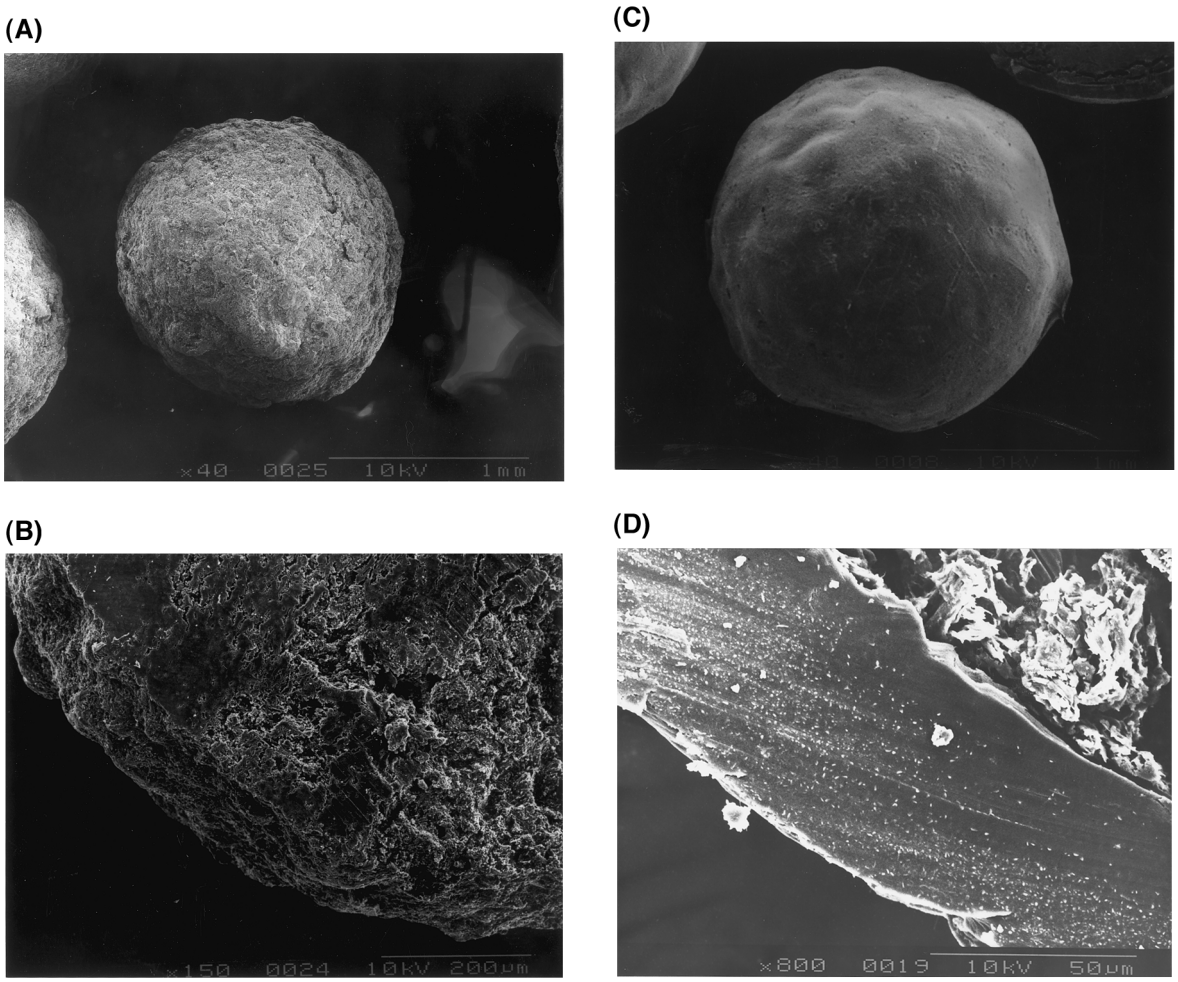

Fig. 1. Scanning electron micrographs of (A) external surface, (B) cross-section of uncoated core, (C) external surface, and (D) cross-section of theophylline pellet coated with pectin (DM 28%) for 10 min.

pectinate coat on the core surface (Sriamornsak et al., 1997). The coated pellets were filtered, washed with water and consequently suspended in a 5% solution of calcium chloride for 5 min. The suspension was filtered, rewashed with water, dispersed in ethanol for 5 min, then filtered and dried at 37°C for 12 h. In a preliminary experiment, the release of calcium from the uncoated cores was measured by complexometric titration with EDTA as described by Lim and Kennedy (1996). About 99% of the calcium diffused from the uncoated cores in 15 min when gently stirred in water (Sriamornsak, 1996).

2.3. Preparation of pectin beads

The conventional method of using drug entrapped in the beads was redesigned using the method as follows. Two grams of theophylline was added to 75 g of 4% (w/w) aqueous solutions of 2 types of pectin (P28 and P36). The dispersions were dropped using a nozzle (0.80 mm inner diameter) into a 5% solution of calcium chloride with gentle agitation at room temperature. The beads formed were allowed to stand in the solution for 20 min, separated and washed with distilled water and then dried at 37°C for 12 h. A

number of variables investigated are summarized in Table 1.

2.4. Analysis and characterization of calcium pectinate beads and CPG coated pellets

Prior to the determination of theophylline content, the coating materials and the beads must be dissolved by 2% sodium citrate. The content of theophylline was later assayed by UV-spectrophotometer (Hitachi U-2000, Japan) in 2% sodium citrate solution at 273 nm. The mean drug content was calculated from four repeated measurements. The ratio of the actual theophylline content in the beads or pellets to the theoretical theophylline content (40%) was termed as encapsulation efficiency (EE).

Scanning electron microscopic examination of the uncoated and coated pellets was performed by evaporation coating them with a 30 nm layer of gold and then observing them with an electron microscope (model S2360N, Hitachi, Japan) at an accelerating voltage of 10 keV. Some specimens were cut in half with a steel blade before coating to examine the internal morphology.

2.5. In vitro release study

Drug release kinetics from uncoated cores, coated pellets and conventional beads were evaluated using an in vitro USP dissolution apparatus I (Pharmatest™, Germany). The dissolution studies were performed in 750 ml of simulated gastric fluid USP minus pepsin (SGF) and distilled water at 37 ± 0.1°C at a rotation speed of 100 rpm. Samples withdrawn from SGF and water at various time intervals were analyzed spectrophotometrically at 270 and 271 nm, respectively. All tests were performed in triplicate.

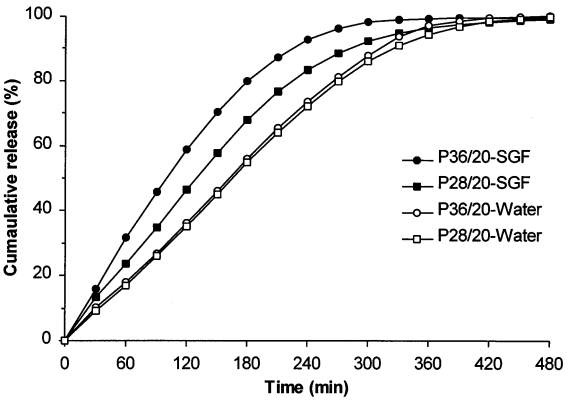

Fig. 3. Effect of dissolution medium on the release of theophylline from CPG coated pellets.

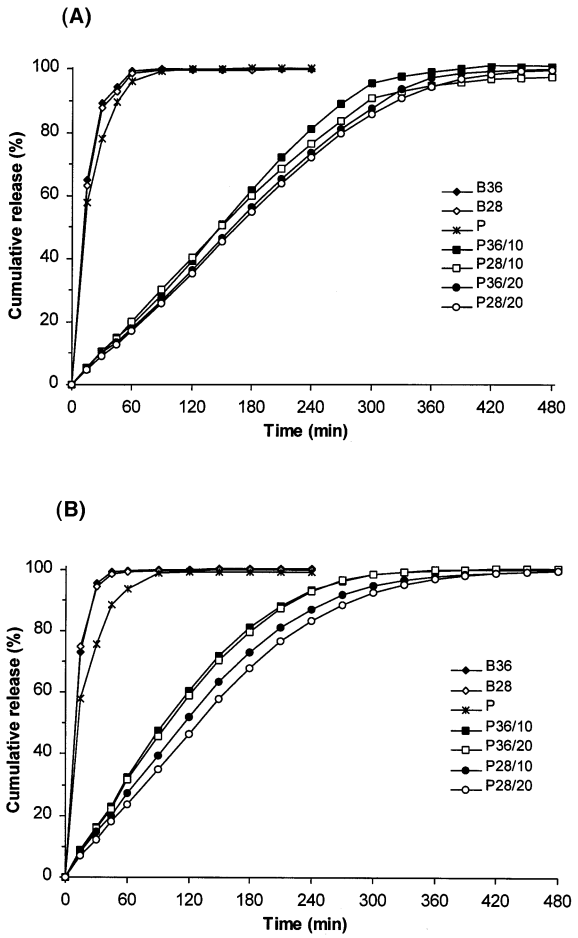

Fig. 2. Release profiles of theophylline from calcium pectinate beads and CPG coated pellets in (A) distilled water and (B) SGF.

3. Results and discussion

3.1. Preparation and characterization of calcium pectinate beads and CPG coated pellets

Calcium pectinate beads were obtained by using ionotropic gelation method and were fairly round spheres. Smooth round cores containing theophylline were prepared by extrusion-spheronization using microcrystalline cellulose and calcium acetate as bulk excipients and sodium carboxycellulose as binding agent. The theophylline pellets were then immersed into a solution of pectin, a growing highly hydrated coat appeared around the pellets. The coat was the result of the crosslinking reaction between pectin in the solution and the free calcium acetate diffusing from the core pellets, and was termed as the diffusion controlled interfacial complexation process. Immediately after the coating of pellets, the coat was flexible, with a yellowish, translucent appearance. To make the coat more rigid and improve its handling characteristics, the coated pellets were treated with calcium chloride and ethanol. At the completion of both treatments, the coat thickness was decreased and the coat was firm with better handling characteristics.

The contents and encapsulation efficiency (EE) of theophylline in the beads and the CPG coated pellets were shown in Table 2. Theophylline content and EE of uncoated pellets was higher than that of the CPG coated pellets and calcium pectinate beads. Moreover, the EE decreased with the increase of coating time which was the results of the loss of theophylline during the coating process (Sriamornsak, 1996) due to the solubility of theophylline and the weight gained due to the CPG membrane.

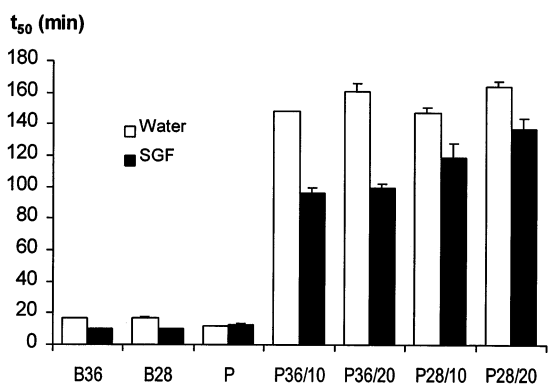

Fig. 4. The t_{50} value of the calcium pectinate beads and CPG coated pellets in distilled water and SGF.

The surface morphology and the cross-section of uncoated and coated pellets using scanning electron microscope (Fig. 1). Fig. 1(a) and Fig. 1(b) shows the appearance of the surface morphology and cross-section of the uncoated pellets. The core pellets are spherical with slightly rough surface and have a porous structure. Fig. 1(c) and Fig. 1(d) shows the surface appearance and cross-section of the dried theophylline pellets coated with P28. The appearance of the pellets coated with P36 was identical. The coated pellets were smoother than the uncoated cores but slightly irregular in shape. The overall size of the pellets was not increased significantly by coating.

3.2. In vitro release studies

The drug release properties in distilled water and SGF of CPG coated pellets containing theophylline were compared to those of the calcium pectinate beads and uncoated pellets (Fig. 2). Similar to the beads, the CPG coated pellets did not disintegrate but swelled in the dissolution medium. However, theophylline was released more rapidly from the calcium pectinate beads than from the CPG coated pellets in both distilled water and SGF. The CPG coated pellets exhibited a zero-order drug release up to the theophylline release percentage of 80–90. As the coating time increased, the drug release rate decreased. In addition, the release of theophylline from CPG coated pellets in distilled water and SGF is illustrated in Fig. 3. The drug was released faster in SGF than in distilled water. A small number of charges present on the SGF might allow somewhat faster drug release due to greater solvent penetration into the calcium pectinate network, followed by greater ion exchange between calcium and hydrogen ions. Hydrogen ions might displace calcium in the gelled structure and partially forming soluble pectinic acid regions, which are more permeable (Sriamornsak, 1996).

The release parameter, the time for 50% release of theophylline (t_{50}), obtained in both media from uncoated pellets, CPG coated pellets and calcium pectinate beads are shown in Fig. 4. The t_{50} values of the CPG coated pellets in distilled water were 12–14-fold greater than both of the uncoated cores and the conventional pectin beads, while in SGF were 7–11 and 9–13-fold greater than both from the uncoated cores and the calcium pectinate beads, respectively. The t_{50} values of the CPG coated pellets in water were slightly greater than in SGF. Additionally, the t_{50} values increased with the increase of coating time. Analysis of variance (ANOVA) showed a statistically significant effect of manufacturing method of the two systems ($p < 0.001$), the coating time ($p < 0.05$) and dissolution medium ($p < 0.05$) on the t_{50} values. The % DM of pectin only affected the t_{50} values of the CPG coated pellets in SGF ($p < 0.05$) but not in water ($p > 0.05$).

4. Conclusion

An approach to solve the setback of a too rapid in vitro release of drug from calcium pectinate beads by the method of CPG coated pellets was initiated. The drug-loaded pellets, coated with calcium pectinate, are successfully prepared using the diffusion controlled interfacial complexation process. The CPG coated pellet system retards the release of drug to a greater extent than the conventional bead system did. Furthermore, % DM of pectin, coating time and dissolution medium influenced the release of drug from CPG coated pellets. Most of all, CPG coating of theophylline pellets would be proper and efficient for an oral theophylline delivery system because the release rate of theophylline was easily controlled without initial burstout release. The detail in vivo pharmacokinetics of CPG coated pellets will be investigated in the future. From the current studies, the sustained release formulation of theophylline using CPG coated pellets may provide as an alternative for oral delivery system.

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