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Membrane penetration enhancement of ibuprofen using supersaturation

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Abstract

Permeation enhancement of ibuprofen from supersaturated solutions formed using the cosolvent technique was investigated using silicone as a model membrane. Hydroxpropyl methyl cellulose and hydroxpropyl-β-cyclodextrin were used to stabilise the supersaturated states. Physical stability studies showed best results for low drug concentrations in a 40:60 propylene glycol/water cosolvent system. Variations in flux across model silicone membranes from saturated solutions were observed as the PG content was increased. The flux of IBU increased with the degree of saturation for solutions prepared in a 40:60 PG/water cosolvent mixture. HPMC and CD were found to be effective in enhancing the stability of supersaturated solutions of IBU. The mechanisms of action are different for the two additives and are discussed.

Keywords: Supersaturation; Ibuprofen; Hydroxypropyl methyl cellulose; Hydroxpropyl-β-cyclodextrin; Diffusion; Stability; Silicone

1. Introduction

Drug delivery through the transdermal route is limited due to the low permeability of the skin. The stratum corneum, the outermost layer of the skin, acts as a major barrier and is often rate limiting. There is a continuous search for novel methods to enhance skin permeation. Physical enhancement techniques include iontophoresis and phonophoresis which are complex and expensive. Chemical enhancers such as oleic acid and Azone® enhance permeation by altering the skin properties. Many of the more potent enhancers are often toxic and can cause skin irritation. Recently increasing thermodynamic activity beyond the saturation value has been explored with success (Davis and Hadgraft, 1991; Pellett et al., 1994, 1997; Megrab et al., 1995; Schwarb et al., 1999; Raghavan et al., 2000). Use of such supersaturated states shows great potential because this technique is inexpensive and avoids altering the integrity of the stratum corneum. However, supersaturated states are thermodynamically unstable leading to crystallization of the drug. This results in a decrease of the flux.

Higuchi (1960) reported that flux from topical formulations can be enhanced by increasing the

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thermodynamic activity beyond its saturated value. The penetration of drugs was found to increase when volatile solvents were used (Coldmann et al., 1969; Kondo et al., 1987). Evaporation of the solvents resulted in a supersaturated state increasing the flux. However producing supersaturation by solvent evaporation is uncontrolled and limits the use of this method as a reproducible method to enhance permeation.

Davis and Hadgraft (1991) used a cosolvent technique to produce supersaturated solutions and enhance the permeation of hydrocortisone acetate. Hydroxypropyl methyl cellulose (HPMC) was used as an antinucleating agent to stabilise the supersaturated solutions. The cosolvent technique was subsequently applied with success to other drugs and using different polymers (Pellett et al., 1994, 1997; Megrab et al., 1995; Schwarb et al., 1999; Raghavan et al., 2000). These studies show that the ability to supersaturate and stabilise drug solution is dependent on the physicochemical properties of the drug.

The aim of the present work is to study methods for enhancing the percutaneous penetration of ibuprofen (IBU), a non-steroidal anti-inflammatory drug, by using supersaturated solutions in cosolvent mixtures of propylene glycol (PG) and water. HPMC as well as hydroxypropyl β-cyclodextrin (CD) was used to stabilise supersaturated systems of IBU. The use of CD to supersaturate Pancrastain, an anti cancer drug for parenteral use (Torres-Labandeira et al., 1990) and to inhibit crystallization of amorphous nifedipine in spray dried powders (Uekama et al., 1992) has been reported. Moreover, the association of CD with IBU has been found to affect the physicochemical properties of the drug (Loftsson et al., 1993; Mura et al., 1998).

In this paper, we report systematic investigations on the physical stability of supersaturated solutions of ibuprofen and permeation of the drug through a model silicone membrane. This was chosen as an initial choice of membrane since it facilitates the interpretation of the data and, importantly, to investigate the properties of the formulation e.g. the chemical potential of the permeant and stabilization of the supersaturated state. Experiments on skin would be more difficult to analyze since the barrier function could be modulated by the presence of the solvents and even CD. In certain publications, CD has been suggested as a permeation enhancer (Masson et al., 1999).

2. Materials and methods

2.1. Materials

Ibuprofen was a generous gift from Whitehall International (Havant, UK). Propylene glycol and HPLC grade acetonitrile were purchased from Fisher Scientific International Company (UK). Hydroxypropyl methyl cellulose grade 65SH viscosity 50cP with the brand name of Metolose was obtained from Shin-Etsu Chemical (Japan). Silicone membranes with a thickness of 300 μm were purchased from Samco (St Albans, UK). Hydroxypropyl-β-cyclodextrin (molar substitution 0.9) was obtained from Wacker Chemicals (Walton on Thames, UK).

All other chemicals were purchased from BDH (Poole, UK) and were used as received. Double distilled de-ionised water was used throughout this study.

2.2. Methods

2.2.1. Solubility studies

A saturated solubility curve of ibuprofen in PG/water cosolvent mixtures (varying from 100% water to 100% PG) was constructed. Saturated solutions were prepared by adding excess drug to the mixtures and stirring for 48 h at 32°C. After this period, the solutions were centrifuged, the supernatant was removed, suitably diluted and assayed using HPLC. Solubility studies were also conducted in a cosolvent mixture of 40% PG and 60% water containing HPMC or CD.

2.2.2. Preparation and stability of supersaturated solutions

The degrees of saturation (DS) achievable by mixing a solution of IBU in PG (at different concentrations; 6, 34 or 165 mg/ml) with water or aqueous solutions of HPMC and CD were calcu-

lated from the saturated solubility curve by dividing the concentration of the drug in the solution by its saturated solubility in the cosolvent mixture.

The physical stability of the supersaturated solutions obtained by mixing a solution of IBU in PG with either water or an aqueous solution of the additive (HPMC or CD at different % w/v) was investigated at 32°C, over a period of up to 36 h after preparation. The presence of crystals in the solutions was detected by optical microscopy using a Vickers microscope at a magnification of $100\times$.

2.2.3. HPLC analysis

HPLC analysis of IBU was performed using a Spectra Series P100 isocratic pump (Thermo Separation Products, Riviera Beach, FL) set at a flow rate of 1.2 ml/min, with a Spectra Series AS100 autosampler, a Spectra Series UV 100 detector set at 225 nm and a Spectra Series SP 4400 integrator. The stationary phase was an Apex reverse phase ODS 5 μm packed column (250×4.6 mm). A guard column (ODS, 4×3 mm) was used in conjunction with the column. The mobile phase was 65% acetonitrile, 35% phosphate buffer ($pH\approx3.2$). Calibration curves were constructed on the basis of the peak area measurements, using standard solutions of known concentrations. Samples were injected via a 20 μl loop and the retention time was ≈5.6 min.

2.2.4. Diffusion studies

The diffusion experiments across silicone membranes were conducted using Franz-type diffusion cells with diffusional areas of approximately 0.64 cm^2 and receptor volumes of ≈2 ml. Silicone grease was used to produce leak-proof seals between the membrane and the two compartments of the diffusion cell. Phosphate buffered saline, pH 7.4, was used as a receptor phase after it was degassed under vacuo and ultrasound. A magnetic bar was used to stir the receptor phase to ensure uniform mixing. The diffusion cells were placed in a water bath at 37°C on a submersible magnetic stirring bed to maintain the silicone membrane and the donor phase at 32°C. The cells were allowed to equilibrate overnight.

A volume of 0.5 ml of the drug solution was placed in the donor compartment which was occluded to prevent any evaporation. At predetermined intervals 0.2 ml of the receptor phase was removed and replaced with an equal volume of pre-thermostated receptor phase. The samples were assayed by HPLC.

The following series of experiments were performed:

1. diffusion of IBU from saturated solutions in different propylene glycol/water vehicles;
2. diffusion of IBU from supersaturated solutions (DS = 2.3) formed by mixing 80% of 165 mg/ml of IBU in propylene glycol with 20% of either water or 1% (w/v) HPMC or 1% (w/v) CD aqueous solution;
3. diffusion of IBU from solutions with different DS in the single cosolvent vehicle of 40:60%v/v propylene glycol/water or propylene glycol/1% (w/v) HPMC or 1% (w/v) CD aqueous solution;
4. diffusion of IBU from supersaturated solutions in a cosolvent mixture of PG/water 40:60 (v/v) containing different amounts of CD.

3. Results and discussion

3.1. Solubility studies

Fig. 1 shows the saturated solubility plot of IBU in the PG/water cosolvent system at 32°C. The drug has a very low aqueous solubility (0.12 mg/ml). With increasing percent of propylene glycol, the solubility of IBU increases exponentially, the solubility in PG (301.3 mg/ml) is almost 3000-fold higher than its aqueous solubility. This is not surprising since PG is used as a solvent in pharmaceutical formulations to increase the solubility of lipophilic compounds.

The DS achievable by mixing a solution of IBU in PG at 6, 34 and 165 mg/ml of drug with different ratios of water are given in Fig. 2. The highest DS that can be achieved with these concentrations is $118\times$ which is obtained by mixing 10% of 165 mg/ml IBU solution in PG with 90% water.

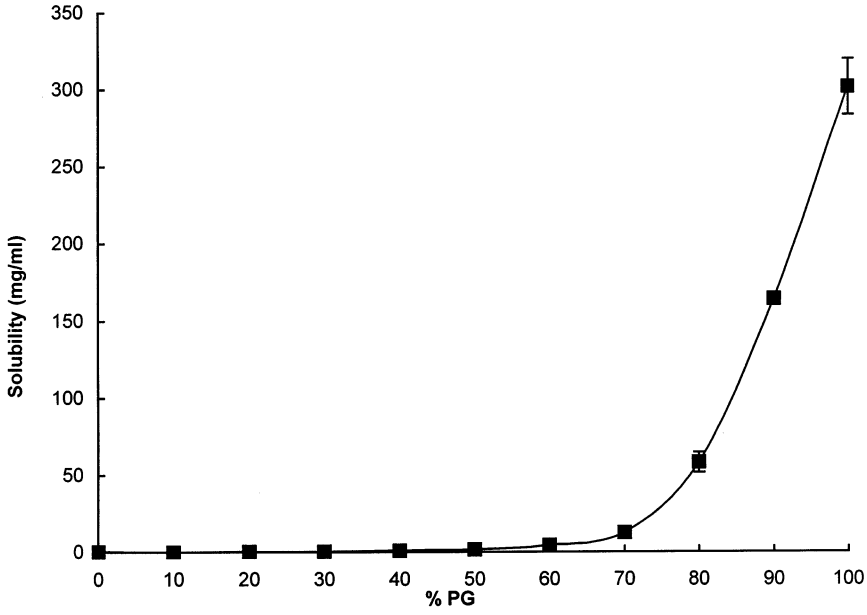

Fig. 1. Solubility of IBU in a PG/water cosolvent system at 32°C ($n = 3$).

3.2. Physical stability

The physical stability of supersaturated solutions of IBU with different DS was studied. Three different concentrations of IBU, namely 6, 34 and 165 mg/ml were used. From the theoretically derived DS given in Fig. 2, supersaturated solutions up to 4.6 × saturation were selected and the data obtained are summarised in Tables 1 and 2. The stability data were obtained by observing the appearance of crystals under the microscope. Table 1 gives the stability data for solutions without any additives. Table 2 gives the data for solutions containing HPMC and CD.

3.2.1. Without additives

At high concentrations of IBU (165 mg/ml), crystals were observed after 30 min at a 2.3 × saturation whereas solutions were stable at this DS when lower amounts of IBU were used. This suggests that high concentrations are not suitable for sustaining stable supersaturated solutions. The solutions (6 and 34 mg/ml) at 2 × saturation were transparent up to at least 36 h. These solutions are in a metastable zone and do not crystallize spontaneously.

Solutions at higher DS were opaque on preparation confirming that nucleation had occurred. The particles were very small and could not be seen under the microscope. In most cases, the solutions remained opaque up to 36 h and did not show observable growth. Crystals were however observed in the 34 mg/ml solution at 4.6 DS after 2 h.

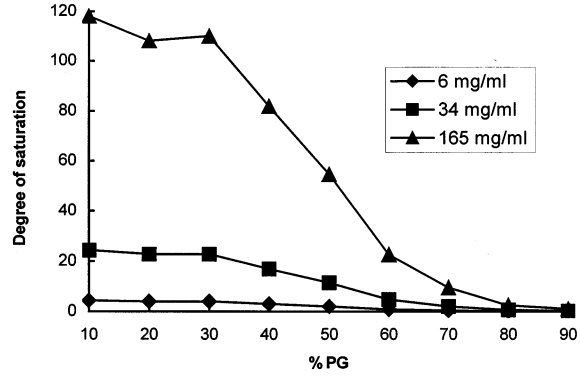

Fig. 2. DS that can be achieved by mixing 6, 34 or 165 mg/ml of IBU in PG with water.

Table 1
Physical stability data at 32°C for supersaturated solutions of varying DS of IBU without additive

IBU conc in PG (mg/ml)	PG (%)	DS	Stability 4 h	Stability 36 h
6	10	4.3	Opaque	Opaque
6	20	4	Opaque	Opaque
6	30	4	Opaque	Crystals
6	40	3	Opaque	Opaque
6	50	2	Transparent	Transparent
34	60	4.6	Crystals	Crystals
34	70	1.9	Transparent	Transparent
165	80	2.3	Crystals	Crystals

3.2.2. With additives HPMC and CD

The stability of IBU supersaturated solutions were studied in the presence of HPMC and CD and the results are summarised in Table 2. The crystallization time in these studies is defined as the time at which crystals could be observed under the microscope (magnification $100\times$). HPMC and CD did not influence the crystallization of IBU at high drug concentrations. The crystallization process was either inhibited or retarded by the presence of the additives when low concentrations of the drug were used. The supersaturated solutions with HPMC containing 6 mg/ml of IBU in PG were translucent on preparation and up to 36 h. However, crystals were not observable under the microscope. Nucleation of IBU appears to take place in the supersaturated solutions in the presence of HPMC. However the polymer inhibits the growth thus producing a stable microsuspension. This was confirmed by particle size analysis using a Coulter Counter. The average particle size determined on preparation was found to be ≈ 1 μm and remained unchanged over the 36 h period. In the case of CD, the solutions were transparent up to 36 h indicating that nucleation is inhibited over this period. CD possibly changes the metastable zone by altering the solubility of the drug. The solubilizing effect of CD on IBU could be involved in the nucleation inhibition process.

When 34 mg/ml of IBU was used, the solutions in the presence of HPMC were translucent and crystals were observed at 36 h whereas in the case of CD, crystals were observed after 3–4 h indicating that CD does not influence the crystallization of IBU. This confirms that the mechanisms of stabilization are different in the two cases.

3.3. Diffusion studies

Diffusion experiments of IBU from subsaturated, saturated and supersaturated solutions were

Table 2
Physical stability data at 32°C of supersaturated solutions of IBU containing either HPMC or CD

Composition	Additive (% w/v)	Crystallization time (h)
	None[a]	>36
DS = 3	1% HPMC[b]	>36
IBU conc. in PG, 6 mg/ml	2% HPMC[b]	>36
40%PG; 60% water	1% CD	>36
	5% CD	>36
	10% CD	>36
	None[a]	2
DS = 4.6	1% HPMC[b]	36
IBU conc. in PG, 34 mg/ml	2% HPMC[b]	36
60%PG; 40% water	1% CD	3
	5% CD	3
	10%CD	4
	None	0.5
DS = 2.3	1% HPMC	2
IBU conc. in PG, 165 mg/ml	2% HPMC	2
80%PG; 20% water	1% CD	1
	5% CD	1
	10%CD	1

[a] Opaque on preparation.
[b] Translucent on preparation.

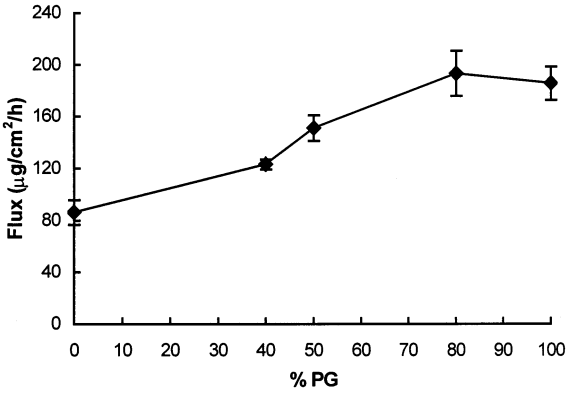

Fig. 3. Flux of IBU from a saturated solution in different PG/water cosolvent mixtures ($n \geq 3$; $\pm$ SD).

performed across silicone membranes. Flux values were determined from the steady state region of the diffusion profiles obtained using linear regression analysis.

3.3.1. Saturated solutions in PG/water cosolvent mixtures

Diffusion experiments were performed on saturated solutions of IBU in the different cosolvent mixtures in the presence of excess drug. From Fig. 3, it can be seen that with a high proportion of water, the flux was less than that from solutions containing a high proportion of PG. In fact, the flux of IBU in 100% PG was twice the value in 100% water. In ideal conditions, the flux from a saturated solution should be constant irrespective of the vehicle used. Variations from this ideal behaviour are attributed to vehicle-membrane interactions (Poulsen, 1972; Barry, 1983; Twist and Zatz, 1986; Pellett et al., 1994). In the example quoted by Pellett et al., there appears to be a discontinuity in the increase in flux with PG concentration. At 60% PG and above, the flux of piroxicam was significantly higher than the values below 60%. In choosing suitable cosolvent systems for supersaturated solutions, the effect of PG on the membrane should be taken into account. In our experiments this variable was avoided by using the same PG/water ratio and by changing the amounts of drug to achieve different DS.

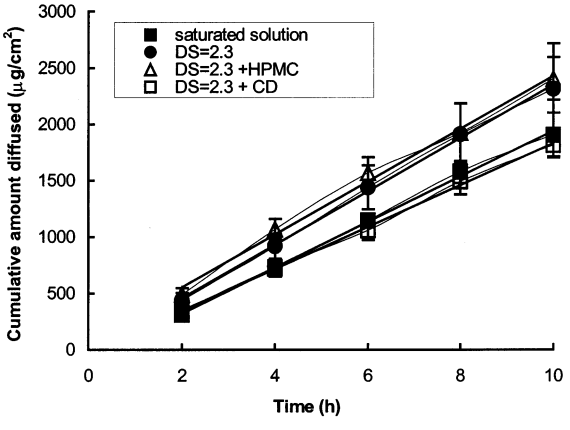

Fig. 4. Diffusion profiles of IBU from supersaturated solutions ($2.3\times$) in 80:20%v/v PG/water in the absence and presence of additives (1% w/v HPMC and 1%CD in water) ($n \geq 3$; $\pm$ SD).

3.3.2. Supersaturated solutions in 80:20 PG/water mixtures

Supersaturated solutions with a DS of 2.3 were prepared by mixing 80% of 165 mg/ml of IBU in PG with 20% of either water or 1% aqueous solutions of HPMC or CD. The diffusion profiles are plotted in Fig. 4. In the case of saturated solutions, excess drug was used in the donor compartment to maintain infinite dose conditions. A slight increase in the flux was observed for the supersaturated solutions with and without HPMC compared to the saturated solution however this increase was not significant. The results of the diffusion as well as the physical stability studies show that supersaturated solutions cannot be stabilised when high concentrations of IBU are used. This confirms difficulties found in previous attempts to stabilise supersaturated ibuprofen solutions.

3.3.3. Solutions at different degrees of saturation in 40:60 PG/water mixtures

Based on the physical stability studies, a different cosolvent system of 40:60 PG/water was chosen. Supersaturated solutions at different DS were prepared using low concentrations of IBU in PG (4–14 mg/ml in PG). The solutions of 0.5 and $1\times$ saturation were prepared by dissolving the appropriate amounts of the drug in the cosolvent mixture. The diffusion experiments were carried out over a period of 4 h at intervals of 30 min because significant depletion of the drug in the

donor compartment occurred after this time (≈ 50% depletion at 6 h for the lowest concentration).

Fig. 5 shows the flux data as a function of the DS for solutions prepared using 40% PG and 60% of water or with the additon of 1% HPMC or CD. An increase in flux compared to that of the saturated system was observed with increasing DS.

3.3.3.1. Without additives. When no additive was present, the flux increased up to 6 DS and decreased at higher DS. The increase was directly proportional to the DS up to 4 × saturation. At 5 and 6 × saturation, the flux started deviating from linear relationship. Moreover, the standard deviation was noticeably higher indicating that these systems are highly unstable. This is also reflected in the 7 × saturated system where the flux decreases almost to that of the saturated solution.

It should be noted that the flux at DS = 1 without excess drug is ≈ 60 μg/cm^2 per h which is half the value of the flux when excess drug is present in the donor phase. The reason for this is not clear at present but further studies are being carried out to understand this behaviour.

3.3.3.2. With HPMC. The flux increased with DS up to 7 × saturation. However, the flux at any DS was slightly lower compared to the flux without any additive apart from the 7 × saturation where a higher flux was obtained. The decrease of the flux could be due to a change in the drug solubility caused by the presence of HPMC. This effect is improbable since the solubility of IBU in a cosolvent mixture of 40:60 PG/1% HPMC solution was found to be very similar to the value obtained for the same system without HPMC. The lower flux could be a result of an interaction between IBU and HPMC. Even though the flux is slightly lower, HPMC helps in sustaining the su-

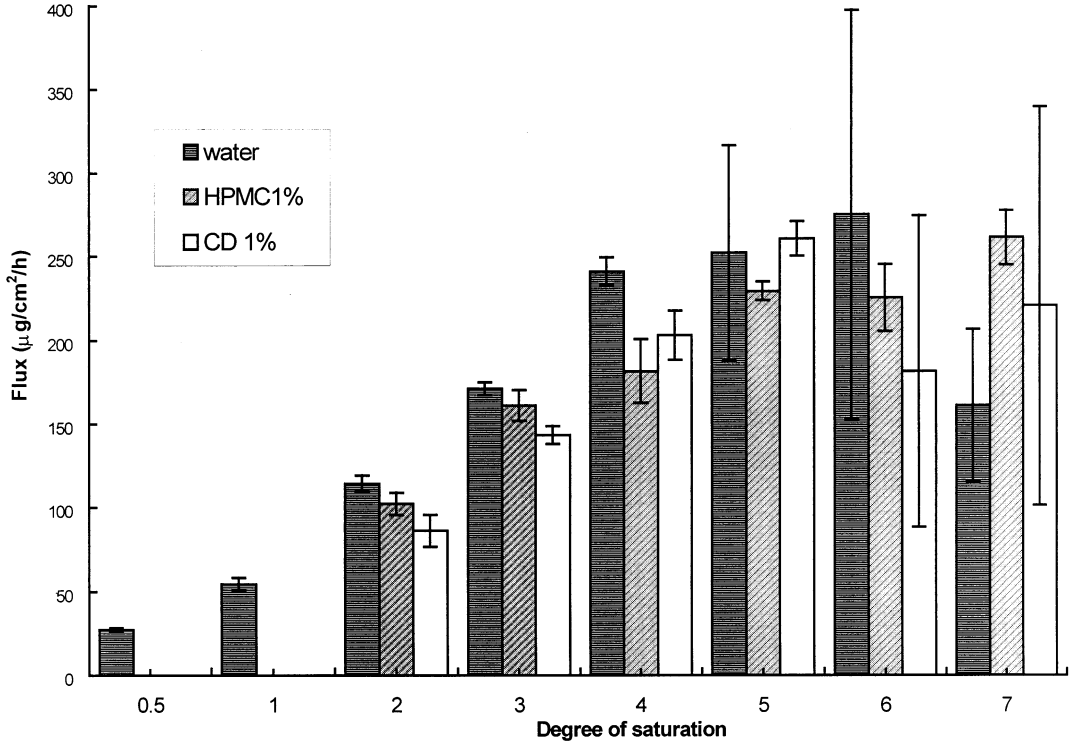

Fig. 5. Flux of IBU from solutions at different DS in the cosolvent mixture PG/water 40:60%v/v in the absence and presence of additives ($n \geq 3$; ± SD).

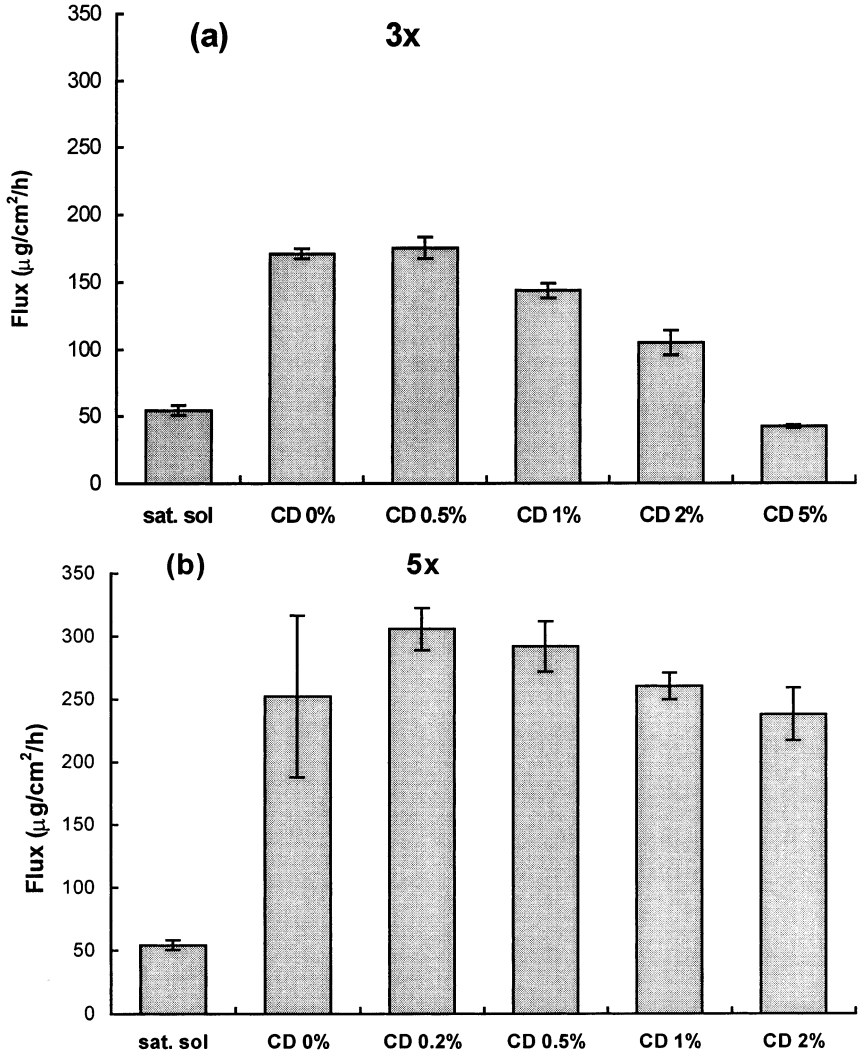

Fig. 6. Flux of IBU from supersaturated solutions at (a) 3 and (b) 5 DS containing different amounts of CD ($n \geq 3$; $\pm$ SD). The flux from the saturated solution is given in the graph for comparison.

persaturated state as seen from the low standard deviations obtained for solutions containing HPMC and the physical stability studies.

3.3.3.3. With CD. The flux from supersaturated systems prepared using a 1% CD solution increased with DS up to 5 × saturation and decreased at higher DS. The maximum enhancement with a low standard deviation was obtained at 5 × saturation. The decrease of flux at higher supersaturations indicates that the solutions are in the labile zone. CD does not influence the crystallization process. As in the case of HPMC, the flux values were lower compared to those from solutions in which no additive was present. The flux behaviour can be attributed to the interaction between IBU and CD.

In order to understand the mechanism of the effect of CD on the flux of IBU, diffusion experiments were performed using a constant amount of the drug (3 or 5 × saturated solutions) in the presence of varying amounts of CD. The results

are presented in Fig. 6a and b. The flux remained unchanged at low concentrations of CD and decreased at higher concentrations.

CD is known to form an inclusion complex with IBU and to change the solubility of the drug in aqueous solutions (Loftsson et al., 1993; Mura et al., 1998). The solubility of IBU was determined in 40:60 PG/aqueous solutions containing different amount of CD (Fig. 7). The solubility increased proportionally with increase in the percentage of CD. The DS were calculated based on these solubility values and were found to be lower. In fact at higher amounts of CD, the calculated DS was lower than 1, i.e. the DS of the saturated solubility of IBU. As a consequence, the thermodynamic activity is reduced resulting in a decrease of the flux. Furthermore, the proportional increase in the solubility demonstrates the formation of the IBU–CD complex in the chosen cosolvent mixture. The complexation reduces the amount of free drug present in the solution. As the permeation of drug–CD complexes is insignificantly low (Loftsson et al., 1991), the total flux of the drug is lowered.

The fluxes were found to be higher than those expected from the degrees of saturation calculated from the solubility values. CD has been suggested to act as a penetration enhancer (Masson et al., 1999). CD is thought to enhance the permeation of the drug by carrying the drug through the aqueous barrier from the bulk solution towards the lipophilic surface of the membrane, where the drug partition from the complex into the lipophilic membrane. In combination with supersaturation, CD appears to have a synergistic effect on the permeation enhancement of IBU.

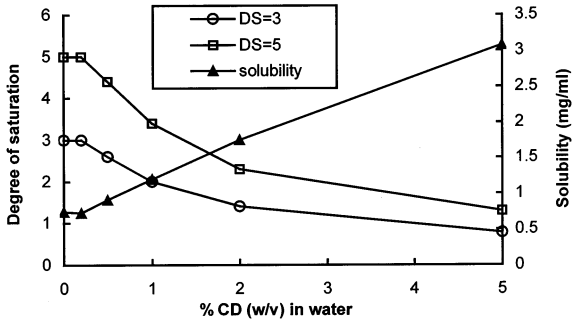

Fig. 7. Solubility and actual DS of IBU in a 40:60 PG/water system containing different amounts of CD ($n \geq 3$; $\pm$SD).

4. Conclusions

Permeation enhancement of ibuprofen from supersaturated solutions was studied. Physical stability studies show that lower concentrations of the drug in a cosolvent mixture containing lower percentages of PG form stable supersaturated solutions. The flux was found to increase with DS both in the absence and presence of the additives HPMC and CD. HPMC was found to sustain the supersaturated solutions at all DS studied while CD was found to be less effective. The mechanisms of actions of the two additives are different. While HPMC acts by crystal growth inhibition, CD affects supersaturation by increasing the solubility of the drug.

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