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AVICEL RC-591/CHITOSAN BEADS BY EXTRUSION-SPHERONIZATION TECHNOLOGY

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ABSTRACT

Beads were successfully prepared using the combination of Avicel RC-591 and chitosan using extrusion and spheronization technology. The effects of different viscosity grades of chitosan (SEACURE 142, 242, 342 and 442) on bead formation and on release profiles were examined using acetaminophen as a model drug. Incorporation of higher viscosity grades of chitosan yielded beads with rough surfaces and slower release characteristics. Seacure 342 was chosen for further studies using acetaminophen and theophylline as model drugs of different solubilities. Beads were prepared with varying proportions of Seacure 342 and Avicel RC-591 (20% drug loading). Drug release from the beads varied with the dissolution method used. Beads were swollen in 0.1 N HCl while the bead structure remained intact. In water, the beads exhibited gel-like structures.

INTRODUCTION

Extrusion-spheronization technology is gaining popularity and increasing acceptance in the pharmaceutical industry. Several reports have been published

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dealing with bead manufacture using this technique (1-4). The number of excipients available for successful spheronization by this technology are limited. Drug release characteristics from beads of different microcrystalline cellulose (MCC) products using the extrusion-spheronization process have been reported (5-7). Ghali et al investigated the release of soluble drugs using blends of two different grades of microcrystalline cellulose and found that release was much faster in acid media compared to that in water (7).

Chitosan is a potentially useful excipient and has shown increasing value in drug and cosmetic industry (8). It has been reported to possess low toxicity and good biocompatibility (9). It is a cationic polyelectrolyte obtained by deacetylation of chitin and swells in acidic environment. Chitosan has been evaluated as a direct compression aid (10) and as a tablet binder (11). It has also been examined as a sustained release vehicle alone (12-13) as well as in combination with some anionic polyelectrolytes (14-15) and citrate complexes (16). The objective of this study was to evaluate the bead formation by extrusion-spheronization technique using blends of chitosan and Avicel RC-591. Four different viscosity grades of chitosan have been initially screened for this purpose (Seacure 142: <20 cps, Seacure 242: 20-200 cps, Seacure 342: 200-800 cps and Seacure 442: 800-2000 cps) and one of the higher viscosity grades (Seacure 342) was then chosen for further studies. Drug release characteristics in 0.1N HCl and distilled water were also studied. Acetaminophen and theophylline were used as model drugs of different solubilities.

EXPERIMENTAL

Materials

Avicel RC-591 (FMC Corporation, Philadelphia, PA) and chitosan (SEACURE 142, 242, 342 and 442; Protan Inc., Portsmouth, NH) were used as the matrix forming materials. The model drugs used were acetaminophen, USP (Ruger Chemical Company, Irvington, NJ) and anhydrous theophylline (Sigma Chemical Co., St. Louis, MO).

Formulation and manufacture of beads

The initial formulations studied contained 20% acetaminophen, 20% chitosan (Seacure 142 or 242 or 342 or 442) and 60% Avicel RC-591. This

was followed by formulations consisting of 20 % drug (either acetaminophen or theophylline) with varying levels of Seacure 342 (20%, 30% and 40%) and Avicel RC-591. Chitosan flakes were reduced to fine powder using a Fitz mill. The control formulation was 20% drug with Avicel RC-591. The batch size was 0.5 kg in all cases.

The ingredients for each formulation were mixed in a planetary mixer (Hobart Corporation) and sufficient water was added to obtain suitable consistency. The wet mass was mixed for five minutes and the wet granulations were passed through an extruder (EXDS-60, LUWA Corporation, Charlotte, NC) fitted with 1.5 mm screen and was operated at 50 rpm. The cylindrical extrudate obtained was immediately processed in the spheronizer (Marumerizer, LUWA Corporation, Charlotte, NC) at a plate rotational speed of 1000 rpm for 2-3 minutes. Beads were collected and dried on paper lined trays in a hot air oven for 12 hours at 40°C.

Bead evaluation

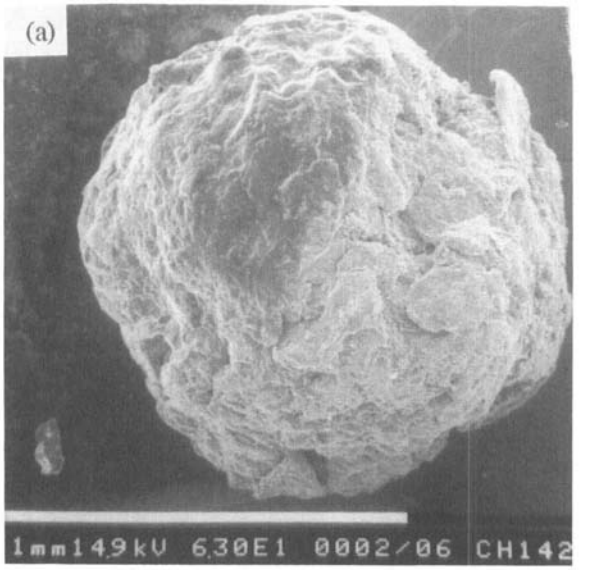
Beads produced using Avicel RC-591 and Seacure 342 were subjected to physical testing. Particle size distribution of the beads was measured using a nest of U.S. standard sieves. The bulk and tapped densities were determined using the standard graduated cylinder method. Friability was determined by subjecting 10 gm bead samples of 14/20 mesh fraction to abrasion in an Erweka friabilator with 200 glass beads for 10 minutes. The abraded samples were sieved on a 20 mesh screen for two minutes. The amount retained on the sieve was weighed and % friability calculated.

Scanning electron microscopy

The scanning electron micrographs were recorded on a Philips Model 515 SEM (Mawaah, NJ, U.S.A.). Samples were sputter coated with 75 nm gold-palladium and mounted on a double stick tape on an aluminum grid. The samples were imaged using a 15 kV electron beam.

In-vitro release studies

The in-vitro dissolution studies were performed, in triplicate, according to USP Method I in both 0.1 N HCl and distilled water at a basket rotational speed



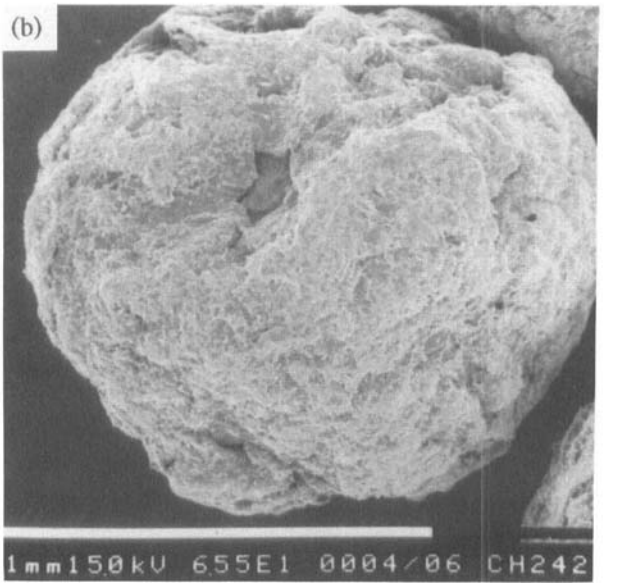


FIGURE 1

Scanning electron micrographs of beads prepared with different grades of chitosan at 20% level
(a) Seacure 142 and (b) Seacure 242.

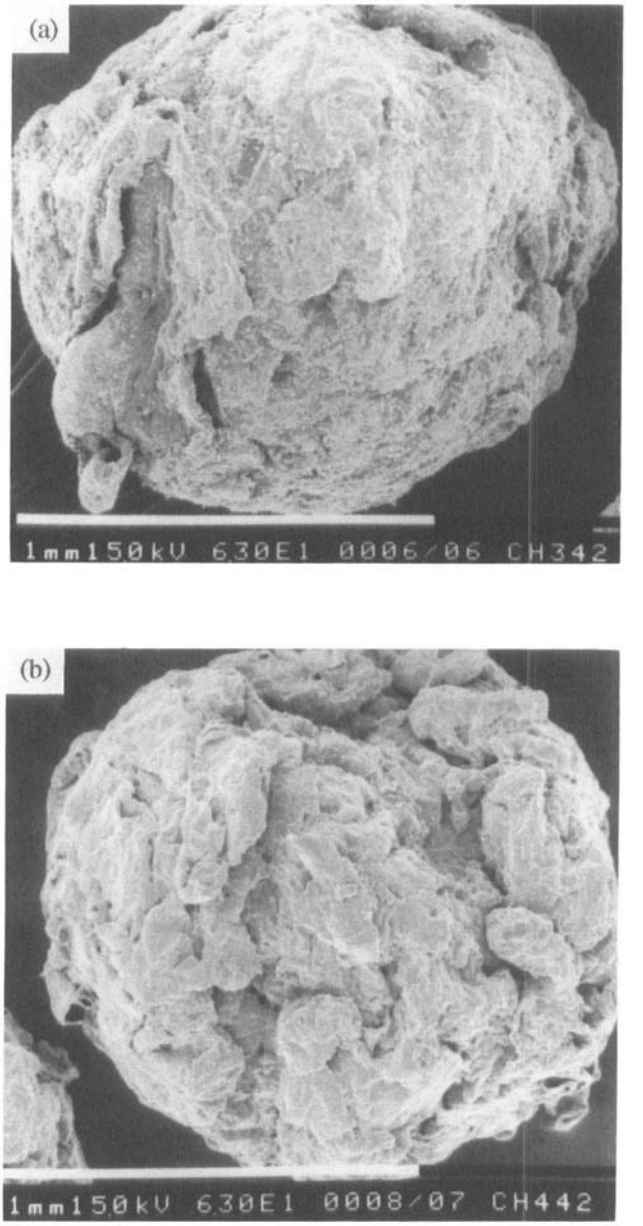


FIGURE 2

Scanning electron micrographs of beads prepared with different grades of chitosan at 20% level
(a) Seacure 342 and (b) Seacure 442.

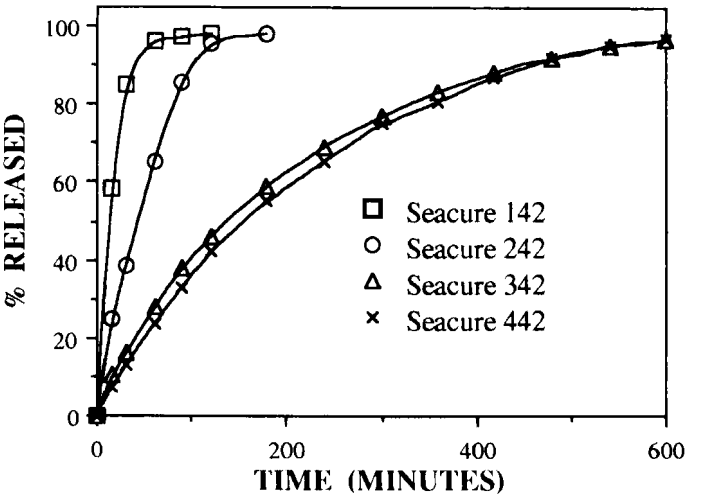


FIGURE 3

Dissolution profiles of 20% acetaminophen beads in 0.1 N HCl using the basket method.

of 50 rpm. Samples were analyzed spectrophotometrically at appropriate wavelengths (acetaminophen, 244 nm; theophylline, 270 nm in acid media and 272 nm in water). One gram bead samples of a 14/16 mesh cut were chosen for dissolution studies to reduce surface area effects on drug dissolution. Dissolution studies were also conducted using USP Method II at a paddle rotational speed of 50 rpm in 0.1 N HCl. The volume of the dissolution media was 900 ml in all cases.

RESULTS AND DISCUSSION

Beads were successfully manufactured using Avicel RC-591 and chitosan blends with 20% drug loading, while our earlier attempts to do the same with blends of Avicel PH-101 and chitosan failed to produce acceptable beads. The success with Avicel RC-591 may be attributed to its increased binding ability brought about by the presence of sodium carboxymethylcellulose (~11%) in it. The scanning electron micrographs (Figures 1 and 2) indicated that higher viscosity grades of chitosan (Seacure 342 and Seacure 442) resulted in a

TABLE 1

Physical properties of acetaminophen and theophylline beads (20% loading)

	Acetaminophen				Theophylline			
Chitosan (Seacure 342)	0	20	30	40	0	20	30	40
Density (g/cm^3)								
Bulk	0.78	0.69	0.68	0.67	0.77	0.70	0.69	0.68
Tapped	0.84	0.75	0.74	0.71	0.83	0.77	0.75	0.73
% Friability	0.15	1.3	0.56	1.9	1.6	0.86	1.0	1.31
Sieve analysis (% retained on)								
12	0	0	0	0	0	0	0	0
14	2.0	2.5	6.0	5.0	1.0	1.5	4.0	1.5
16	20.0	24.0	26.5	25.0	16.0	21.0	22.5	15.0
20	56.0	54.0	58.0	60.0	60.0	63.0	70.0	66.0
30	9.0	6.5	6.1	7.2	10.0	6.5	1.3	10.0
40	12.5	12.2	1.9	0.1	12.5	7.5	0.6	4.3
pan	0.5	0.8	1.5	2.7	0.5	0.5	1.6	3.2

decrease of bead sphericity and an increase in the surface roughness. Additionally, drug release with these grades was slower in acidic medium , when acetaminophen was used (Figure 3). Seacure 342 was chosen for further studies based on the bead nature and release characteristics.

The results of physical testing of the beads are shown in Table 1. The results indicated a narrow particle size distribution (more than 75% in 14/20

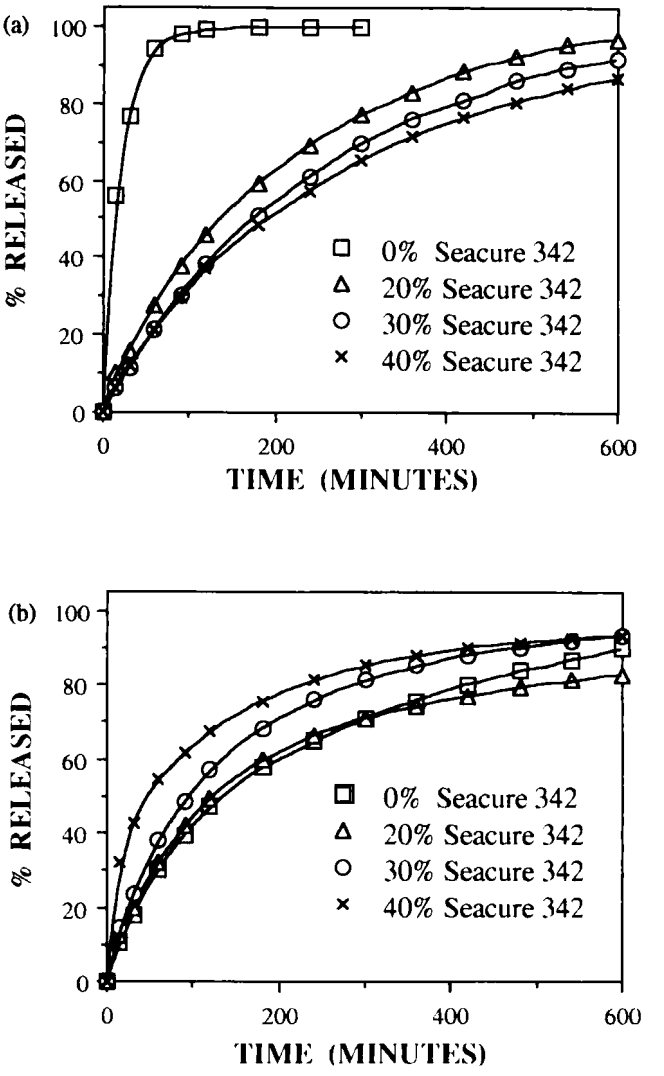


FIGURE 4

Dissolution profiles of 20% acetaminophen beads with varying levels of Seacure 342 using the basket method (a) 0.1 N HCl and (b) water.

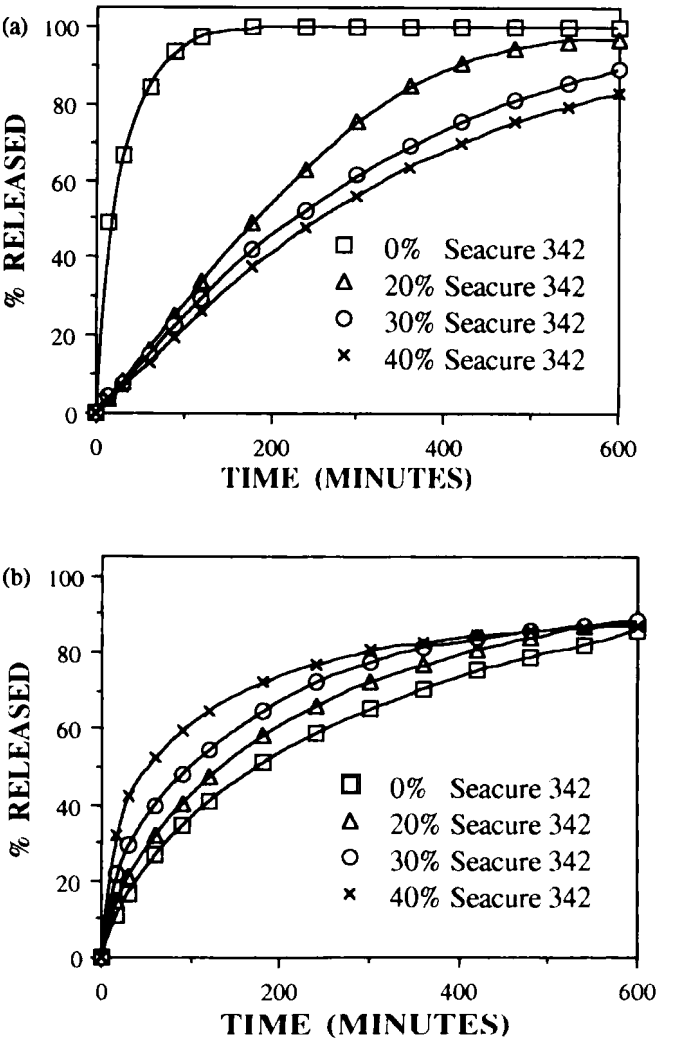


FIGURE 5

Dissolution profiles of 20% theophylline beads with varying levels of Seacure 342 using the basket method
(a) 0.1 N HCl and (b) water.

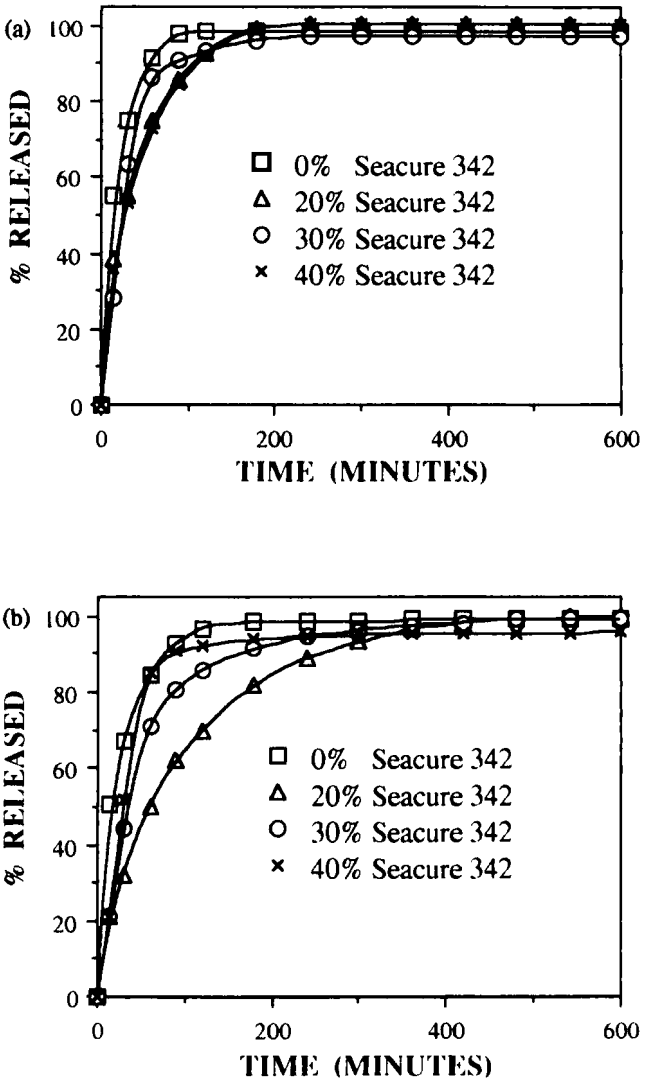


FIGURE 6

Dissolution profiles of drug loaded (20%) beads with varying levels of Seacure 342 in 0.1 N HCl using the paddle method (a) acetaminophen and (b) theophylline.

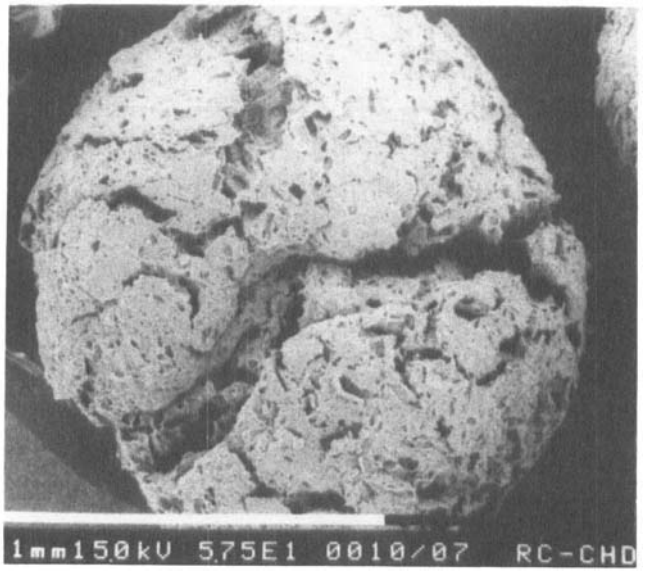


FIGURE 7

Scanning electron micrograph of a bead after dissolution testing (over ten hours) using the basket method in 0.1 N HCl.

mesh fraction). Bead density seemed to decrease with an increase in chitosan content in the formulation. Tapped densities were consistently greater than the corresponding bulk densities. Low friability was also observed suggesting harder pellets suitable for further processing.

Dissolution profiles for beads are presented in Figures 4, 5 and 6. They were found to be dependent both on the dissolution medium and the method used. Drug release was over seven hours in all cases when tested in a basket. Increasing amounts of Seacure 342 slowed the release in acid media, but enhanced it in water, which is consistent with published reports (12). Chitosan is known to slow the release, due to its swelling nature in acid media, but acts as a disintegrant in water. The bead structure appeared swollen but did not disintegrate after dissolution in acid using the basket method (Figure 7). The beads in the basket exhibited a gel-plug structure in water which slowed drug release to a great extent.

The formation of such a gel-plug in the basket may be due to sodium carboxymethylcellulose in Avicel RC-591 as previously suggested (7) in the case of Avicel RC-581. Drug release was complete in less than three hours when dissolution was conducted using the paddle method in acid media. The swollen beads ruptured, presumably due to the shear exerted by the paddle, while the structure was intact using the basket method.

CONCLUSIONS

The results of this investigation showed that spherical beads can be successfully manufactured using combinations of Avicel RC-591 and different viscosity grades of chitosan. Such a combination of spheronizable excipients may prove useful in designing beads with release modifying properties. Dissolution profiles were found to be both method and media dependent. Beads prepared from Avicel RC-591/chitosan blends appeared swollen in acid media, while gel-like structure was evident in water.

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