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RELEASE KINETICS OF INDOMETHACIN FROM POLYMERIC MATRICES

Jin-Shing Lai[1], Chiao-Hsi Chiang[2] and Tsui-Hung Wu[2]

[1] Veterans Pharmaceutical Plant, Chung-Li, Taiwan, ROC

[2] School of Pharmacy, National Defense Medical Center, Taipei, Taiwan, ROC

ABSTRACT

Polymeric matrices containing three different concentrations of indomethacin 1, 2 and 4% preparations were prepared. The release kinetics of indomethacin from matrices followed Higuchi equation. The effective diffusivity of indomethacin (D_m) was $1.32 \times 10^{-7} \pm 7.4\%$ cm^2/sec. The amount released in 24 hours from 10 cm^2 matrices with three different concentrations of indomethacin, were 12.0, 18.6 and 25.0 mg respectively. These matrices may potentially be developed as a transdermal therapeutic system.

INTRODUCTION

Indomethacin is one of the most potent nonsteroidal anti-inflammatory agent which benefits approximately 25% rheumatoid

arthritis patients by relieving pain, reducing swelling and tenderness of the joints, and increasing grisp strength. Unfortunately, adverse reactions occur with dosage exceeding 100 mg, primarily in the central nervous system and gastrointestinal tract. Side-effects seem to be related to the high initial plasma concentration (1).

In order to optimize the usefulness of indomethacin in the treatment of rheumatoid arthritis and to reduce its side-effects, indomethacin sustained-release oral tablet had been developed. However it doesn't exhibit a lower side-effects profile in comparison with conventional tablets (2). Another approach, indomethacin ointment had been studied (3,4). However, this preparation has some shortages, such as an uncertain surface area depending on the user, contaminating the clothing, and its short duration time. In this investigation, indomethacin polymeric matrices were designed and the *in vitro* release kinetics were studied. The purpose of this study is to overcome the disadvantages of ointment and to develop indomethacin polymeric matrix as a potential transdermal therapeutic system.

EXPERIMENTAL

Chemicals

The following drugs and chemicals were used as received from the manufactures. Indomethacin (USP grade), glycerin (USP grade), polyvinyl alcohol (BF-26, Chang Chung Chemical Co., Taiwan),

povidone (K-30, GAF Co., Linden N.J.), sodium acetate (E. Merck, Darmstadt), acetic acid, tetrahydrofuran and methanol (chromatographic grade, Alps Chem. Co., Taiwan).

Preparations of Matrices

The polymeric matrices for various concentrations of indomethacin were prepared according to Keith method (5). A polymeric matrix with 2% concentration of indomethacin was prepared as followings. Glycerin 30 g, previously mixed with a suitable amount of distilled water, was heated to 70 °C in a water bath. Polyvinyl alcohol 15 g and povidone 8 g were slowly added, then the temperature was elevated to 90 °C, until all ingredients were dissolved. Indomethacin 2 g was added, and then distilled water to make weight of 100 g. The obtained semi-solid was decanted into a stainless mold to form a disc which has a thickness of 2.5 mm with a surface area of 10 cm^2. For other concentrations, 0, 1 and 4% indomethacin preparations were prepared as the same procedure, but the weight of indomethacin were balanced with polyvinyl alcohol.

Release from Polymeric Matrices

The polymeric matrix disc was installed in a Franz diffusion cell, the top side was covered with an aluminum foil and the receptor-side has a capacity of 6 ml which was filled with a pH 7.4 of phosphate buffer as diffusion medium. A constant temperature water was circulated at 35 ± 1 °C for the cell. At each sampling interval, an aliquot of the diffusion medium was

drawn off and assayed spectrophotometrically. The volume of the solution was kept constant by replacing the volume of samples with equal amount of the diffusion medium. Each preparation was determined in four diffusion cells.

Solubilities in the Polymeric Matrix

A plain matrix disc without indomethacin (0%) was used to determine the solubility of indomethacin in the polymeric matrix. Three 50 ml-volumetric flasks containing a saturated indomethacin solution (pH 7.4 phosphate buffer) 25 ml were used. Three pieces of plain matrix discs were placed in these flasks which were shaked intermittently in a 35 °C water bath, and equilibrium state was obtained after five days. The drug concentration in the solution and the content of drug in the polymeric matrix were determined separately by HPLC method. The plain matrix density was determined by a pyconometer using water as medium. The content of drug in the polymeric matrix was divided by the weight then multiplied by the density to obtain the indomethacin solubility with a unit of mg/cm .

Assay Procedures

Total drug content of the polymeric matrix was determined by dissolving accurately weighed portion of matrix in 100 ml of distilled water by heating at 90 °C. A portion of liquid was filtered and diluted ten times. The drug concentration was determined spectrophtometrically by reading the absorbance at 318 nm.

A standard curve with slope of 0.02 for indomethacin concentration from 2.5 μg/ml to 45 μg/ml was constructed.

For the study of the release kinetics of various concentrations of indomethacin preparations, diffusion media (pH 7.4 phosphate buffer) in the receptor of the diffusion cells, were also analyzed spectrophotometrically, Samples were diluted five to ten times with distilled water before measurement.

HPLC system with a mobile phase-methanol/teterahydrofuran/acetate buffer (pH 3.2) 60:3:37, flow rate 2 ml, detector UV 254 nm and C18 μBondapak column (stainless, 3.9 mm (ID) x 30 cm) was used to determine the solubility of indomethacin in the polymeric matrix. Indomethacin has a retention time of 6.5 minutes in this system. The HPLC method also showed that the other ingredients of polymeric matrix did not interfer the assay of indomethacin in the spectrophotometric method.

RESULTS AND DISCUSSION

The release characteristics of different concentrations of indomethacin from the polymeric matrix over a twenty-four hours period is shown in Figure 1. The increase of the indomethacin in the receptor medium at different time interval was not linear, but the cumulative amount released versus the square root of time plot showed good linearlity for all three different concentrations of indomethacin preparations, they are shown in Figure 2 and Table 1.

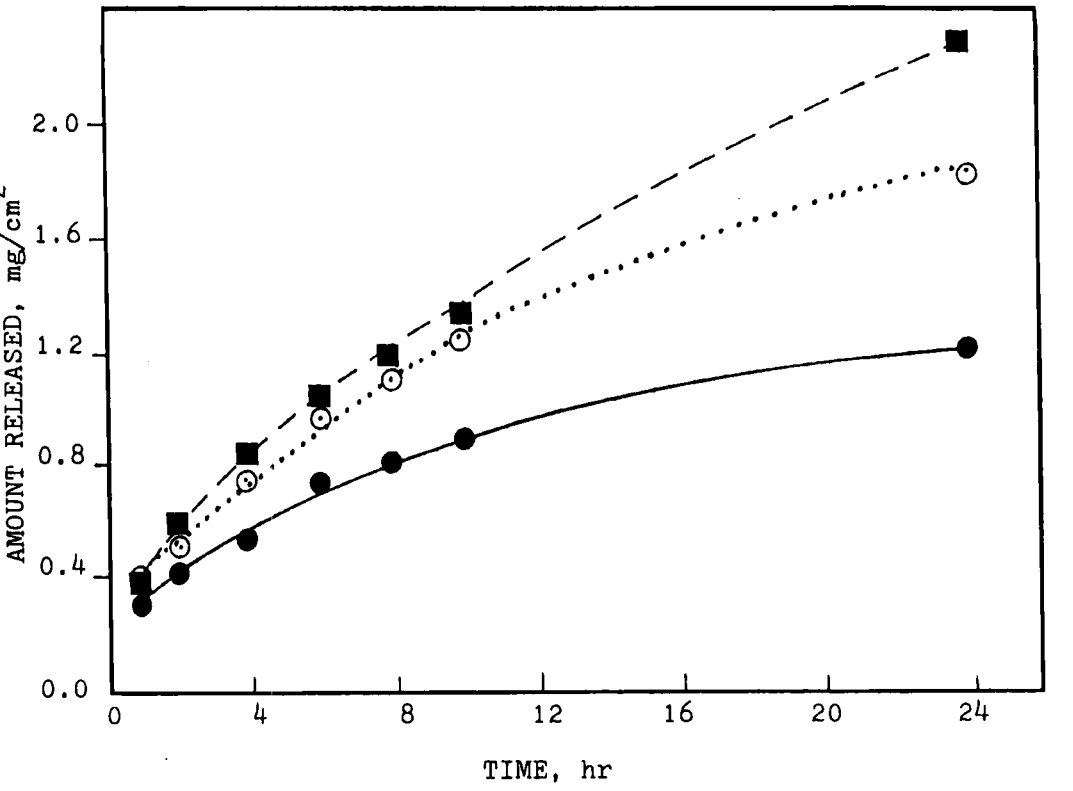

FIGURE 1

Release profiles for three different concentrations of indomethacin polymeric matrices. Key: (—●—) 1%, (··⊙··) 2% and (--■--) 4%.

According to Figure 2, the release kinetics of indomethacin from polymeric matrix may be described using the Higuchi equation (6):

$$Q=\sqrt{D_m(2A-C_p)C_p\,t} \qquad (1)$$

where Q is the cumulative amount of drug released from a unit surface area of disc, D_m is the effective diffusivity of drug in the polymeric matrix, A is the initial amount of drug

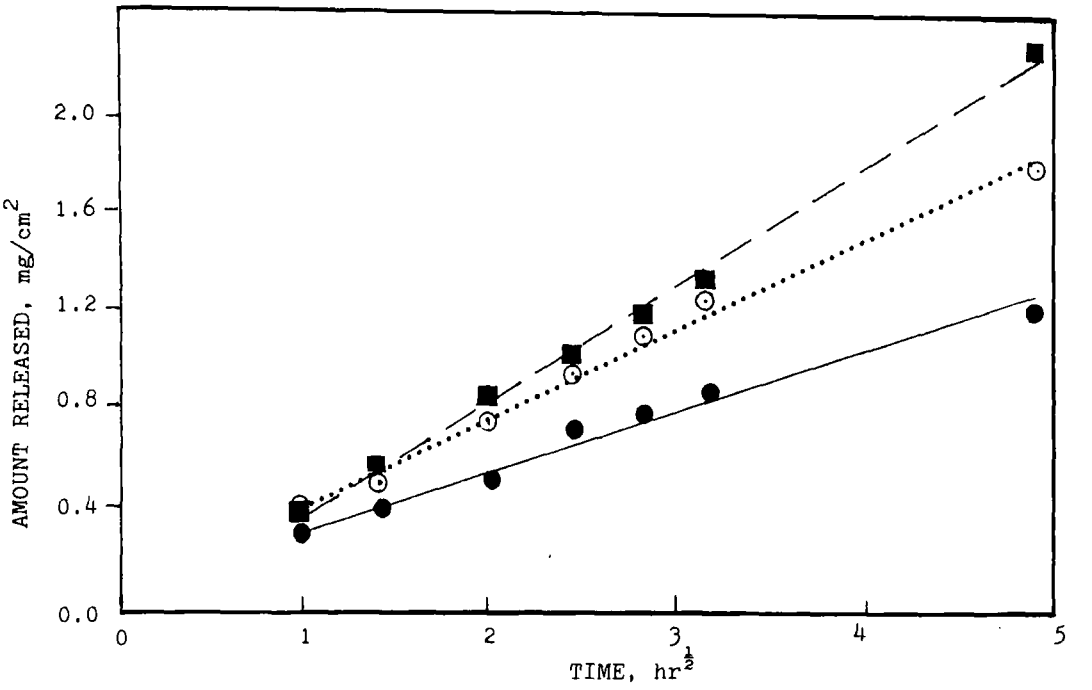

FIGURE 2

The cumulative amount released vs. the square root of time plots for three concentrations of indomethacin polymeric matrices. Key: (—●—) 1%, (··⊙··) 2% and (-■-) 4%.

TABLE 1

The Flux of Drug from Three Differnt concentration of Indomethacin Polymeric Matrices

Indomethacin Concentration	$Q/t^{\frac{1}{2}}$* ($mg/cm^2/hr^{\frac{1}{2}}$)	Regression Correlation Coefficient
1%	0.245	0.989
2%	0.380	0.997
4%	0.510	0.999

* Q is the in vitro cumulative amount of drug released per unit area of disc and $t^{\frac{1}{2}}$ is the square root of time.

TABLE 2

The Data for the Determination of the Effective Diffusivity of Indomethacin in Three Different Concentration Preparations

Indomethacin Concentration	$(2A-C_p)C_p$	$(Q/t^{\frac{1}{2}})^2$	D_m (10^{-7} cm^2/sec)
1%	116.8	0.060	1.43
2%	321.2	0.144	1.24
4%	730.1	0.260	1.28

Average of D_m = $1.32 \times 10^{-7} \pm 7.4\%$ cm^2/sec

incorporated in a unit volume of matrix, C_p is the solubility of drug in the polymeric matrix, t is the time. Using Q vs. $t^{\frac{1}{2}}$ plot, the slope is equal to $(D_m(2A-C_p)C_p)^{\frac{1}{2}}$, where A is obtained by using the indomethacin concentration (mg/g) to multiply the density of the plain matrix (1.09 g/cm^3), C_p was determined to be 9.36 ± 0.37 mg/cm^3 (n=3). Since A and C_p are known, then D_m can be calculated from the slope which is shown in Table 2. The average value of D_m for indomethacin is 1.32×10^{-7} cm^2/sec which is similar to the other compounds with a range of 10^{-7} cm^2/sec to 10^{-8} cm^2/sec (7,8).

The release amount of three different concentrations of indomethacin in 24 hours from 10 cm^2 discs are calculated

from their slope which was then multiplied by 4.9 ($\sqrt{24}$) and surface area 10 cm^2. They are 12.0, 18.6 and 25.0 mg respecttively for 1, 2 and 4% indomethacin concentration.

The bioavailability of indomethacin ointment had been studied (9), the results showed that the absorption peak is eariler than the oral administration, which shows that indomethacin has good skin penetration. Therefore, the polymeric matrix may be potentially developed as a transdermal therapeutic system to control the release of indomethacin. The polymeric matrix disc could be applied to the loc. dol. to relieve pain or reduce the side effects due to the lack of fluctuation of indomethacin concentration in the systemic circulation.

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