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PREPARATION AND RELEASE TEST OF ROTUNDINE-PIC POLYSACCHARIDE GRANULES†

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ABSTRACT

Rotundine, an analgesic drug, has been entrapped in a PIC polysaccharide granule. It was prepared in a two-step process, i.e., first granulation of a chitosan acetated solution containing Rotundine and then complexation of the polycationic component on the granular surface with a polyanionic solution of carboxymethyl glucomannan (CMGM). The granule has an average diameter of 1.38–1.53 mm and the drug content reaches 62.8%. The external release tests show that the T_{50} is at 45 min and total release period is 4 h, while in an artificial intestinal fluid no more than 60% of the drug has been released within 4 h. Some factors affecting the external release were examined, which included the *DS* of CMGM and its aqueous concentration, preparation and after-treatment conditions, etc.

†Dedicated to Otto Vogl on the occasion of his 65th birthday.

INTRODUCTION

Recently, as applications of polyion complexes (PIC, or symplex) have been extended [1], a two-polysaccharide PIC system was used as a carrier of bioactive agents. In our previous studies, Rotundine [2], an analgesic drug, was entrapped in a slightly crosslinked chitosan granule [3] and in a chitosan-alginate PIC granule [4], and external release tests were reported. The PIC carrier is capable of being shaped as film, sheet, fiber, cylinder or granule, etc. A unique merit of the polysaccharide PIC carrier is its excellent biocompatibility without toxic side effects or antigenic response. The PIC granule is swellable in aqueous media, while its integrity can be perfectly maintained over a wide pH range as a result of the strong coulombic attraction between oppositely charged sites on the macromolecule. The texture features of PIC granules, such as the nature and density of the resident charges on the complexed body and the pore parameters, can be properly regulated through varying the component ratio, employing inert additives, or modifying the macromolecular structure to meet the requirements needed in practice. Additionally, the preparation of Rotundine-PIC polysaccharide granules does not need the addition of an organic crosslinking agent (ECH or glutaraldehyde), and the complexing process is conveniently carried out at room temperature.

This study is aimed at providing one more polysaccharide PIC granule containing Rotundine. This one is composed of chitosan as the polycationic component and carboxymethyl glucomannan (CMGM) as the polyanionic one. For testing, it was released in an artificial GI liquid.

EXPERIMENTAL

Materials

Chitosan was prepared by deacetylation of chitin (Haimen Biochemical Plant, Guangdong, China) according to a general process [5]. CMGM is a derivative of Konjac glucomannan (89%) etherified with chloroacetic acid (CP) in a 0.35–0.70: 1.00 molar ratio (based on a pyranosic residue) in an alkaline medium. Rotundine is a white powder, of medical grade (Shifang Pharmaceutical Plant, Sichuan, China), and it was ground and sieved through 100 mesh prior to use.

Preparation of Rotundine-PIC Granule

Chitosan (3.0 g) was dissolved in 100 mL distilled water containing 1.5% acetic acid to give a chitosan acetated solution (185–210 mPa·s, 25°C). A desired quantity of Rotundine was added to the solution and dispersed thoroughly with a magnetic stirrer. The viscous solution was directly dropped into an alkaline alcoholic solution through a syringe needle (No. 8), and thus a chitosan granule containing Rotundine was formed. After being washed in distilled water, the granules in both the wet and dry states were separately complexed with a given concentration of CMGM solution. The Rotundine-PIC granules obtained were dried atmospherically at 60°C. For comparison, a portion of wet complexed granules was treated through the freeze-drying process.

Analysis and Release Test

Degree of deacetylation (*DDac*) of chitosan and degree of substitution (*DS*) of CMGM were determined by potentiometric titration. The intrinsic viscosities of both chitosan and CMGM were measured with an Ubbelohde viscometer as polyelectrolyte solutions. The MW of chitosan was calculated according to the following formula [5]:

$$[\eta] = 1.81 \times 10^{-3} \, MW^{0.93}$$

The determination of the pore parameters of the Rotundine-PIC granules was made with a Micromaritic Auto-pore (Model 9200). Rotundine dissolution was tested on a Beckman Spectrometer (Model DU-65) by the rotary basket method (100 ± 1 rpm, 37 ± 0.5°C, artificial GI juice) with the absorbance recorded at 282 nm. The linear regression equation for the concentration and the absorbance of Rotundine in the medium is

$$A = 9.231 \times 10^{-3} + 0.01520C \qquad (n = 6)$$

where A is the absorbance at 282 nm and C is the concentration of Rotundine (μg/mL). DSC was carried out on a Perkin-Elmer Thermal Analyzer (7 Series System) at a heating rate of 10.0°C/min.

RESULTS AND DISCUSSION

A Rotundine-PIC granule has been prepared in a two-step process, i.e., granulation of a chitosan solution containing Rotundine and then complexing of the chitosan on the granular surface with CMGM solution. The drug-containing chitosan solution could also be granulated in a one-step process by dropping the polycationic solution into a polyanionic solution. However, only granules of low uniformities in terms of drug content and shape were obtained by the latter process. The formulas and the main properties of the materials and the PIC (unloaded) are listed in Table 1.

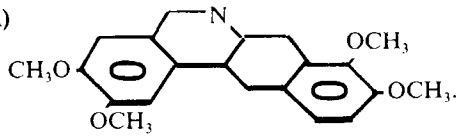
Chitosan, as a novel biomedical material, has been reported in a huge number of research works and some products have been recently developed [6]. Konjac glucomannan is also a natural polysaccharide with some pharmacological actions [7–9]. An oral acute toxicity test has demonstrated it to be nontoxic and safe [10].

In a test of drug dissolution it has been found that PIC granules swell but do not dissolve in media of 1.0–9.0 pH. It is assumed that the complexed surface of the Rotundine-PIC granule is a crosslinked network layer built up by salt-forming ions which not only plays the role of a rate-limiting barrier but retains the granular integrity in the media. It is also believed that a complexing solution of CMGM with a higher *DS* will result in a denser salt-bridge network when the other conditions remain equal, and that will be reflected by the increase in the time needed for release of 50% of the drug (T_{50}). Table 2 shows that an increase of *DS*(CMGM) from 0.26 to 0.40 leads to an increase of T_{50} from 35 to 53 min for wet granules (superscript a) and an increase from 38 to 43 min for dry granules (superscript b).

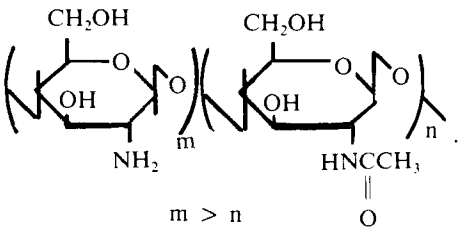
TABLE 1. Formulas and Properties of Main Materials Used for Preparing Rotundine-PIC Granules

Material	*DS* (*DDac*)	MW ([η][a])	Ttr (°C)[b]	Formula[c]
Rotundine			143.5 (mp)	(A)
Chitosan	(78.3%)	4.46×10^5	132.6	(B)
CMGM	0.26–0.40	(7.24–9.28)	299.8	(C)
PIC (unloaded)	(d. 1.38–1.53 mm)		305.1 (decomp)	

[a][η] in dL/mL.
[b]DSC data.
[c](A)



(B)



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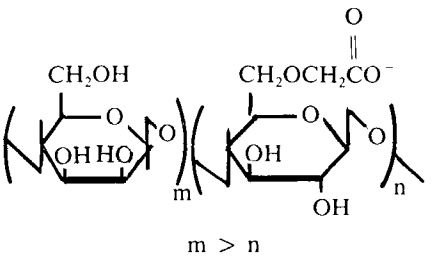

TABLE 2. Effects of *DS*(CMGM) and the Complexing Process on Rotundine Release (artificial gastric fluid, 37 ± 0.5°C)

	No.					
	1[a]	2[a]	3[a]	4[b]	5[b]	6[b]
DS	0.26	0.31	0.41	0.26	0.31	0.41
Drug content (%)	57	52	53	54	52	51
T_{50} (min)	35	38	53	30	37	48
Total amount released (%)[c]	100	94	86	100	99	96

[a]Wet granule.
[b]Dry granule.
[c]4 h.

Comparison of the data in Table 2 indicates that the samples complexed by the wet process (Nos. 1, 2, and 3) have a higher T_{50} than the corresponding samples complexed by the dry process (Nos. 4, 5, and 6). This may be attributed to the former having a larger swollen pore, which favors impregnation for the counterion portion, building of a thicker rate-limiting barrier, and reduction of drug release.

One more merit of the process used for the preparation of the Rotundine-PIC granule is that preblending the drug into an ionized polysaccharide solution conveniently increases the drug content to the desired region without compromising the strength and uniformity of the final granules. The Rotundine content can reach about 60%, but a blank chitosan granule crosslinked by ECH through soaking in a protonated Rotundine solution contains no more than 31% of the drug.

The Rotundine content also affects T_{50}. As shown in Table 3, a sample of 21% drug content has T_{50} at 32 min. On the other hand, one of 52% content has T_{50} at 45 min. On the average, the higher the Rotundine content, the more rapidly is the drug released.

It is expected that Rotundine release from the PIC granule occurs mainly by dissolution and leaching. A higher content of the drug will create more pores within the granule when the entrapped Rotundine has been dissolved and leached out. As a result, a greater number of pores, more surface area, and more channels are provided for the medium to contact and, in turn, to dissolve an additional quantity of the drug.

An attempt was made to qualitatively learn the effects of the complexed quantity of CMGM on the drug release rate. Five samples were prepared by complexing a granulated chitosan with various concentrations of CMGM (*DS*, 0.31) solution. Figure 1 shows the drug release profiles of these samples (pH 1.0). In Curve a (zero concentration), the granules broke 12 min after immersion; Curves b, c, d, and e show an increasing tendency in the release-sustaining effect as the complexing concentrations of CMGM solutions increase from 0.5 to 2.0%. However, there is a lack of qualitative distinction among the underbalanced, charge-neutralized, and overbalanced polyions. The kind, density, and distribution of the resident charges on the granular surface are key variables needing further study.

Curve f was drawn from a sample with the same formulation as Sample e, differing only in the aftertreatment being freeze-drying. Sample f contains Rotundine as high as 62.8% as compared to Sample e with only 53%. This should be attributed to its smaller equilibrium water content (not tested). For the sake of comparison, some properties of Samples e and f are shown in Table 4.

TABLE 3. Effects of Rotundine Content on T_{50}

	No.				
	1	2	3	4	5[a]
Drug content (%)	21.1	33.2	42.0	52.9	62.8
T_{50} (min)	32	38	40	45	78
Total amount released (%)[b]	89	92	100	100	100

[a]Freeze-dried.

[b]4 h, artificial gastric fluid.

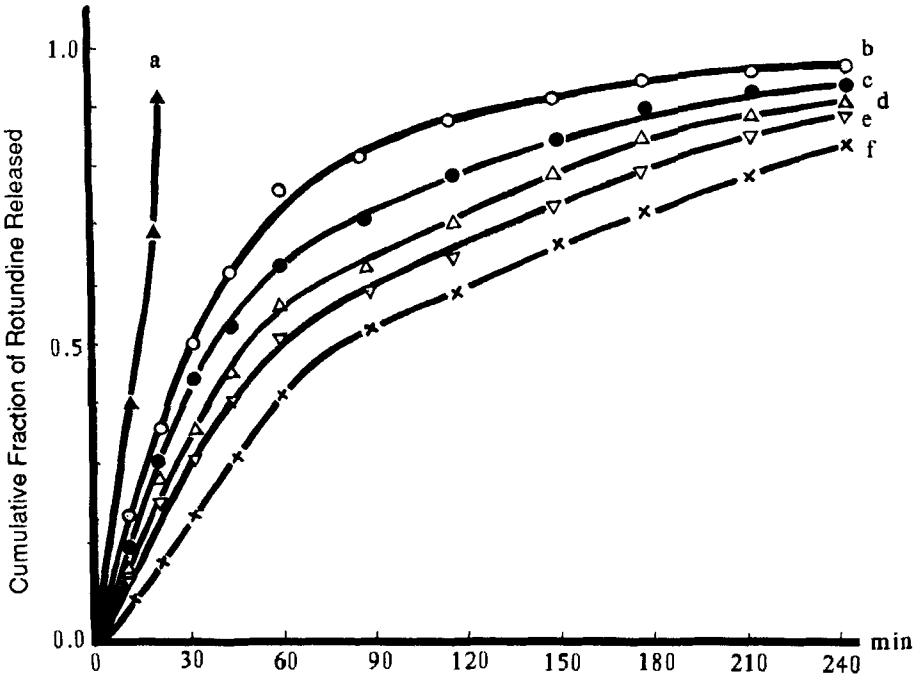

FIG. 1. External drug release of Rotundine (54 ± 3%)-PIC granules complexed with various concentrations of CMGM solutions. Concentrations: a, 0%; b, 0.5%; c, 1.0%; d, 1.5%; e and f, 2.0%. a–e were dried in the atmosphere at 60°C; f was freeze-dried.

T_{50} of Sample f is almost twice that of Sample e. The swelling degree (volume) of the unloaded PIC granules was determined at various pH values. The correlated values (pH) obtained are 25.52% (1.0), 21.75% (3.0), 19.40% (5.0), 16.10% (7.0), and 25.32% (9.0), respectively. The release test for the Rotundine-PIC granule was also carried out in an artificial intestinal fluid. A notable difference of the release curves is displayed in Fig. 2, where a slowly swelling stage lasts 65 min and has a longer total release time. No more than 60% of the drug was released within 4 h.

TABLE 4. Differences of Properties for Rotundine-PIC Granules Dried by Various Ways (refer to Fig. 1)

Sample	Conditions of drying	$\overline{A}_{pore}$, m^2g	$\overline{r}_{pore}$, μm	Porocity, cm^3/g	Drug content, %	T_{50}, min
e	60°C, atmosphere	0.97	20.48	6.97	53.0	39
f	Freeze-drying	22.24	71.90	5.11	62.8	71

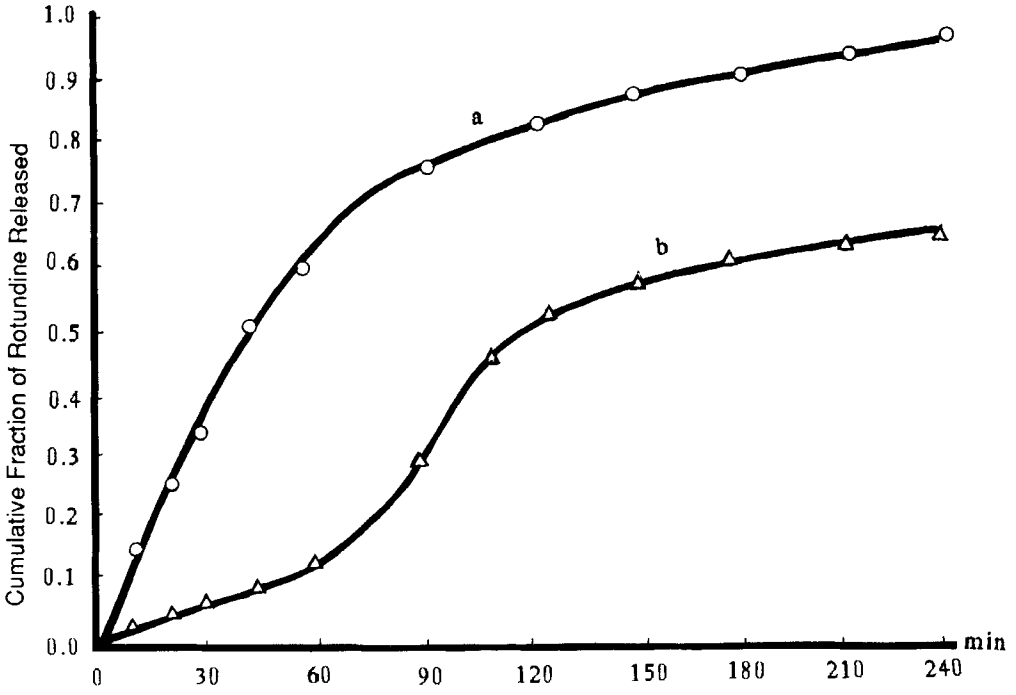

FIG. 2. External release of Rotundine-PIC granule in different media. a: In an artificial gastric fluid. b: In an artificial intestinal fluid.

CONCLUSION

A PIC granule composed of two iongenic derivatives from natural polysaccharides has been prepared and applied to the formula of a carrier entrapping Rotundine, an analgesic drug. A preliminary test of light-focus scorching of the tail of an animal has shown its pain-relieving effect. By regulation of the component ratio, course of preparation, and after-treatments, it is hoped that a novel oral dosage form for Rotundine delivery can be developed.

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