Drug Development and Industrial Pharmacy, 24(6), 541-547 (1998)

RESEARCH PAPER

Physical Characteristics and Release Behavior of Salbutamol Sulfate Beads Prepared with Different Ionic Polysaccharides

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ABSTRACT

Salbutamol sulfate beads were prepared using anionic and cationic polysaccharides, Gelrite and chitosan, respectively. Alginate beads were also prepared for comparison. The mean diameter, porosity, and drug content of the beads were determined. The beads were examined by scanning electron microscopy (SEM), DSC, and x-ray diffraction. The drug release from the beads was studied in 0.1 N HCl (pH 1.2), distilled water, and phosphate buffer (pH 7.4). The physical examination of the beads indicated the presence of drug crystals with no interaction between the drug and polymers. The drug release was dependent on the ionic properties of the polymers and the pH of the release media. In acidic pH, chitosan beads showed a rapid drug release, whereas a sustained drug release was obtianed from Gelrite beads. In contrast, the drug release in phosphate buffer was rapid from Gelrite, and chitosan showed a sustained drug release. The results of drug release from Gelrite were comparable to that from alginate beads. Gelrite is recommended as an anionic polysaccharide for sustained-release preparations.

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INTRODUCTION

Recently, the use of natural polymers as drug carriers has received much attention in the pharmaceutical field because of their good biocompatibility. In particular, natural polysaccharides such as chitosan (1–3) and sodium alginate (3,4) have been studied for broad application and usage in the design of various dosage forms.

A new anionic polysaccharide, Gelrite (5), has many potential applications in the pharmaceutical and food industries, aided by its lack of toxicity (6). Gelrite was prepared by deacetylation of gellan gum which is secreted by *Pseudomonas clodea*. It has the unique property that when dispersed in low concentration (<1%) in water, it forms a slightly viscous solution, which can subsequently increase markedly in apparent viscosity when introduced into the presence of physiological levels of cations (6,7). Gelrite has been used as a base for hydrophilic gels containing drugs for ophthalmic use (5,6).

The cationic polyelectrolyte chitosan was useful for the preparation of beads (3), granules (8), and tablets which exhibited sustained release of drugs (9,10). Sodium alginate has been evaluated as a release-controlling diluent in sustained-release capsules (11,12). In addition, the ability of alginate to form gel with divalent cations has been utilized in the production of calcium alginate matrices, intended for oral controlled drug delivery systems (13,14).

Salbutamol is a direct acting sympathomimetic agent with a selective action on β_2-adrenergic receptors. It is used for the treatment of both acute and chronic asthma. It can be given by the pulmonary, oral, and parenteral routes. Salbutamol has been given by mouth in a dose of 2–4 mg three or four times daily (15).

The purpose of this study was to prepare salbutamol sulfate beads using anionic (Gelrite) and cationic (chitosan) polysaccharide. The effect of the ionic character of the polymer on drug release was evaluated. Further comparison between the two anionic polymers, Gelrite and alginate, was assessed.

EXPERIMENTAL

Materials

Salbutamol sulfate, Gelrite (phytagell), sodium alginate (viscosity of 2% solution at 25°C was approximately equal to 14.000 cps), and chitosan were obtained from Sigma Chemical Co. (St. Louis, Mo). Other chemicals were reagent grade.

Preparation of Beads

Two grams of salbutamol sulfate was dissolved in 100 ml of aqueous solution of the polymers. The polymer solutions (4% w/v Gelrite and 2% w/v for chitosan and sodium alginate) were prepared by dissolving chitosan in 5% acetic acid solution; Gelrite and sodium alginate were dissolved in deionized water. Each polymer solution containing the drug was dropped using a disposable syringe into 300 ml of gently stirred, iced ethylacetate, 5% sodium pyrophosphate, and 5% $CaCl_2$ for Gelrite, chitosan, and sodium alginate, respectively. Different batches were stirred to various time intervals. The gel beads were separated by filtration, rinsed with distilled water, and dried at 40°C under vacuum. Also, various batches of beads were prepared from the different polymer solutions containing salbutamol, but the counterion solutions ($CaCl_2$ and sodium pyrophosphate) contained different concentrations of the drug.

Determination of Porosity and Mean Particle Size

The true density of the beads was determined using a helium pycnometer. After the bulk density was determined, the porosity of the beads was calculated (16). The mean diameter of the beads was determined by the sieve analysis technique (17).

Determination of Salbutamol Content

The dried beads (100 mg) were allowed to disintegrate completely in 100 ml of either 0.1 N HCl, distilled water, or phosphate buffer (pH 7.4) for chitosan, Gelrite, and alginate beads, respectively. The solutions were filtered and the drug content was determined spectrophotometrically at 276 nm in both 0.1 N HCl and distilled water and at 245 nm in phosphate buffer.

Scanning Electron Microscopy (SEM)

Photomicrographs were obtained using the Cambridge® Steroscan 250 scanning electron microscope. The beads were coated under reduced pressure with carbon (Emscope® TB500 sputter coater) before being coated with a thin gold–platinum film (Eiko Engineering ion coater IB.2).

X-ray Diffraction

The x-ray diffraction patterns of pure drug and polymers as well as the beads loaded with the drug were

obtained using a Philips® PW 1050/70 diffractometer system, CuK_α radiation, and a scan speed of 2 θ min^{-1}. The samples were packed into the aluminum sample container.

Differential Scanning Calorimetry (DSC) Analysis

The thermograms of salbutamol, different polymers, and the beads were recorded on a Du Pont® series 99 thermal analyzer programmer. The instrument was calibrated with an indium standard. The thermal behavior was studied by heating 5-mg samples at a heating rate of 10°C min^{-1} in a crimped aluminum pan with a crimped empty pan as a reference. The study was conducted from 30 to 250°C under nitrogen purge.

Release Study

The release of salbutamol sulfate was studied in 0.1 N HCl, distilled water, and phosphate buffer (pH 7.4) using USP XXI rotating paddle apparatus. A weight of the beads equivalent to 8 mg drug was placed in 900 ml of the dissolution medium at 37°C and stirring speed of 80 rpm. Samples of 2 ml were withdrawn at different time intervals, filtered through Millipore filter (45 μ) and immediately replaced with an equal volume of fresh dissolution medium. The samples were then diluted with the respective dissolution medium and assayed spectrophotometrically at 276 nm in both distilled water and acid medium, and at 245 nm in phosphate buffer. The percent of drug dissolved was calculated after correction for dilution.

RESULTS AND DISCUSSION

Mean Diameter and Porosity

The porosity of the beads (Table 1) was found to be in the following decreasing order: Gelrite > alginate > chitosan. The results in Table 1 also show that the mean diameter of the beads was in a good correlation with that of the porosity, because the mean diameters have the same order of arrangement as those of the porosity. The yield values (percent) of the beads (Table 1) have the following arrangement: alginate > Gelrite > chitosan.

Drug Content

The drug content (Table 2) in the dried salbutamol beads decreased with an increase of the stirring time (gelation time) of cured beads prepared from chitosan and alginate. This could be due to the migration of drug from the gelled beads to the counterion solutions. Con-

Table 1

Physical Characteristics of Salbutamol Sulfate Beads

Type of Beads	Bulk Density (gm/cm^3)	True Density (gm/cm^3)	Porosity (%)	Mean Diameter (mm)	Yield Value (%)
Gelrite	0.17	0.20	15.0	1.84	69.2
Alginate	0.33	0.38	13.15	1.45	72.5
Chitosan	0.25	0.28	10.71	1.25	60

Table 2

Effect of Stirring Time and Salbutamol Sulfate Concentration in the Counterion Solutions on Percentage Drug Content of the Beads

	Stirring Time in min[a]				% of Drug in Counterion Solutions[b]			
Bead Type	5	15	30	60	0.0	0.1	0.2	0.3
Gelrite	2.58	2.54	2.52	2.50	—[c]	—	—	—
Alginate	3.25	2.50	1.70	0.98	3.25	3.40	3.75	4.00
Chitosan	3.18	2.40	1.80	0.88	3.18	3.34	3.82	4.10

[a]The counterion solutions did not contain drug.
[b]Stirring time was 5 min.
[c]Salbutamol sulfate is insoluble in ethyl acetate.

versely, the presence of drug in the counterion solutions led to an increased amount of drug loaded in chitosan and alginate beads (Table 2). Moreover, the drug concentration increased with an increase of the drug concentration in the gelation medium (Table 2). Thus, it could be concluded that to entrap water-soluble drugs in the gelled beads, the drug should be included in both the polymer solution and its gelation medium. In addition, the stirring time should be as short as possible. Conversely, Gelrite beads were not affected by stirring time because of the insolubility of salbutamol sulfate in ethylacetate.

SEM

Plain beads [Fig. 1(a)] were nearly spherical in scanning electron micrographs (chitosan is a representative example), whereas the beads loaded with the drug [Fig. 1(b)] were irregular and partially shrunken. The micrographs of Gelrite beads taken before dissolution [Fig. 1(c)] showed low porosity compared to those taken after drug release in 0.1 N HCl [Fig. 1(d)]. This might be due to the release of solid drug from the matrix, which leaves pores behind.

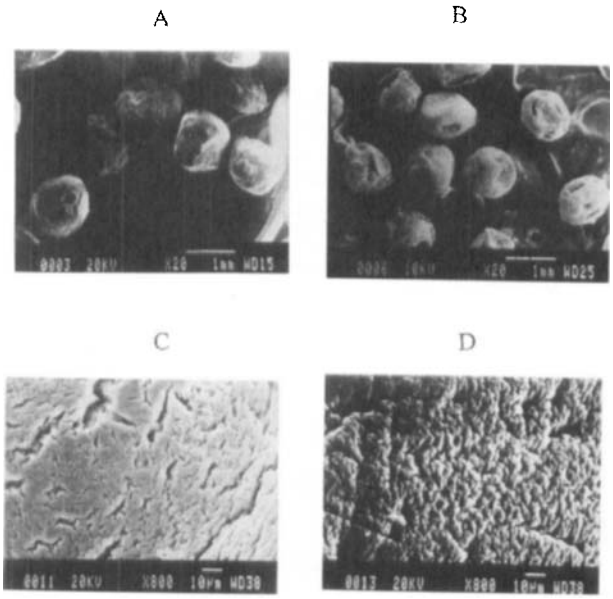

Figure 1. Scanning electron micrographs of plain chitosan beads ×20 (a), salbutamol-loaded chitosan beads ×20 (b), Gelrite beads before dissolution ×800 (c), and Gelrite beads after release in 0.1 N HCl ×800 (d).

DSC

The DSC thermograms of salbutamol sulfate (trace 1 of Fig. 2) show an endothermic melting peak with an onset from 185°C to reach a maximum peak at 195.48°C. Traces 2 and 3 of Fig. 2 indicate the DSC thermograms of Gelrite and chitosan, respectively. The polymers' endothermic peaks were shallow and broad. Traces 4 and 5 of Fig. 2 are the thermograms of salbutamol beads with Gelrite and chitosan, respectively. Obviously, no interaction occurred between the drug and the polymers, because the DSC thermograms reflect the characteristic feature of the drug alone. The different appearances found in peak shape and height-to-width ratio were due to the possible geometric differences in the drug–polymers (18) and were not due to interaction.

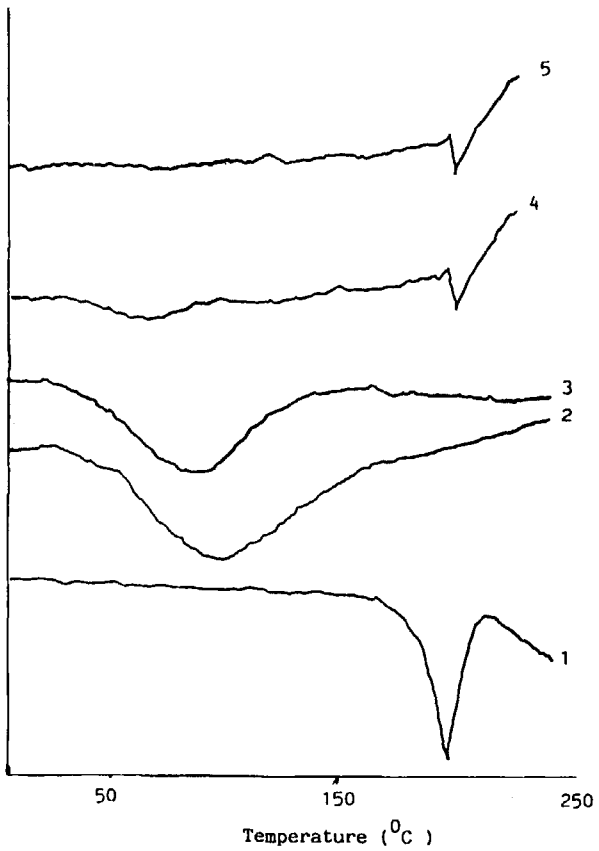

Figure 2. DSC thermograms of salbutamol sulfate (1), Gelrite (2), chitosan alone (3), and salbutamol sulfate in Gelrite beads (4) and chitosan beads (5).

X-ray Diffraction

The x-ray diffraction was performed to characterize the physical state of the drug and polymers in the beads. The x-ray diffraction peaks characteristic of the drug and polymers were visible in the diffraction scans of the beads (Fig. 3). These results and those of DSC indicated that the drug was present in its crystalline state in the beads.

Drug Release

The analysis of release data of salbutamol sulfate from the different beads showed the best fit was with the square root of time model (r = 0.99). Furthermore, excellent correlation was obtained with double logarithmic plots of fractional release as a function of time (19), the gradients of which allowed the values of diffusional exponent, n, to be calculated (Table 3). The values of n indicated Fickian diffusion (n = 0.50) for all beads in all release media with the exception of Gelrite beads in distilled water, which showed non-Fickian diffusion (n = 0.63). The release rate of drug from chitosan beads (Table 3) followed the order: 0.1 N HCl > distilled water > phosphate buffer. The rapid drug release in 0.1 N HCl might be attributed to the cationic character of chitosan, which dissolves below pH 6 (20). On the contrary, the drug release pattern from Gelrite (Fig. 4) and alginate (Table 3) was higher from phosphate buffer than that from both 0.1 N HCl and distilled water. Both polymers were insoluble in 0.1 N HCl but swelled in phosphate buffer. The swelling of Gelrite and alginate matrices in phosphate buffer (pH 7.4) resulted from the exchange of hydrogen ions for Gelrite and the crosslinked calcium ions in alginate with sodium ions of the dissolution medium (13,21). The partial formation of sodium Gelrite and sodium alginate in the beads induced water uptake in the dehydrated gels (21). The swelling of both polymers might be the cause of the rapid drug release in phosphate buffer.

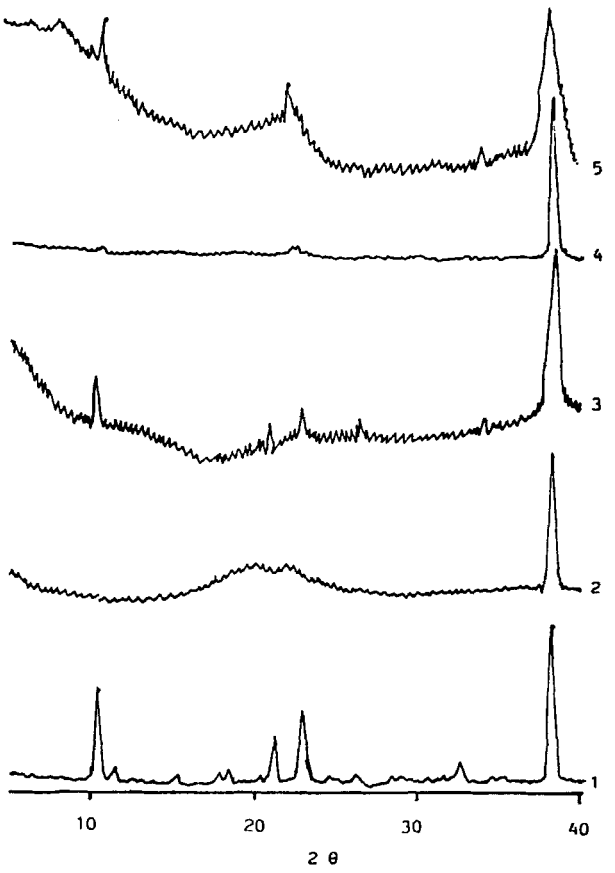

Figure 3. X-ray diffractograms of salbutamol sulfate (1), Gelrite alone (2) sodium alginate alone (3), and salbutamol sulfate in alginate beads (4) and Gelrite beads (5).

The release rate of drug from Gelrite beads (Table 3) was higher in distilled water than in 0.1 N HCl . This may be attributed to the partial ionization of the anionic Gelrite and subsequent solubility in distilled water. In

Table 3

The Values for the Diffusional Exponent, n, and the Release Rate Constant ($mg/hr^{1/2} \times 100$) of Salbutamol Sulfate from Beads in Different Release Media

	0.1 N HCl		Distilled Water		Phosphate Buffer pH (7.4)	
Beads	n	Rate	n	Rate	n	Rate
Gelrite	0.51	20.14	0.63	23.49	0.48	29.18
Alginate	0.49	20.53	0.52	19.34	0.49	28.53
Chitosan	0.47	25.18	0.48	21.91	0.48	20.17

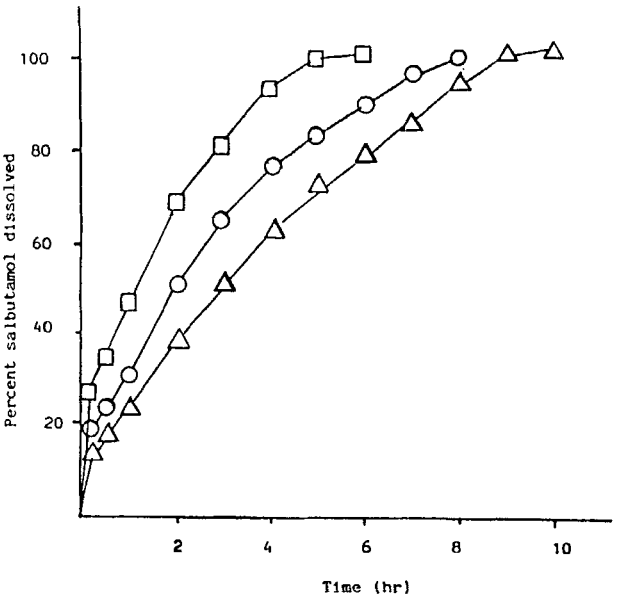

Figure 4. Release profile of salbutamol sulfate from Gelrite beads in 0.1 N HCl (Δ), distilled water (○), and phosphate pH 7.4 (□).

contrast, the drug release from alginate beads was higher in 0.1 N HCl than in distilled water. Salbutamol sulfate powder dissolved almost immediately in the investigated media. Hence, the rapid drug release from alginate matrices in acid medium can only be explained by a change in the matrix properties on contact with acid (22). The calcium ions in alginate beads were totally discharged in an acid environment and the carboxyl groups were shifted to an un-ionized form. This might alter the matrix properties, including the release characteristics of the incorporated drug (23).

When the drug release from different beads in the applied release media (Table 3) were compared, it was found that the sustained drug release in acid medium from Gelrite was more prolonged than from chitosan. Conversely, in phosphate buffer medium the drug release was more sustained from chitosan compared to Gelrite beads. The sustained-release effect of Gelrite beads was nearly comparable to alginate beads in all the investigated media. During dissolution Gelrite and chitosan beads floated on the dissolution medium. This is an interesting property of the beads, because sustained-release oral delivery has been achieved by using formulations that float on gastric juice (24).

In conclusion, the sustained-release behavior of the drug from the beads not only depends on the ionic character of the polymers and pH of the release media, but also on the type of the cations conjugated with the polymers. Gelrite matrices, because of their slow drug release in acid medium, can be considered more suitable than chitosan for preparation of sustained-release dosage forms intended for oral use.

REFERENCES

1. Y. Sawayanagi, N. Nambu, and T. Nagai, Chem. Pharm. Bull., 31, 2064 (1983).
2. Y. Kawashima, T. Handa, A. Kasai, H. Takenka, S. Y. Lin, and Y. Ando, J. Pharm. Sci., 74, 264 (1985).
3. S. Miyazaki, A. Nakayama, M. Oda, M. Takada, and D. Attwood, Biol. Pharm. Bull., 17, 745 (1994).
4. K. Tateshila, S. Sugawara, T. Imai, and M. Otagiri, Biol. Pharm. Bull., 16, 420 (1993).
5. A. Rozier, C. Mazuel, J. Grove, and B. Plazannet, Int. J. Pharm., 57, 163 (1989).
6. P. Fitzgerald and C. Wilson, in *Polymeric Biomaterials* (S. Dumitriu, ed.), Marcel Dekker, Inc., New York, 1994, p. 386.
7. P. B. Deasy and K. J. Quigley, Int. J. Pharm., 73, 117 (1991).
8. H. Miyazaki, H. Yamaguchi, C. Yokouch, M. Takara, and W. M. Hou, J. Pharm. Pharmacol., 40, 642 (1988).
9. Y. Sawayanagi, N. Nambu, and T. Nagai, Chem. Pharm. Bull., 30, 2935 (1982).
10. A. Nigalaye, P. Adusumilli, and S. Bolton, Drug Dev. Ind. Pharm., 16, 449 (1990).
11. S. Ojantakanen, A. M. Hannula, M. Harvola, E. Klinge, and M. Makipaa, Eur. J. Pharm. Biopharm., 39, 197 (1993).
12. P. Veski and M. Marvola, Pharmazie, 48, 757 (1993).
13. C. K. Kim and E. J. Lee, Int. J. Pharm., 79, 11 (1992).
14. A. A. Badwan, A. Abumalooh, E. Sallam, A. Abukalaf, and O. Jawan, Drug Dev. Ind. Pharm., 11, 239 (1985).
15. J. E. F. Reynolds, *Martindale: The Extra Pharmacopeia*, 30th ed., The Pharmaceutical Press, London, 1993, p. 1255.
16. J. T. Carstensen, in *Pharmaceutial Principles of Solid Dosage Forms*, Technomic Publishing Co., Inc., PA, 1993, p. 20.
17. A. Martin, *Physical Pharmacy, Physical Chemical Principles in the Pharmaceutical Sciences*, Lea & Febiger, Philadelphia, PA, 1993, p. 431.
18. S. A. Lin and R. Y. Han, Pharmazie, 47, 266 (1992).
19. P. L. Ritger and N. A. Peppas, J. Controlled Release, 5, 23 (1987).

20. R. Bodmeir and O. Paeratakul, J. Pharm. Sci., 78, 964 (1989).
21. T. Ostberg, E. M. Lund, and C. Graffner, Int. J. Pharm., 112, 241 (1994).
22. T. Ostberg and C. Graffner, Int. J. Pharm., 111, 271 (1994).
23. T. Yotsuyanagi, I. Yoshioka, N. Segi, and K. Ikeda, Chem. Pharm. Bull., 38, 3124 (1990).
24. J. Timmermans and A. J. Moes, J. Pharm. Sci., 83, 18 (1994).