Application of Curdlan to Controlled Drug Delivery. III.
Drug Release from Sustained Release Suppositories in Vitro

Motoko KANKE,*a,b Emi TANABE,a Hirokazu KATAYAMA,a Yoko KODA,a and
Hironori YOSHITOMIa

Fukuyama University, Faculty of Pharmacy and Pharmaceutical Sciences,§ 985 Higashimura-cho, Fukuyama, Hiroshima
729-02, Japan and Kyoritsu College of Pharmacy,§ 1-5-30 Shibakoen, Minato-ku, Tokyo 105, Japan.
Received February 14, 1995; accepted May 3, 1995

The use of curdlan, a natural β-1,3-glucan, in the preparation of sustained release suppositories was studied in vitro. To prepare the suppositories, indomethacin, prednisolone or salbutamol sulfate was mixed with curdlan gel. Preparation conditions, including heating time and curdlan concentrations of 5 and 10%, had little effect on the drug release. The toxicity (hypotonic or isotonic) of the media for the suppository preparation and for in vitro drug release study also had little effect on drug release. However, the heating temperature during gel preparation, the drug amount in the suppository and the type of release media did affect drug release. It was found that drug release was sustained and diffusion-controlled in the three drugs. And finally, curdlan can be applicable for use in a sustained release suppository.

Key words curdlan; sustained release; suppository; gel; diffusion-controlled

There are two types of suppositories available on the market regarding drug release: a suppository which softens or melts by body temperature prior to the release of the drug (medication); and a suppository which releases a medicament by dissolving in the rectal fluid. In both cases, medicaments are released as the suppositories disintegrate or liquefy prior to absorption. Medicaments are released or dissolved in the rectal fluid in a short time and are then spread through the sigmoid colon, often up to the descending colon. Then medicaments are absorbed into the systemic and/or portal circulation. However, if a rectal dosage form could stay and the drug be released in the lower rectum, a hepatic first-pass effect could be avoided. In addition, if the dosage form could release a sufficient but minimum amount of medicament at a constant rate for an extended period of time, it would be an ideal dosage form, locally or systemically.

Recently, the application of hydrogel to rectal dosage forms was reported.1 The polysaccharide, curdlan (β-1,3-glucan), is produced by a mutant strain (10C3K) of the bacteria Alcaligenes faecalis var. myxogenes 10C3.2 Curdlan is not water-soluble but forms a gel when its hot aqueous suspension is cooled.3 When the suspension is heated up to 60°C, thermally reversible gel is obtained (low-set gel). When it is heated above 80°C, thermally irreversible gel is formed (high-set gel).

In the previous study, spray-dried curdlan/theophylline particles were used for the preparation of controlled-release tablets. It was concluded that curdlan is an appropriate vehicle for the controlled release of drugs which are absorbed through the extended GI tract.4

In this study, curdlan gel suppositories were prepared and drug release was investigated in vitro in order to develop an ideal dosage form for local and systemic applications.

MATERIALS AND METHODS

Materials Curdlan, indomethacin (IM) and prednisolone (PD) were purchased from Wako Pure Chemicals (Osaka, Japan). Salbutamol sulfate (SS) was supplied by Hitachi Chemical Co., Ltd. (Tokyo, Japan). Mikametan® and Indacin® suppositories were purchased from Mikasa Pharmaceutical Co., Ltd. (Tokyo, Japan) and Banyu Pharmaceutical Co., Ltd. (Tokyo, Japan), respectively. All other chemicals and solvents used were of analytical reagent grade and used without further purification.

Preparation of Suppositories A drug was dissolved or suspended in either distilled water, isotonic sodium chloride solution (0.9% NaCl), or pH 7.4 isotonic phosphate buffered saline (PBS). Next, curdlan was added to the drug solution or suspension in order to obtain a drug-containing curdlan suspension (3—13% as curdlan concentration). One g of the suspension was poured into a glass test tube, then heated to and maintained at 60 or 95°C for 10 min in a water bath. The suspension was then kept at room temperature until completely cool. After being unmolded, the suppository was placed in a covered petri dish and stored in a refrigerator until use. Each suppository containing either 5, 10 or 20 mg of IM, 20 mg of PD, or 20 mg of SS in a 1 g suppository was used for in vivo release studies.

In Vitro Release Study The in vitro drug release from the suppositories at 37°C was determined by using a JP dissolution apparatus (DE-1S type, Tokyo Rikakikai Co., Ltd., Tokyo, Japan). The dissolution medium (distilled water, 0.9% NaCl or PBS; 300 ml) was placed in a round-bottomed flask and stirred at 50 rpm with a paddle stirrer at 37 ± 0.5°C. A suppository was placed in the flask at time zero. One ml of the dissolution medium was removed and the medium was replenished with the same volume of the medium. The drug amounts in a sample solution were determined spectrophotometrically (265 nm for IM, 245 nm for PD and 275 nm for SS).

Solubility of Drugs A quantity of drug powder in excess of its solubility was added into a glass vial containing 10 ml of the dissolution medium (distilled water, 0.9%}

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NaCl or PBS). The vials were shaken continuously (90 strokes/min) at 37°C. At appropriate intervals, aliquots of the suspension were withdrawn, filtered (pore size 0.45 μm, Millipore Corporation, Bedford, MA, U.S.A.), and immediately diluted with the medium. The drug amounts in the solution were determined spectrophotometrically as mentioned above.

Scanning Electron Microscopy (SEM) Surface and crosscutting sections of the suppositories before and after drug release were observed by a scanning electron microscope (Alpha-25-A type, Hitachi Akashi, Tokyo, Japan).

RESULTS AND DISCUSSION

Effects of Curdlan Concentrations on Drug Release

Suppositories prepared from less than 3% curdlan concentrations were not rigid, and were hard to unmold. In addition, syneresis in the gel was observed. On the other hand, the viscosities of curdlan suspension with concentrations larger than 13% were so high that it was difficult to pour it into molds. Therefore, curdlan concentrations of 5 and 10% were used for these drug release studies. Watanabe et al. reported that prednisolone release increased as xanthan gum and locust bean gum (vehicle) concentration increased in the range of 1—20%. They explained that the higher the gum concentrations, the higher the density of the network structure in the gels so that the prednisolone release was slowed down. However, 5 and 10% curdlan suppositories showed no difference in drug release. It is suspected that the network structures in 5 and 10% curdlan suppositories are similar regarding drug diffusion in the gel.

Effect of Heat Treatment during Preparation on Drug Release

It is known that heating conditions affect gel structure and strength. There is also a possibility that drug release might be affected by the gel structure. Therefore, IM suppositories were prepared with 10% curdlan, and heat was applied at 60 and 95°C for 10 min in order to investigate the heat effect on the gel structure in drug release. The Higuchi plots of the data on curdlan suppositories prepared by both temperatures showed linear release profiles (data not shown). These indicate that IM release from curdlan suppositories prepared at both 60 and 95°C are diffusion-controlled. The slope in the Higuchi plots for the suppositories prepared at a higher temperature was about 11% lower than the slope for the suppositories prepared at a lower temperature. Therefore, it can be said that the structure difference in low-set gel and high-set gel affects drug release.

Hereafter, suppositories were prepared with either 5 or 10% curdlan with a heat application of 95°C for 10 min.

Comparison with Marketed IM Suppositories

IM release from curdlan suppositories was compared with Mikametan® suppositories and Indacin® suppositories available on the market. The results are shown in Fig. 1. In the in vitro dissolution studies, IM release from the curdlan suppositories was more depressed than that from the commercial suppositories. It suggests that the effect could be sustained for a longer period by the curdlan suppository. In addition, both the curdlan suppositories and Mikametan® suppositories maintained their shape throughout the dissolution experiment with or without a sinker. Their drug release profiles are also identical in each set of suppositories regardless of the presence of a sinker. However, the drug release of Indacin® suppositories obtained without a sinker was much quicker than the drug release obtained with a sinker. This is because the suppository disintegrated when a sinker was not used, thus increasing the release surface area in the early stage of the experiment. However, the shape of the suppository did not change for up to 6 h when a sinker was used. Thus, the release surface area was kept constant for that period.

Effect of Drug Amount in Suppositories on Drug Release

To investigate the effect of varying drug amounts in a suppository, suppositories with three different amounts of IM were prepared. As seen in Fig. 2, the drug release rates increased with initial drug loads. The Higuchi plots shown in Fig. 2B show a linear release profile, indicating that IM release from curdlan suppositories is diffusion-controlled. If \( A > C_s \), Higuchi's equation is written as follows;

\[
Q = k \cdot t^{1/2}
\]

\[
k = (2 \cdot A \cdot D \cdot C_s)^{1/2}
\]

where \( Q \) is the amount of drug released per unit area of matrix at time \( t \), \( A \) is the total amount of the drug in unit volume of matrix, \( D \) is the diffusion coefficient of the drug in the matrix, \( k \) is a constant and \( C_s \) is the drug solubility. Parameter \( k \) obtained from the slope of each curve in Fig. 2B increased as the loading dose, parameter \( A \), increased (\( k = 0.0459 \cdot \text{loading dose}^{1/2} + 0.265 \), \( r = 0.973 \)). However, the degree of the increase was smaller than that expected from Eqs. 1 and 2, suggesting that \( D \) decreases as the loading dose increases.

Effect of Media for Suppository Preparation and for In Vitro Release Study on Drug Release

Three kinds of
Fig. 2. Effect of IM Contents on Drug Release from 10% Curdlan Suppositories in Distilled Water (300 ml) by Paddle Method (50 rpm)
[A] Amount released vs. time, [B] Higuchi plots of Fig. 2A. Each point represents the mean ± S.D. of 3 runs. IM contents: ○, 5 mg; ●, 10 mg; △, 20 mg.

Fig. 3. Release Profiles from 10% Curdlan Suppositories Prepared by Different Media in Various Release Media
Each point represents the mean ± S.D. of 3 runs. Each suppository contained 20 mg IM. ○, distilled water; ●, 0.9% NaCl; △, PBS.

Fig. 4. Release Profiles from 10% Curdlan Suppositories Containing 20 mg of Various Drugs in Distilled Water (300 ml) by Paddle Method (50 rpm)
[A] Amount released vs. time, [B] Higuchi plots of Fig. 4A. Each point represents the mean ± S.D. of 3 runs. ○, SS; △, PD; ■, IM.
IM-containing curdlan gel suppositories were prepared with distilled water, 0.9% NaCl and PBS. *In vitro* release studies were also carried out in the 3 kinds of media which were used for suppository preparation. As shown in Fig. 3A, B, the IM release profiles of the suppositories prepared from distilled water and from 0.9% NaCl were almost identical in the two media of distilled water and 0.9% NaCl. However, the suppository prepared from PBS showed a much greater release rate in the two media than the rates from the other 2 kinds of suppositories. On the other hand, as shown in Fig. 3C, the drug release rates of the suppositories prepared from distilled water and 0.9% NaCl were greater in the PBS medium than the rates obtained in distilled water and 0.9% NaCl, while the suppository prepared from PBS showed similar release behaviors in all 3 media (Fig. 3A, B, C). The conclusions obtained from the results are as follows:

1. The tonicity (hypotonic or isotonic) of curdlan hydrogel does not affect the drug release from the gel suppositories into various media.

2. Solubilities of the drug in the release media affected the drug release from the suppository since the solubility of IM at 37°C is higher in PBS (1.6 mg/ml) than in distilled water (0.009 mg/ml) and in 0.9% NaCl (0.009 mg/ml).

3. IM release from the suppositories is confirmed to be diffusion-controlled in the three media by evaluating the data in Fig. 3, although the Higuchi plots are not shown here.

**Comparison of Release Behavior from Suppositories Containing Various Drugs** Suppositories containing 20 mg of either IM, PD or SS in 10% curdlan were prepared and the drug release was studied in distilled water. The results obtained are shown in Fig. 4. The quickest release was observed with SS, followed by PD.

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**Fig. 5. Schematic Cross Section and Scanning Electron Micrograms of Suppository 72 h after Prednisolone Release**

Each photo shows its corresponding section in the scheme. Photo: 1, A—D; 2, A; 3, B; 4, C; 5, D; 6, A; 7, C.
and IM. The Higuchi plots for these drugs show linear release profiles (Fig. 4B). These indicate that drug release from curdlan suppositories is diffusion-controlled. The solubility of SS in distilled water at 37°C (230 mg/ml) is higher than that of PD (0.26 mg/ml) and IM (0.009 mg/ml). Parameter $k$, obtained from the slope of the IM or PD curve in Fig. 4B, nearly correlated with $C_s^{1/2}$ (Eqs. 1 and 2). However, parameter $k$ of SS was greater than that expected from Eqs. 1 and 2, suggesting that $D$ for SS is greater than for the others. It is summarized that drug release from the curdlan suppository was sustained and the release mechanism was diffusion-controlled for the 3 drugs used in this study.

SEM The curdlan suppository maintained its intact shape, even for 72 h, in the dissolution medium. Cross sections of the curdlan suppository observed by SEM 72 h after the drug (PD) release are shown in Fig. 5. It is easily estimated that the drug release occurred from the outer layer, since the drug particles are still packed in the center section corresponding to [A] in the scheme in Fig. 5, while only a small amount of drug particles exists in [C] and no particles in [D]. From the photos, it can be estimated that the drug release occurred by the diffusion of saturated drug solution into the bulk medium. In addition, the surface of the suppository looks smooth and does not show apparent holes by a magnification of 100 × (photo 5), even 72 h after dissolution.

In conclusion, curdlan gel is a suitable vehicle for sustained release suppositories. Drug release was found to be diffusion-controlled by the use of 3 model drugs.

REFERENCES


