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DISSOLUTION PROFILES OF CEFTIZOXIME SUPPOSITORY

Sotoo Asakura, Hiroko Ueda and Norio Ohnishi
Technological Developemnt Laboratories
Fujisawa Pharmaceutical Co., Ltd. Osaka, Japan

ABSTRACT

The in vitro dissolution rates of ceftizoxime suppository were compared using a rotating dialysis cell method, a dialysis membrane method and the JP XI rotating basket method. Only small variations in the dissolution rates were found with the rotating dialysis cell method and the rotating basket method, while the dialysis membrane method indicated rather large variation than other methods. In the rotating basket method, it was observed that a part of suppository bases came out through the wire mesh of the basket and spread over the surface of the dissolution medium. In the case of dialysis membrane method, it seemed that the large variations in dissolution rate was depending on a skill of the apparatus used.

As to obtain a good results, a selection of the rotating dialysis cell method was important. In vitro dissolutions of Ceftizoxime(CZX) suppository by using the rotating dialysis cell method were very rapid and also consistent with the absorption characteristics reported previously by Motohiro after rectal dose in pediatric subjects.

INTRODUCTION

From the standpoints of therapeutics and quality control of suppositories, one important attribute is their ability to release an active ingredient. For testing drug release rates of suppositories in

vitro, rotating basket, dialysis method, membrane diffusion and continuous flow methods have been proposed.[1-4] It was reported that each method has its own particular disadvantages, which are poor reproducibility and no good correlation between in vivo and in vitro data.[5] Yanahara and coworkers[6] have compared the methods for evaluating dissolution apparatuses by using commercially obtained indometacin suppositories. They have reported that good reproducibilities were obtained with dialysis membrane method and rotating dialysis cell methods.

The purpose of the present study was to evaluate the dissolution profiles of Ceftizoxime (CZX) suppository by using the rotating dialysis cell method.

EXPERIMENTAL

Materials

The CZX suppository 125 mg and the CZX suppository 250 mg (Fujisawa. Pharm. Co.) were employed. CZX solution used as a control was prepared by dissolving the CZX 125 mg in JP XI 2nd medium 5 ml.

Dissolution method

1) Rotating dialysis cell method

The apparatus (PTSW) obtained from Pharma Test Apparatebau GmbH was used. The amounts of the outer and the inner liquids were 900 ml and 3 ml, respectively. The wings and dialysis cell rotated simultaneously with the rate of 25 rpm.

Durapore filter HVLP 0.45 μm(hydrophilic, Polyvinyliden Floride), Durapore filter HVHP 0.45 μm(hydrophobic, Polyvinyliden Floride), Fluoropore filter FSLW 3.0μm (Polytetrafluoroethylene) and SSWP 04700 3.0μm were used as a membrane. All filter were obtained from Millipore Co.,Ltd.

2) Rotating basket method of JP XI

The apparatus of the JP XI rotating basket method was employed. Nine hundreds milliliters of JP 2nd test solution was used. Rotation speed of basket was 100 rpm.

3) Dialysis membrane method

The dissolution apparatus for suppositories (Toyama Industrial Co.) was used. The quantities of the outer and the innner liquids were 300 ml and 3 ml, respectively. The stirring rate of the cell was 25 rpm. Millipore SSWP 04700 3.0 μm membrane was employed.

Analytical method

Samples were taken at appropriate intervals and analyzed spectrophotometrically (HITACHI 200 - 20, double beam spectrophotometer) at the wavelength of 240 nm.

RESULTS AND DISCUSSION

1. Dissolution profiles of CZX suppository in the rotating dialysis cell method

Three kinds of filter used to the rotating dialysis cell method were evaluated. In case of HVLP filter, no significant differences were found in dissolution profile between the CZX suppository and CZX solution as shown in Fig. 1-A, indicating that the drug release from the suppository was very rapid through the HVLP(hydrophilic) filter. Similar dissolution profiles were also found with HVHP(hydrophobic) filter as shown in Fig. 1-B.

These findings suggest that the drug passes through the two types of polyvinyliden filter with the almost same rates regardless of their hydrophilic and lipophilic characters.

Figure 1-C shows the dissolution profiles in the FSLW filter. No drug release from the CZX suppository was observed. The drug diffusion of the CZX solution through the FSLW filter was also slower than those of the HVHP and the HVLP filter in spite of bigger pore size. This result suggests that CZX is so hydrophilic that it could not go through easily the high hydrophobic membrane such as Fluoropore filter.

From these results, it becomes clear that the FSLW filter is not suitable for dissolution test of the CZX suppository. It demonstrate that determination of filters provide a crucial results to the rotating dialysis cell method. The replicate runs of three times were performed to find the reproducibilities of dissolution rate with the rotating

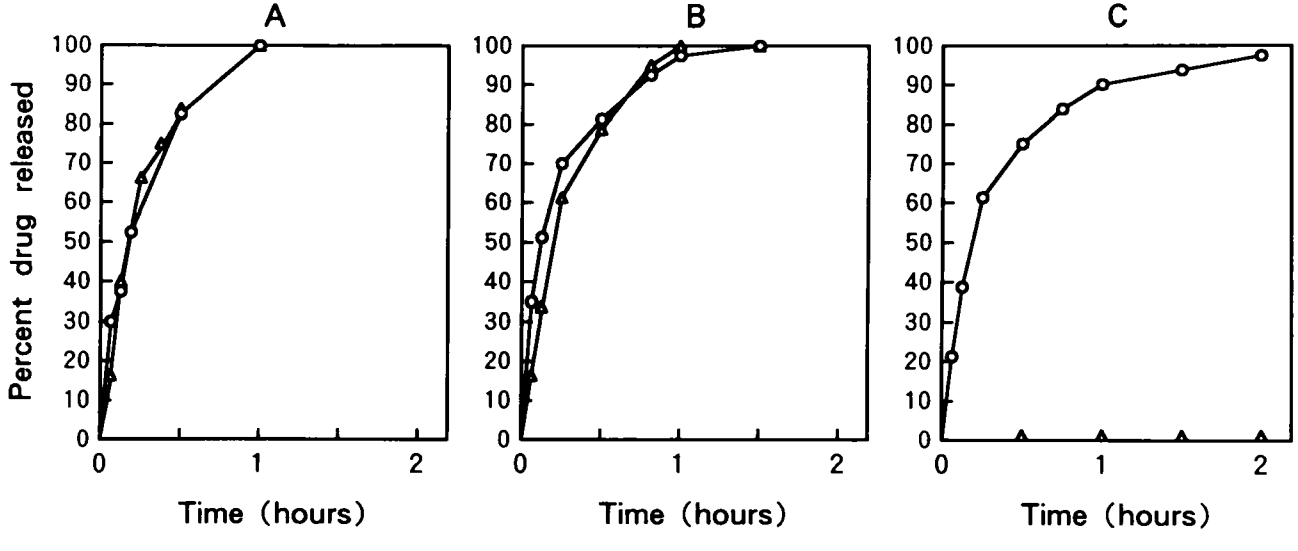

FIGURE 1

Dissolution profile of CZX from suppository and solution by the rotating dialysis cell method with three types of membrane

Membrane ; HVLP(A), HVHP(B), FSLW(C)
Sample ○ ; CZX solution (118mg/5ml)
△ ; CZX suppository 125mg potency
Liquid ; JP XI, 2nd medium
Rotation ; 25 rpm
Temperature ; 37 ℃

TABLE 1

Reproducibility of CZX release from the suppository by the rotating dialysis cell method

Sampling Time(min)	Released % (X± S.E.)	C.V.(%)
10	30.1 ± 4.19	13.9
20	57.9 ± 3.95	6.8
30	73.8 ± 3.22	4.4
45	88.7 ± 3.75	4.2
60	95.5 ± 2.16	2.3
90	101.1 ± 1.40	1.4

(n=3)

dialysis cell method equipped HVLP filter. As shown in Table 1, the results were reproducible and it was also suggested that this method is proposed for quality control of suppository.

2. Comparison of dissolution profile of CZX suppository in various method

Dissolution studies of the CZX soppository were also carried out with the rotating basket method of JP XI and dialysis membrane method in order to compare the data obtained from the rotating dialysis cell method. The dissolution profiles obtained from the rotating dialysis cell method and the rotating basket methods were reproducible as shown in Fig.2-A and 2-B respectively. As for rotating basket method, it was observed that a part of suppository base came out through the wire mesh of the basket and spread over the surface of the dissolution medium. It seems that this fact leads to a possibility of accidentally results accompanied with unreliable sampling and interfering of analysis.

The CZX release from the suppository was very rapid and reproducible because of high solubility in water(>500 mg/ml). In the rotating dialysis cell method, the inner surface of filter was maintained with dissolution liquid and the leaking of the ingredient to the outer liquid was not observed.

On the other hand, comparative large variation was observed with dialysis membrane method in Fig.2-C. It might be due to the fact that suppositories softened and sticked over the rotating shaft and the side

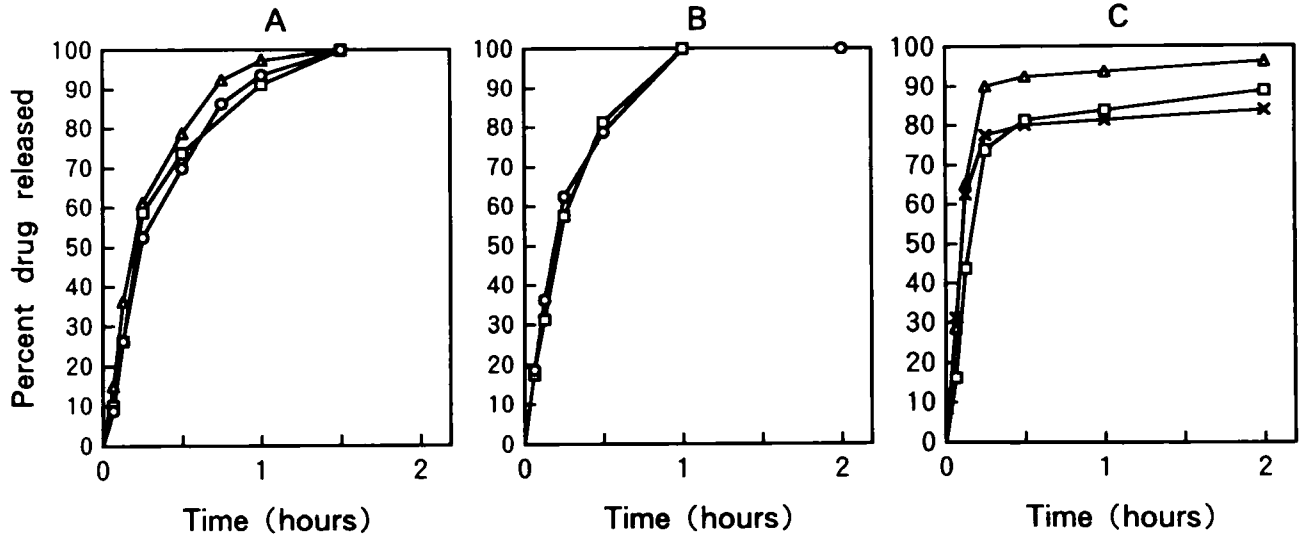

FIGURE 2

Replicate dissolution experiments for the release CZX from the rotating dialysis cell method(A), rotating basket method(B) and dialysis membrane method(C)

Sample ; CZX suppository 250mg potency
Membrane ; (A)HVLP
(C)Millipore filter SSWP04700(Cellulose acetate)
Liquid ; JP XI, 2nd medium
Rotation ; 25 rpm
Temperature ; 37 ℃

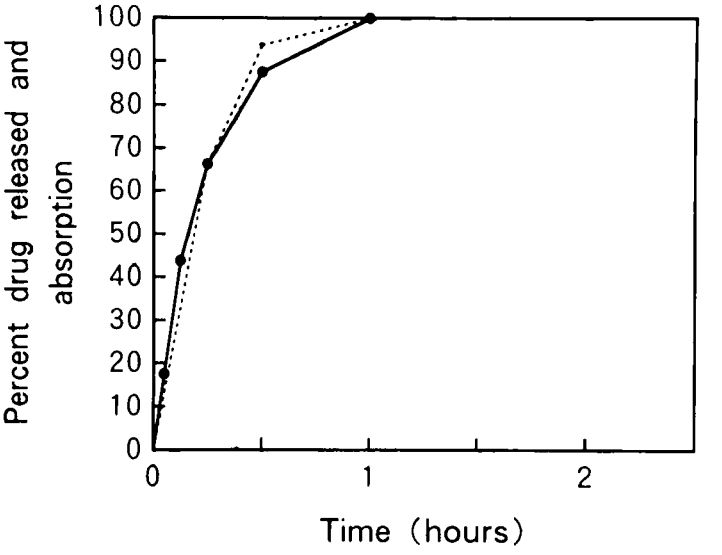

FIGURE 3

Comparison of the absorption rates of CZX calculated with Loo-Riegelman method and dissolution profile from CZX suppository

—●— CZX dissolution profile
(CZX suppository 125mg potency, HVLP membrane)
…… Absorption profile
(CZX suppository 125mg potency)

wall of the cell could not dissolve into the inner liquid. From these results, it was found the rotating dialysis cell method is suitable for evaluation of dissolution characteristics of CZX suppository.

3. Correlation between dissolution profile and in vivo absorption profile

The CZX serum levels after rectal dose in pediatric subjects have been reported by Motohiro and coworkers.[7] In order to compare the in vivo and in vitro behaviors of CZX suppository, the absorption rates of the CZX calculated with Loo-Riegelman method[8] and the drug dissolution rates were shown comparatively in Fig.3. The data suggested that the rectal absorption was very rapid and completed within 1 hour after rectal administration. It was concluded that there are relatively good

correlation between in vitro dissolution rates and in vivo absorption rates in the CZX suppository.

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