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COMMUNICATION

Permeation of Naproxen from Saturated Solutions and Commercial Formulations Through Synthetic Membranes

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ABSTRACT

The release of naproxen through synthetic membranes, mounted in modified Franz-type diffusion cells, was evaluated, either from saturated solutions or from commercially available topical formulations containing 10% naproxen. The results obtained showed that the porous type synthetic membranes chosen (cellulose acetate and polyethersulphone) can be used for assessing product performance in quality control procedures. The formulations interacted with the solid membranes (silicone and EVA) to change their diffusional characteristics. However, transfer in the membrane, and not the formulation was rate controlling. These membranes could not therefore be used in assessing product release performance for quality control.

Key Words: In vitro release tests; Naproxen; Synthetic membranes.

INTRODUCTION

The permeation of topical and transdermal drugs through the skin is influenced by many factors. Physicochemical properties, such as $\log P$, are particularly important as emphasized by Beetge et al.[1] for naproxen and other nonsteroidal anti-inflammatory agents.[1] In addition, the formulation can significantly influence the absorption process. It is often difficult to identify diffusion experiments that can be used to evaluate release, and the literature is confused about the appropriate choice of membranes for this. Human and animal skin have been used as in vitro models; in general,

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animal tissue is more permeable than human tissue. Good correlations can be found when in vitro and in vivo human studies are compared. However, the intrinsic variability of biological tissue often masks subtle formulation effects that can be important in assessing batch-to-batch conformity.

Several synthetic membranes have been investigated in attempts to evaluate the percutaneous absorption of topically applied drugs. In view of the problems of accessing human tissue, this would be an ideal solution; however, to date, it has proved rather unsuccessful. Synthetic membranes can be used to monitor the release properties of formulations provided an appropriate choice of membrane is made. They can then be used in quality control procedures, assuring batch-to-batch uniformity of topical products. They should be chosen to provide reproducible data with minimum variability using a simple methodology. These release processes have been studied for solution and suspension systems in semisolid formulations for many years.[2–5]

In this investigation, we have examined the permeation of naproxen through a number of synthetic membranes. Simple saturated solutions and commercial formulations have been used to determine the relative effects of the formulation and to determine which membrane system is most appropriate for this type of product. The aim is to produce a simple in vitro system that is reliable and reproducible for assessing the release kinetics of naproxen.

MATERIALS AND METHODS

Sodium chloride, disodium hydrogen phosfate, sodium dihydrogen phosfate monohydrate, potassium hydrogen phthalate, boric acid, phosphoric acid, acetic acid, and sulfuric acid, as well as acetonitrile (HPLC grade) were purchased from Merck (Germany). Naproxen was kindly supplied by Janssen-Cilag Farmacêutica, Lda (Portugal).

The commercial formulations included in this study were Reuxen® gel 10% w/w (lot 6J065A, expiry date 08/99 and lot 7L027A, expiry date 11/00) manufactured by Tecnifar, Ind. Farm. S.A. (Portugal) and Naprosyn® gel 10% w/w (lot 7C514, expiry date 03/00 and lot 8A036A, expiry date 01/01) manufactured by Janssen-Cilag Farmacêutica, Lda (Portugal). The release experiments were conducted before the expiry dates.

Solubility Studies

Since naproxen is a weak acid, the effects of pH on solubility were examined. Excess naproxen was placed in sealed conical flasks containing different aqueous solvent systems in the pH range from 1.0 to 9.0. These included hydrochloric acid solutions at pH 1.0, 3.0, and 5.0, and buffer solutions at pH 6.8, 7.4, and 9.0. The saturated solutions were magnetically stirred for 24 h in a water bath adjusted to $32 \pm 0.5^{\circ}C$. Samples were filtered through a 0.45-μm Gelman Sciences filter. The concentration of naproxen was then determined by a high-pressure liquid chromatography (HPLC) method. Samples of 20 μL were injected into a Merck LiChrospher 100 RP-8, 125×4 mm, 5 μm column. The solvent, a mixture of acetonitrile, water, and acetic acid (50:49:1), was pumped at a flow rate of 1 mL/min, with detection set at 280 nm. Under these conditions, naproxen had a retention time of 3 min.

Release Studies

Diffusion of naproxen from saturated solutions and commercial gels was performed in all glass Franz-type diffusion cells, with a 1-cm^2 diffusion area and a 4-mL receptor chamber. Aliquots of 1 mL saturated solution (containing excess naproxen crystals) or 1 g gel were added to the donor compartment. The diffusion cells were kept at $32 \pm 0.5^{\circ}C$ during the entire experiment. The receptor compartment was filled with isotonic pH 7.4 phosphate buffer, and 0.1- to 1.0-mL aliquots were withdrawal at predetermined time intervals and analyzed by HPLC.

Several synthetic membranes were tested and mounted on the diffusion cells. These were 0.2 μm pore size cellulose acetate and 0.45 μm pore size polyethersulphone, both supplied by Gelman Sciences. Polydimethylsiloxane was supplied by Technical Products, Inc., and 28% ethyl vinyl acetate (EVA) was supplied by 3M Pharmaceuticals Inc. All experiments were conducted with four replicates.

RESULTS AND DISCUSSION

Naproxen, a weak carboxylic acid, has an estimated (Advanced Chemistry Development Inc., Toronto, Canada) pK_a of 4.2. This estimated value is very good (the SRC PhysProp database gives an experimental value of 4.15) and means that at pH 7.4, most of the drug is ionized. To avoid confusion with

changing degrees of ionization, pH 7.4 phosphate buffer was used for preparing the saturated solutions of naproxen and as the receptor medium in all diffusion experiments. The solubility of naproxen at different pH values is shown in Table 1. A measured value of 5.4 g/L was obtained at pH 7.4.

Release from Saturated Solutions

The diffusion of naproxen from saturated solutions across the membranes is shown in Figs. 1 to 3. A reasonable linear relationship between the amount of drug released and the square root of time is observed for cellulose acetate (Fig. 1b). This suggests that the rate-controlling step is the diffusion within the saturated solution. From visual examination of the data, the last points appear anomalous and if the data points beyond 3 h are removed (Fig. 1b), the correlation is better and the measured gradient larger (Table 2). This indicates a mechanistic change in the system after 12 h. The observed gradient is a reflection of the diffusion coefficient of naproxen in the saturated solution. The reason for the break point could be due to bulk liquid flow through the porous structure of the membrane, settling of crystals on the membrane surface blocking the pore structure, or transport becoming limited by dissolution of the excess crystals present.

The results obtained for the polyethersulphone membrane are very similar (Figs. 2a,b), although in this case, there is a larger increase in the gradient. Data similarity demonstrates that the experiment is reporting on the diffusion through the saturated solution and is not being significantly affected by the diffusion through the porous membrane. If fluid flow were occurring at the earlier time points, a linear relation with square root of time would not be anticipated. A different behavior is observed with the other two types of membrane, EVA and polydimethylsiloxane (Figs. 3a,b). Here the membrane is solid and the drug transfer process has to occur via a partition diffusion mechanism. A linear relationship is not observed for the square root of time graphs (not shown). The amount of naproxen permeated is proportional to time, suggesting that simple partition and diffusion is taking place which can be modeled according to Fick's first law of diffusion. Interestingly, a very short lag time is observed and steady-state diffusion is rapidly established. The very much slower penetration also indicates that the membrane has become rate controlling and that partition and diffusion in the membrane dominates the transfer

Table 1. The solubility of naproxen as a function of pH.

pH	Measured solubility (mg/mL)
1.0	0.0016
3.0	0.0103
5.0	0.035
6.8	2.7
7.4	5.16
9.0	3.15

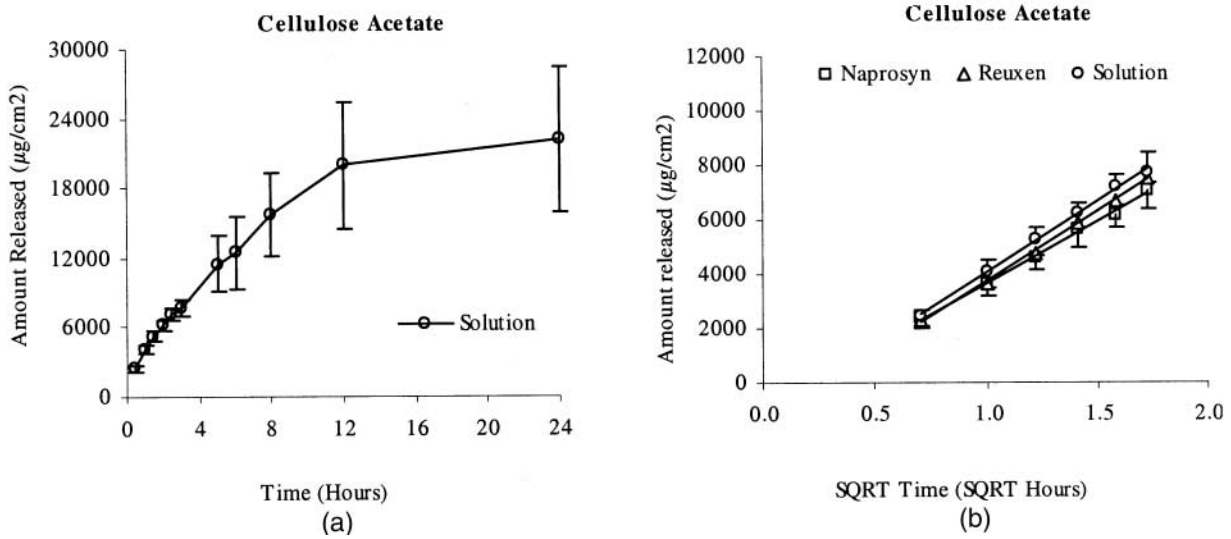

Figure 1. (a) and (b) Diffusion of naproxen across cellulose acetate.

Table 2. Release rate of naproxen across cellulose acetate and polyethersulphone membranes.

	Formulations		
Release rate	Solution Avr ± SD	Naprosyn Avr ± SD	Reuxen Avr ± SD
$\mu g/cm^2/h$			
$t_{0\rightarrow 24\,h}$			
Cellulose acetate	4,948.3 ± 1,715.1		
Polyethersulphone	5,549.0 ± 45.3	4,959.7 ± 547.4	4,947.4 ± 382.8
$\mu g/cm^2/\sqrt{h}$			
$t_{0\rightarrow 3\,h}$			
Cellulose acetate	5,153.9 ± 536.3	4,511.5 ± 230.8	5,135.6 ± 386.0
Polyethersulphone	5,088.5 ± 322.0	4,689.3 ± 414.8	4,856.7 ± 250.8

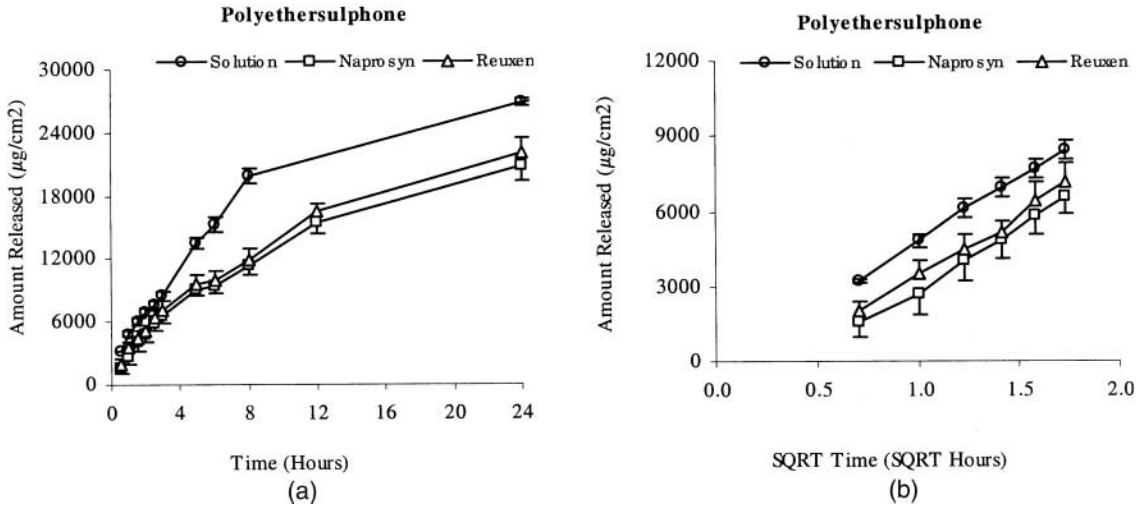

Figure 2. (a) and (b) Diffusion of naproxen across polyethersulphone.

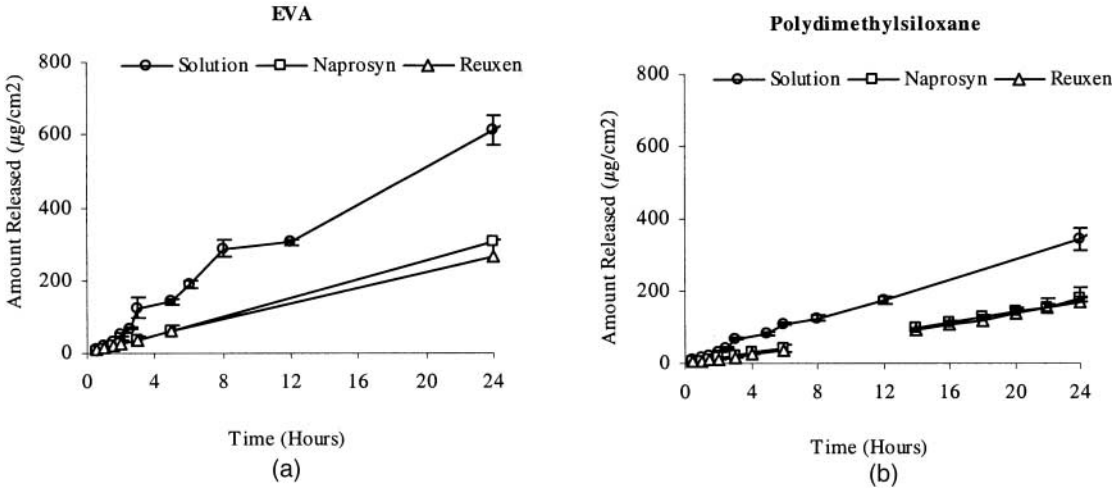

Figure 3. Diffusion of naproxen across (a) EVA and (b) silicone.

Table 3. Release rate of naproxen across EVA and polydimethylsiloxane membranes.

	Formulations		
Release rate	Solution Avr ± SD	Naprosyn Avr ± SD	Reuxen Avr ± SD
$\mu g/cm^2/h$			
$t_{0\rightarrow 24\,h}$			
EVA	25.6 ± 1.5	12.7 ± 0.8	10.7 ± 1.9
Polydimethylsiloxane	14.1 ± 1.2	7.3 ± 1.0[a]	5.6 ± 0.2[a]
		8.1 ± 2.0[b]	7.6 ± 2.1[b]

[a]0 to 6 h.
[b]14 to 24 h.

process. Partition of naproxen into the lipophilic environment will be low, since log D is small at pH 7.4 [predicted values (ACD software)]. As seen in Table 3, the gradients are within a factor of two of each other, 25.6 and 14.1 $\mu g/cm^2h^{-1}$, respectively, indicating that the overall barrier properties of the two membranes are very similar to one another. As rate control is within the membrane it is unlikely that these could be used to discriminate batch-to-batch variability between formulations containing naproxen.

Release from Naprosyn Gel

The diffusion of naproxen from the gel matrix of Naprosyn through cellulose acetate and polyethersulphone (Figs. 1b, 2b) shows a square root of time dependency similarly observed for the saturated solutions. The gradients of the lines are comparable for the two membranes, indicating that the experiments are just reporting on the diffusion properties of the formulation. A similar result was obtained for the saturated solutions, which implies that the drug is close to saturation in the gel matrix, and that diffusion in the gel medium is similar to that in an aqueous environment. It is the microviscosity not the bulk viscosity of the gel that is important in controlling the diffusion of naproxen.

In contrast, linear relationships with time were observed when polydimethylsiloxane (Fig. 3b) and EVA (Fig. 3a) membranes were used. As in the case of the saturated solutions, the membranes are rate controlling. For both membranes, the experiments were conducted for short and longer periods of time. The results demonstrate that sufficient data can be obtained in a 6-h period, giving an accurate measure of the steady-state flux (Table 3). Again, as observed for the saturated solutions, the steady-state flux for the EVA membrane was slightly faster. However, the flux from the formulations was slower than that from the saturated solution, suggesting that components from the formulation were entering the membrane and lowering the ability of naproxen to partition into it.

Release from Reuxen Gel

The results obtained for Reuxen gel are very similar to those obtained for Naprosyn, as observed in Figs. 1b to 2b. The square root of time graphs show that the gradients for Reuxen are slightly higher that those obtained for Naprosyn (Table 2). Steady-state fluxes for the silicone and EVA membranes are very similar to each other and in accordance with Naprosyn fluxes for the same set of membranes (Table 3). The slightly lower flux for Reuxen could indicate formulation components from the formulation partitioning into the membrane, lowering its partition coefficient in the same way that Naprosyn was lower than the saturated solution.

CONCLUSIONS

The release characteristics of the two gel formulations containing naproxen at the same concentration 10% w/w, through different membranes, have allowed the identification of a set of experimental conditions capable of characterizing the release process of the drug from the product. The identified experimental conditions may be used as a tool for comparing the in vitro release profiles of these gel formulations, assuring batch-to-batch uniformity, and can be used for supporting possible changes in formulations or their processing.[6] Comparison of the results obtained with those from the saturated solution revealed interesting aspects of the product

characteristics, namely the possible near-saturation naproxen content in the gels. It was also apparent that components from the formulations influenced the diffusional properties of the silicone and EVA membranes.

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