[Chem. Pharm. Bull. 30(11)4213—4215(1982)]

Use of Chitosan for Sustained-release Preparations of Water-soluble Drugs[1)]

YOICHI SAWAYANAGI,* NAOKI NAMBU, and TSUNEJI NAGAI

Faculty of Pharmaceutical Sciences, Hoshi University,[2)] Ebara-2-4-41, Shinagawa-ku, Tokyo 142, Japan

(Received May 28, 1982)

The applicability of chitosan as a vehicle for sustained-release preparations of water-soluble drugs was examined. Propranolol hydrochloride was selected as a model substance for this evaluation. Zero-order controlled release of propranolol hydrochloride from tablets containing chitosan was obtained in JP X disintegration medium No. 1 and in disintegration medium No. 2 following exposure to No. 1. Chitosan could be a useful vehicle for the controlled release of water-soluble drugs.

Keywords——chitosan; sustained-release; controlled release; zero-order release; dissolution; water-soluble drug; propranolol hydrochloride

Chitosan has been reported to be useful for pharmaceutical preparations.[3)] In previous papers the authors investigated the preparation of directly compressed tablets containing chitin or chitosan in addition to lactose or potato starch,[3c)] and confirmed that some drugs of low molecular weight pass through chitosan membrane.[3d)] Miyazaki *et al.*[3b)] reported the usefulness of chitosan as a vehicle for sustained-release preparations of indomethacin and papaverine hydrochloride, which are practically insoluble and sparingly soluble drugs, respectively.

The purpose of this study was to develop a sustained-release preparation of a water soluble drug as a part of a series of studies on pharmaceutical applications of chitin and chitosan, and propranolol hydrochloride was selected as a model substance for the evaluation of sustained-release of water-soluble drugs from the tablets containing chitosan in addition to lactose.

Experimental

Materials——The combined lactose/chitosan powders described in a previous paper[3c)] were used. Propranolol hydrochloride was purchased from Aldrich Chemical Company, Inc. To prepare tablets, 0.4 g of propranolol hydrochloride and 5.6 g of combined lactose/chitosan powders (chitosan content, 20, 40, 60, 80, and 100%) were blended in a mortar, then compressed into tablets.

Tablet-making by Direct Compression——Flat-faced tablets of 300 mg weight, 13 mm diameter and about 1.7 mm thickness were made by compressing the given amount of powder directly under 200 kg/cm^2 for 30 s using a Shimadzu hydraulic press for KBr tablets for infrared spectroscopy.

Measurement of Hardness of Tablets——A Kiya hardness tester was used at a relative humidity between 55 and 65%.

Dissolution Study——Dissolution of propranolol hydrochloride was tested in a JP X dissolution test apparatus (Method I) in 500 ml of JP X disintegration medium No. 1 (pH 1.2) or No. 2 (pH 6.8) or No. 1 for 1 h followed by No. 2 at an agitation speed of 50 rpm at 37°C. A tablet containing 20 mg of propranolol hydrochloride was used. Five ml of sample solution was withdrawn at appropriate intervals through a membrane filter (pore diameter 0.45 μm) and immediately replaced with an equal volume of the test medium. The sample was analyzed for propranolol hydrochloride by the ultraviolet(UV)absorption method at 288 nm using a Hitachi 124 spectrophotometer. Experiments were done in triplicate and the mean values were obtained.

Results and Discussion

The hardness of tablet is shown in Table I. The greater the chitosan content, the harder the tablet, as was the case in the previous paper.[3c)]

Table I. Effect of Chitosan Content on the Hardness of Chitosan/Lactose Tablets containing 6.67% Propranolol Hydrochloride

Content (%)	18.7	37.3	56.0	74.7	93.3
Hardness (kg)[a]	3.6±0.25	3.7±0.39	6.2±0.58	9.7±0.28	10.6±0.49

a) Mean of 5 determinations±S.D.

Dissolution profiles of propranolol hydrochloride from the tablets containing chitosan in addition to lactose in disintegration medium No. 1, and No. 2 following No. 1 are shown in Figs. 1 and 2, respectively. The greater the amount of chitosan, the greater was the retarding effect, that is, high levels of chitosan retarded the drug release. This was attributed to the extent of gel formation and the hardness of the tablets. The dissolution of the drug from the tablets in disintegration medium No. 2 alone was completed within 10 min because chitosan has little gel-forming ability at pH 6.8 and consequently disintegration occurred prior to gel-formation. The zero-order controlled release of the drug from the tablets in disintegration medium No. 1 was attributed to gel formation in the test medium, and this gelled structure was retained on transfer to disintegration medium No. 2, as was the zero-order controlled release of the drug, as shown in Fig. 2. The gelled structure was still retained even after 24 h, in contrast to the bulk solution. This gel-forming property of chitosan at low pH range may be useful for sustained-release preparation because a constant release of the drug from the gel in the gastrointestinal fluid should be obtained, and the gel might prevent irritation to the stomach. Most gel-forming polymers examined for sustained-release preparations, such as pectin,[4] konjac,[5] and sodium polyacrylate,[6] form gels or viscous solutions at high pH.

Since the cost of chitosan is low, these results suggest that chitosan might be a promising vehicle for sustained-release preparations of water-soluble drugs.

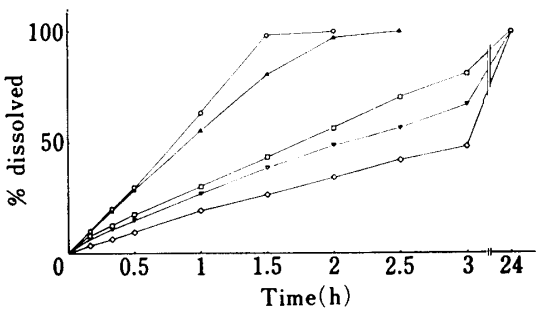

Fig. 1. Dissolution of Propranolol Hydrochloride from Chitosan/Lactose Tablets containing 6.67% Propranolol Hydrochloride in JP X Disintegration Medium No. 1 at 37°C

Chitosan content (%): ○, 18.7% ; △, 37.3%; □, 56.0 %;▽, 74.7%; ◇, 93.3%.

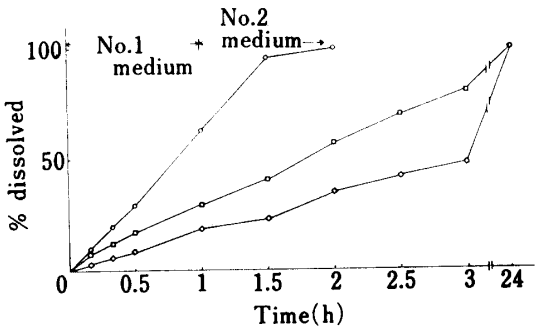

Fig. 2. Dissolution of Propranolol Hydrochloride from Chitosan/Lactose Tablets containing 6.67% Propranolol Hydrochloride in JP X Disintegration Medium No. 1 for 1 h followed by Medium No. 2 at 37°C

Chitosan content (%): ○, 18.7%; □, 56.0%; ◇, 93.3%.

Acknowledgement The authors are very grateful to Mr. Takashi Teshigawara and Miss Kayoko Kambai for their assistance in the experimental work.

References and Notes

1) This paper forms Part XXXI of "Pharmaceutical Interactions in Dosage Forms and Processing." The preceding paper, Part XXX: K. Takayama, H. Imaizumi, N. Nambu and T. Nagai, *Chem. Pharm. Bull.*, **30**, 3701 (1982).
2) Formerly, *Hoshi Institute of Pharmaceutical Sciences.*

3) *a*) R.A.A. Muzzarelli, "Chitin," Pergamon Press, Oxford, 1977; *b*) S. Miyazaki, K. Ishii, and T. Nadai, *Chem. Pharm. Bull.*, **29**, 3067(1981); *c*) Y. Sawayanagi, N. Nambu, and T. Nagai, *ibid.*, **30**, 2935 (1982); *d*) Y. Sawayanagi, N. Nambu, and T. Nagai, *ibid.*, **30**, 3297 (1982); *e*) Y. Sawayanagi, N. Nambu, and T. Nagai, *ibid.*, "in press'; *f*) Y. Sawayanagi, N. Nambu, and T. Nagai, *ibid.*, **30**, 4216 (1982).
4) Y. Takahashi, N. Nambu, and T. Nagai, *Chem. Pharm. Bull.*, **26**, 3836 (1978).
5) M. Nakano, K. Takikawa, and T. Arita, *Membrane*, **3**, 141 (1978).
6) Y. Sawayanagi, T. Sonobe, H. Kawata, N. Nambu, and T. Nagai, "in preparation."