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Research paper

Modulation of release rate and barrier transport of Diclofenac incorporated in hydrophilic matrices: Role of cyclodextrins and implications in oral drug delivery

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ABSTRACT

The aim of this work was to investigate how the incorporation of a hydrophilic cyclodextrin (CD) inside erodible hydrophilic matrices affects drug-release behavior and transport properties through artificial and biological membranes. To this purpose, Diclofenac (Dic) was incorporated in poly(ethyleneoxide) (PEO) matrices as poorly soluble free acid (DicH) or freely water-soluble sodium salt (DicNa) in the presence or absence of hydroxypropyl-β-cyclodextrin (HPβCD). Preliminary experiments demonstrated that HPβCD increased Dic apparent solubility as a function of its amount in the solution and medium pH due to complex formation. Permeation of ionized Dic through porcine buccal mucosa gave higher values of J_{SS} and K_p as compared to silicon membranes and depended on the presence of HPβCD. Incorporation of HPβCD in PEO tablets resulted in an increase of release rate for both forms of Dic whereas cumulative drug flux through silicon membranes and porcine buccal mucosa was increased for DicH and decreased for DicNa. An interpretation of this behavior was attempted on the basis of the presence of a transport resistance occurring inside the hydrated gel matrix as modified by the presence of CD. In conclusion, this study has demonstrated that the use of CDs in hydrophilic matrices intended for oral drug delivery should be rationalized since their modulator effect relies not only on drug-dissolution rate but also on environment where drug release occurs (aqueous medium, membrane interface).

1. Introduction

Hydrophilic cyclodextrins (CDs) have been recently proposed as modulators of drug-release rate from delivery systems based on different polymer types [1]. CDs have been found to affect transport properties of the drug once incorporated in polymeric platforms such as hydrogels [2], gels and erodible hydrophilic matrices [3–10] as well as biodegradable microspheres [11,12]. In delivery systems based on hydrophilic polymers, CDs were demonstrated to speed up or slow down drug-release rate in aqueous media depending on drug loading of the matrix and diffusivities of drug, CD and their complexes in the hydrated polymer. In particular, the addition of CDs in hydrophilic erodible platforms containing poorly water-soluble drugs, which are not completely solubilized in the progressively hydrating layer, was found to increase drug-release rate by increasing drug-dissolution rate inside the tablet [4–8,13]. A progressive increase of drug-release rate could be achieved by loading tablets with drug/HPβCD binary systems obtained by different procedures and displaying progressively higher dissolution rates [4–6,11,13]. Overall, these studies suggested that the effect of CDs could be mainly ascribed to how polymer and CDs are combined in the system and to the occurrence of drug/CD interactions inside the matrix (since complexation changes drug solubility inside the delivery system). On the other hand, much less is known on the effect of CDs added in hydrophilic matrices containing highly water-soluble drugs which are completely solubilized inside the swollen layer. In a previous paper, we observed that CD incorporated in a rapidly swelling hydrogel produced a decrease in drug-release rate as a function of the amount of CD incorporated. A rationalization of this behavior by a mathematical treatment evidenced that a reduction in the effective drug diffusivity as a function of the stability constant of drug/CD complex and loaded-drug/complexant ratio occurred in the gel [2]. Analogously, the release rate of a hydrophilic drug from erodible and swellable matrices of hydroxypropyl methylcellulose was found to decrease or remain unaltered in the presence of CD [5].

Due to their excellent bioadhesive properties, poly(ethyleneoxide) (PEO) tablets have been proposed as buccal delivery systems [6,14,15]. The development of buccal delivery systems intended for the systemic delivery of poorly water-soluble drugs is generally a very challenging task. Actually, lipophilic drugs are well absorbed through oral epithelia but produce limited drug fluxes due to a low

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chemical potential gradient, which is the driving force for transport. The role of CDs in the formulation of sustained-release hydrophilic tablets made of PEO and incorporating carvedilol, a poorly soluble drug, was extensively studied in our previous paper [6]. The addition of hydroxypropyl-β-cyclodextrin (HPβCD) in the tablets was found to be a suitable strategy to accelerate drug-release rate while maintaining good bioadhesive properties. Interestingly, we found that, in the presence of HPβCD, carvedilol released from PEO tablets permeated through porcine buccal mucosa at a progressively higher rate as the release rate from the tablet increased [6]. This result prompted us to better understand the potential of CD-containing tablets for buccal drug delivery where their use remains still very limited and enlarge the investigation to water-soluble drugs.

The possible role of CD in affecting drug transport through biological membranes has been recently discussed [16,17]. Although the effect of CD on drug transport properties remains uncertain, some general indications can be drawn. First, a contribution to drug transport through buccal membrane is given by the presence of an unstirred water layer (UWL) lining buccal epithelium mainly formed by mucin and water (∼95%) and with a thickness of approximately 70–100 μm. Considering that the resistance to the transport of UWL is higher as compared to that of buccal membrane, transport through UWL substantially controls the drug absorption. Therefore, the addition of CDs in a buccal delivery system can be expected to change concentration gradient between UWL and membrane as well as to alter transport properties of a given drug in UWL.

Along this direction, the aim of this contribution is to get an insight into the effect of HPβCD incorporation inside hydrophilic matrix tablets loaded with a drug in a poorly or highly water soluble form on release rate and transport properties through artificial and biological membranes. To this purpose, Diclofenac (Dic), a weak acid available in solid form as free acid (DicH) or sodium salt (DicNa), was selected. The effect of HPβCD addition on Dic solubility/dissolution rate and permeation through artificial (silicon) and biological (porcine buccal mucosa) barriers from solutions at different pH values was preliminarily assessed. Then, PEO or PEO/CD tablets incorporating DicH or DicNa were characterized and evaluated for release and permeation properties.

2. Materials and methods

2.1. Materials

Diclofenac sodium (anhydrous, DicNa) was kindly supplied by Fisiopharma (Palomonte, Italy), whereas Diclofenac acid (DicH) was obtained by crystallization from a DicNa solution. Hydroxypropyl-β-cyclodextrin (HPβCD, DS 0.99) was kindly donated by Roquette Frères (Lestrem, France), whereas NF grade PEOs (Polyox WSR 205, approximate MW 600 kDa; Polyox WSR 301, approximate MW 4000 kDa) were kindly supplied by Dow Chemical Company (Midland, MI, USA). Pharmacopoeial grade magnesium stearate was a gift of NEW.FA.DEM. (Giugliano, Italy). All the other chemicals were of analytical reagent grade. De-ionized water was used throughout the study.

2.2. Diclofenac quantitative analysis

In phase solubility, partition and dissolution/release studies, Dic was quantified spectrophotometrically at 281 nm on a model 1204 spectrophotometer (Shimadzu, Japan) fitted out with 1-cm quartz cell. In permeation studies, Dic was quantified by HPLC on a chromatographic apparatus (Shimadzu, Japan) equipped with a HPLC LC-10AD pump, a 7725i injection valve (Rheodyne), a SPV-10A UV–Vis detector set at the wavelength of 281 nm and a C-R6 integrator. The column was a Luna 5μ C18 (250 × 4.6 mm) equipped with a precolumn (ODS, 4 × 3 mm) (both from Phenomenex, Torrance, CA). The mobile phase was acetonitrile/water adjusted at pH 3 with orthophosphoric acid (70:30 v/v) run at 1 ml/min.

2.3. Preparation of Diclofenac acid

Five grams of DicNa were dissolved in water (1.5 L) and acidified with 1 N HCl. An opalescent suspension was formed from which the precipitate was collected on a sintered glass filter and washed with water up to neutrality of the washing solution. The solid was collected, dried for 24 h at room temperature and finally solubilized in diethylether. After solvent evaporation, DicH crystals were obtained, grounded in a mortar and sieved through a #170 sieve (90 μm). The final product was analysed by mass spectroscopy and its melting temperature was assessed.

2.4. Solubility studies

Solubility studies were performed according to the method described by Higuchi and Connors. An excess of DicH or DicNa (30 mg) was added to 15 ml of water or 0.05 M phosphate buffer saline (2.38 g Na_2HPO_4, 0.19 g KH_2PO_4, 8 g NaCl per liter adjusted with orthophosphoric acid, referred as PBS in the following) at pH 3.0 and 6.8, containing increasing amounts of HPβCD ranging from 5.0×10^{-3} to 2.8×10^{-1} M (close to maximum water solubility of HPβCD), and was shaken in screw-capped glass vials at 25 °C. At equilibrium, an aliquot was withdrawn, filtered (filter HA-0.45 μm, Millipore) and analysed for Dic content by spectrophotometry. Solubilities of DicH and DicNa were obtained from suspensions without HPβCD. Supposing the formation of a complex with a 1:1 stoichiometry, the apparent stability constant ($K_{1:1}$) was calculated from the linear graph obtained by plotting the molar concentration of Dic in the solution versus each HPβCD molar concentration according to the equation $K_{1:1} = \text{slope}/(1 - \text{slope}) \times \text{intercept}$. Each experiment was performed in triplicate; the coefficient of variation associated to each measurement was never greater than 3%.

2.5. Partition studies

Lipophilicity values for Dic alone or in the presence of different amounts of HPβCD were derived from partition coefficient between *n*-octanol and an aqueous phase determined according to the "shake flask" procedure [18]. The aqueous phase was a 0.05 M PBS at pH 6.8. *n*-Octanol and the aqueous phase were mutually saturated by shaking, and were then separated. Octanol-saturated aqueous phases (20 ml) containing DicNa (1, 3 and 5 mg) or DicNa/HPβCD (1:1 up to 1:20 molar ratio) were partitioned with 20 ml of buffer-saturated *n*-octanol by gentle shaking, and were separated by centrifugation (4000 rpm, 15 min). The aqueous solution was analysed for Dic content by spectrophotometry. The results are reported as $\log D_{6.8} \pm$ SD of three replicates.

2.6. Dissolution rate of Diclofenac/HPβCD physical mixtures

DicH/HPβCD and DicNa/HPβCD physical mixtures at 1/2 (mol/mol) stoichiometric ratio were prepared by mixing in a Turbula apparatus (W.A. Bachofen, Switzerland) at a speed of 90 g/min, for 30 min. Dissolution profiles of DicH, DicNa and physical mixtures with HPβCD were evaluated according to USP 26, apparatus 2 method in a Sotax AT7 system (Sotax, Italy). Powders (amount equivalent to 10 mg of DicH or DicNa) were placed in 1 L of PBS at pH 6.8 and 37.0 ± 0.1 °C, with a paddle rotation speed of 30 rpm. The results are reported as dissolved Dic fraction ± SD of four replicates.

2.7. Preparation and characterization of Diclofenac-containing PEO tablets

Tablets were prepared by direct compression of DicH or DicNa, HPβCD, Polyox WSR 205, Polyox WSR 301 and magnesium stearate according to the compositions reported in Table 1. The effect of replacement of HPβCD with corn starch, spray-dried lactose and microcrystalline cellulose was assessed too. Each component was previously screened through a #170 sieve. Powders were mixed in a Turbula apparatus at 90 g/min for 10 min and then compressed in a single punch hydraulic press (Specac Inc., Woodstock, GA) at 1000 kg/cm^2 for 5 s using a flat-faced die (diameter 5 mm). Tablet thickness was measured by a model IP54 electronic outside micrometer, whereas hardness was evaluated by a Hardness Tester (Monsanto Type).

Release profiles of Dic from tablets were evaluated according to USP 26, apparatus 1 method. The tablet was placed in the basket and immersed in 500 ml of PBS at pH 6.8 (referred also as simulated saliva) at 37 °C and at a rotation speed of 30 rpm. At predetermined times, 4 ml of medium were withdrawn and analysed for Dic content by spectrophotometry. The concentration of Dic in the surrounding medium was always below maximum solubility. The results are reported as percentage of Dic released ± SD of four replicates.

2.8. Permeation of Diclofenac through silicon membranes and porcine buccal mucosa

Silicon membranes (SAMCO, UK) had a thickness of 0.3 mm. Porcine buccal tissue (cheek) was obtained from a freshly killed pig (slaughterhouse in Avellino, Italy) weighing about 100 kg. After removal, the tissue was stored in PBS at 4 °C and used within 2 h. The buccal mucosa was separated from the underlying tissue using surgical scissors.

Silicon membranes or buccal mucosa with an approximate area of 1.5 cm^2 were mounted between the donor and receiver chambers of Franz-type diffusion cells (diffusional area of 0.785 cm^2). Permeation was assessed from both saturated Dic solutions and PEO tablets. For permeation study through silicon membrane on saturated Dic solutions, the donor chamber was filled with 1 ml of a filtered DicH saturated solution in PBS at either pH 3.0 or 6.8. For permeation study through porcine buccal mucosa on Dic saturated solutions (unless differently specified), the donor chamber was filled with 1 ml of a filtered DicH solution in PBS at pH 6.8 without or with HPβCD (0.5–1% w/v). Dic permeation from PEO tablets was measured by sticking a tablet, previously wetted with PBS (300 μl for silicon membrane and 100 μl for porcine mucosa) to the membrane/mucosa at the donor side. Receiving medium was a 0.05 M PBS at pH 7.4 maintained at 37 ± 1 °C under gentle stirring. At predetermined times, 200 μl of receiving medium was collected and replaced by an equivalent volume of fresh medium. The results are reported as μg/cm^2 or μg of permeated Dic ± SD of five experiments. The steady state flux (J_{SS}) was derived from the slope of the linear part of the cumulative amount of drug permeated versus time plot, and are expressed as μg/cm^2 h^{-1}. Permeability coefficient was calculated by the ratio between J_{SS} and drug solubility in the donor compartment.

Table 1
Composition and characteristics of tablets produced for the study.

Formulation code	DicNa (mg)	DicH (mg)	PEO (mg)	HPβCD[a] (mg)	Thickness (mm)	Hardness (N)
PEO/DicNa	4	–	21	–	1.098 ± 0.048	3.5
PEO/CD/DicNa	4	–	21	25	2.107 ± 0.088	4.0
PEO/DicH	–	4	21	–	1.127 ± 0.051	3.5
PEO/CD/DicH	–	4	21	25	2.093 ± 0.094	4.0

[a] In some experiments, HPβCD was replaced with an equivalent amount of corn starch, spray-dried lactose or microcrystalline cellulose.

3. Results

3.1. Solubility/dissolution study

DicH and DicNa exhibit a pH-dependent solubility profile, with the solubility changing as a function of ionization degree (Table 2). The addition of HPβCD increases apparent Dic solubility depending on the amount added in the solution (data not shown). Higher solubility enhancement factors (calculated for solutions at 35% w/v of HPβCD) are observed for DicH and DicNa at pH 3.0 as compared to pH 6.8. This effect is particularly evident for DicH which displays an equilibrium solubility lower than DicNa. Phase solubility and UV studies highlight that both DicH and DicNa are able to form soluble complexes with different stability at pH 3.0 and 6.8. Log $D_{6.8}$ for ionized Dic is 1.50 ± 0.01, whereas in the presence of increasing amount of HPβCD, log $D_{6.8}$ decreased down to 1.35 ± 0.01 at 1:30 Dic/HPβCD molar ratio.

Dissolution profiles of DicH, DicNa and DicH/HPβCD physical mixture in 0.05 M PBS at pH 6.8 and 37 °C are reported in Fig. 1. DicNa is instantaneously solubilized, whereas DicH exhibits a slower dissolution rate. The presence of HPβCD as a physical mixture with DicH does not significantly alter its dissolution rate.

3.2. Release of Diclofenac from PEO tablets

Release profiles of Dic from different tablets in 0.05 M PBS at pH 6.8 and 37 °C are reported in Fig. 2. In panel A, the effect of PEO blending with HPβCD on Dic-release rate is analysed. As it can be seen, a faster Dic-release rate is observed for PEO/HPβCD tablets

Table 2
Effect of cyclodextrin addition on Diclofenac solubility at different pH values.

	pH	Equilibrium solubility (μg/ml)	EF[a]	$K_{1:1}$
DicH	3.0	1.1 ± 0.4	276	414 ± 20
	6.8	281 ± 14	2	18 ± 2
DicNa	3.0	35.7 ± 5.9	29	42 ± 5
	6.8	1113[b]	n.e.	85 ± 9[c]

[a] EF (Enhancement factor) represents the increase in Dic solubility observed in the presence of a 35% w/v of HPβCD.
[b] From Ref. [22].
[c] Stability constant was evaluated by a UV-based method.

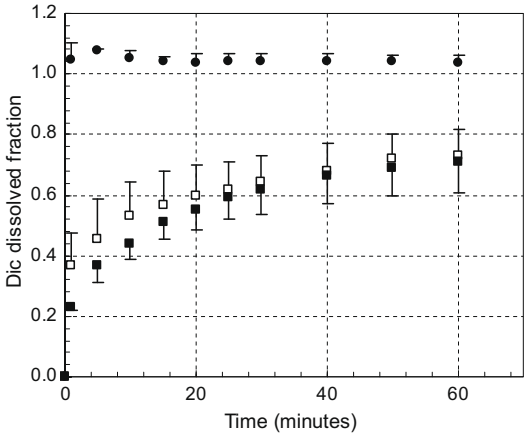

Fig. 1. Dissolution profiles of DicH (■), DicH/HPbCD 1:2 mol/mol physical mixture (□) and DicNa (●) in 0.05 M PBS at pH 6.8 and 37 °C. Results are reported as mean ± SD (n = 4).

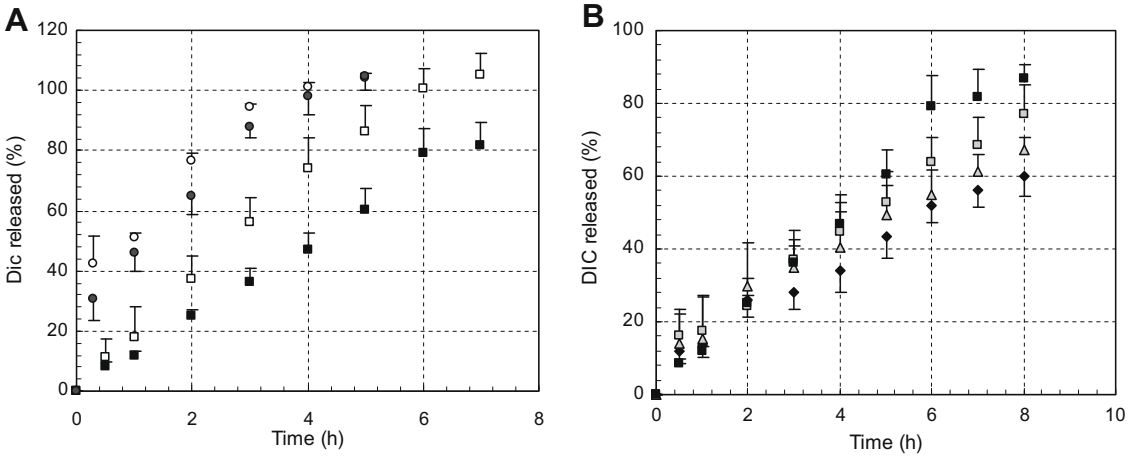

Fig. 2. Release profile of Diclofenac from different tablets in 0.05 M PBS at pH 6.8 and at 37 °C. (A) Tablets of PEO/DicH (■), PEO/CD/DicH (□), PEO/DicNa (●) and PEO/CD/DicNa (○). (B) Tablets of PEO/starch/DicH (♦), PEO/microcrystalline cellulose/DicH (△), PEO/lactose/DicH (□) and PEO/DicH (■). Results are reported as mean ± SD (n = 4).

as compared to PEO tablets, this effect being more evident for DicH-loaded matrices. In panel B, release profiles of Dic from DicH-containing PEO tablets where HPβCD is replaced with different excipients are shown (release rate from PEO/DicH is reported for comparison). Tablet geometry (thickness and thereby initial release surface) and hardness were comparable for all the formulations tested. The addition of corn starch, spray-dried lactose or microcrystalline cellulose in PEO tablets loaded with DicH does not increase drug-release rate as compared to tablets without HPβCD.

3.3. Permeation of Diclofenac from aqueous solutions

Results of the permeation study carried out on both an artificial silicon membrane and a porcine buccal mucosa on Dic saturated solutions are reported in Table 3. Experiments on silicon membranes were performed by using as donor medium a PBS at pH 3.0 (giving unionized Dic) or at 6.8 (giving ionized Dic) to study the effect of Dic ionization on permeation. Experiments on porcine buccal mucosa were conducted only in physiologically relevant conditions, that is, at pH 6.8 (a value which simulates the pH of saliva) at which Dic is ionized. Results demonstrate that J_{SS} of ionized and unionized Dic is close, whereas very different K_p values of 0.005 and 0.25 cm/h for ionized and unionized Dic, respectively, are obtained. Permeation data through porcine mucosa of ionized Dic indicate higher values of J_{SS} and K_p as compared to silicon membrane. The addition of an increasing amount of HPβCD in the donor medium increases DicH apparent solubility and results in a change of J_{SS} and K_p as a function of the amount of HPβCD present. A decrease in J_{SS} is observed when in the donor compartment Dic concentration is kept constant and HPβCD amount is increased.

Table 3
Permeation of Diclofenac through a silicone membrane and porcine buccal mucosa.

Barrier	Donor phase pH	Dic concentration (μg cm^{-3})[a]	HPβCD amount (% w/v)	J_{SS} (μg cm^{-2} h^{-1})	K_p (cm/h)
Silicon membrane	3.0	2.7	–	0.67 ± 0.12	0.248 ± 0.044
	6.8	162	–	0.88 ± 0.07	0.005 ± 0.001
Porcine buccal mucosa	6.8	206	–	6.93 ± 0.79	0.034 ± 0.004
	6.8	640	0.5	24.36 ± 2.65	0.038 ± 0.004
	6.8	640[b]	1	13.98 ± 1.41	0.022 ± 0.003

[a] Diclofenac concentration in the donor phase was evaluated by HPLC.
[b] An unsaturated solution was used.

3.4. Permeation of Diclofenac from PEO tablets

Permeation profiles of Dic from tablets containing DicH (panel A) or DicNa (panel B) through a silicon membrane are reported in Fig. 3. Cumulative flux of Dic released from DicH-containing PEO/CD tablets increases more than twofolds at 48 h as compared to the tablets of PEO without HPβCD. On the other hand, the amount of Dic permeated through the silicon membrane after 48 h from DicNa-containing tablets is half-reduced in the presence of HPβCD. Similar results are obtained from permeation studies on porcine buccal mucosa (Fig. 4). Cumulative flux at 7 h of Dic released from DicH-containing tablets (panel A) shows an increase of about fourfolds in the presence of HPβCD, while in the case of DicNa-containing tablets (panel B) a six-time decrease is observed. It is worthy to note that Dic cumulative fluxes at 7 h obtained for the PEO/DicH and PEO/HPβCD/DicNa tablets are similar.

4. Discussion

Recently, our group has focused on the understanding of the potential of CDs in modulating the technological properties of polymeric drug delivery systems. The use of CDs in this sense is very attractive since it allows to modify the transport in a polymeric matrix leaving its overall properties substantially unaltered. For several polymeric systems, both hydrophilic (degradable and non-degradable) and hydrophobic (biodegradable) [2,6,7,11], we have singled out different effects of CD addition depending mainly on (i) changes in drug-dissolution rate; (ii) formation of drug/CD complexes; and (iii) changes of polymer properties (e.g., dissolution rate for hydrophilic polymers). On the other hand, the way by which CDs are introduced in the system was considered another key fundamental to achieve accelerated drug-release rate. In the previous papers on hydrophilic erodible tablets made of PEO and incorporating carvedilol, a poorly water-soluble drug, we observed that an increase in the drug-release rate could be achieved by introducing HPβCD in the polymeric matrix [6,7]. Nevertheless, an increase in drug-delivery rate was found to increase the cumulative amount of drug permeated through porcine buccal mucosa. Here, we try to go further and extend this study to drugs with different solubilities. To this purpose, we selected Dic as a model drug, which is available as a crystalline-free acid or sodium salt. Data reported in Table 2 highlight that pH and HPβCD addition affect DicH and DicNa solubilities in aqueous solution. For both drug forms, solubilities measured at pH 3.0 and 6.8 were in good agreement with values reported in a recent paper [19]. HPβCD increased

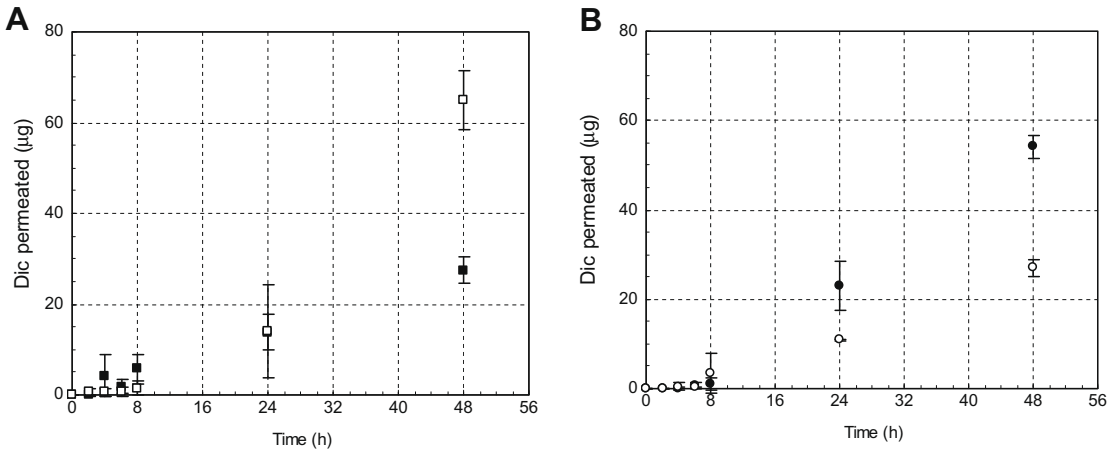

Fig. 3. Permeation profiles of Diclofenac from tablets through a silicon membrane. (A) PEO/DicH (■) and PEO/CD/DicH (□). (B) PEO/DicNa (●) and PEO/CD/DicNa (○). Donor medium: 0.05 M PBS at pH 6.8. Receiving medium: 0.05 M PBS at pH 7.4. Results are reported as mean ± SD (n = 4).

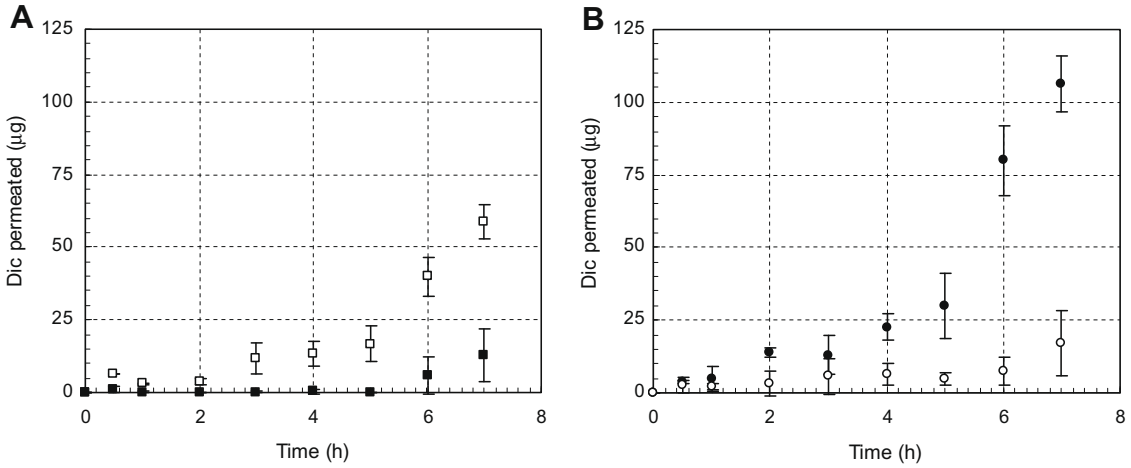

Fig. 4. Permeation profiles of Diclofenac from tablets through porcine buccal mucosa. (A) PEO/DicH (■) and PEO/CD/DicH (□). (B) PEO/DicNa (●) and PEO/CD/DicNa (○). Donor medium: 0.05 M PBS at pH 6.8. Receiving medium: 0.05 M PBS at pH 7.4. Results are reported as mean ± SD (n = 4).

Dic apparent solubility independently of drug ionization due to complex formation. Furthermore, solubility enhancement occurred with a higher efficiency when the undissociated form predominated in solution, i.e., at pH 3.0, probably due to a more efficient complexation ability of HPβCD toward the lipophilic unionized form. As indicated by $K_{1:1}$ values calculated by UV, the ionized form of Dic was also able to form a soluble complex with HPβCD. Despite the formation of soluble complexes at pH 6.8, Dic/HPβCD physical mixture did not show an improved dissolution rate as compared to DicH probably due to the fact that drug crystallinity was maintained in Dic/HPβCD binary system analogously to that we found for Dic/βCD powders [20]. However, when both DicH and DicNa were incorporated inside a PEO matrix containing HPβCD (Dic/HPβCD molar ratio in the tablet was the same as that for physical mixture), Dic-release rate increased as compared to the matrix that was formulated in the absence of HPβCD (Fig. 2). For PEO/CD/DicH tablets, this result could be seen as controversial since a lack of increase in drug-dissolution rate of DicH/HPβCD powders was observed. However, if we assume that HPβCD is instantaneously solubilized in a confined hydrated PEO layer where it operates as a rate controlling agent, dissolution enhancer properties of HPβCD toward drug could be amplified. As a consequence, a higher diffusive flux develops, which increases the amount of mobile species free to diffuse out in the medium. Nevertheless, PEO/CD tablets eroded faster than PEO tablets (about 10 h versus 24 h) [6], likely due to an increased water uptake driven by HPβCD osmotic properties and a possible solubilizing effect of CD on PEO. Thus, the faster degradation of CD-containing tablets could contribute to the speed-up of Dic-release rate. An increased Dic-delivery rate from PEO/CD/DicNa tablets as compared to PEO tablets also suggests that HPβCD does not decrease the mobility of the drug in the swollen external layers of hydrophilic tablet, i.e., HPβCD, solubilized Dic and their complex have similar diffusivities. The solubilizing properties of HPβCD were determinant to accelerate the delivery rate of Dic as demonstrated in release experiments where HPβCD was replaced by other diluents that are known to be unable to affect drug-dissolution rate inside the tablet.

To understand how changes in drug-release rate could operate on drug transport through biological barriers, preliminary permeation studies on Dic and Dic/HPβCD solutions were carried out. Experiments were performed on an artificial silicon membrane, which is a model of lipophilic barriers occurring in vivo, and a biological barrier such as porcine buccal mucosa which is characterized by the presence of an UWL [16] and is a good model for human buccal mucosa. The permeation study on Dic-saturated solutions through a silicon membrane highlighted that although ionized Dic is much less permeable than unionized Dic, J_{SS} obtained for both forms were similar due to different solid drug solubilities in the donor compartment. Nevertheless, ionized Dic is the only relevant species to permeate through a mucosa in an in vivo situation since pH of saliva drives Dic dissociation toward ionized form. We found that ionized Dic was transported through porcine

buccal mucosa although J_{SS} measured was several orders of magnitude lower than those observed by El-Samaligy et al. [21] probably due to the difference in the buccal membrane used (chicken pouch membrane in that case). On the basis of lipophilicity values, it is evident that a $\log D_{6.8}$ of about 1.5 measured for ionized Dic is still high enough to allow drug transport of an ionized species through buccal mucosa. In the case of experiments in the presence of HPβCD, we found that when HPβCD increased Dic apparent solubility in the donor compartment, J_{SS} through mucosa increased too likely due to a higher driving force for diffusion. This effect is difficult to understand if the chemical potential of a drug-saturated solution containing CDs is considered to be constant (i.e., the amount of free drug molecules which can diffuse through the membrane is constant since drug/CD complexes are not partitioned in the membrane due to their unfavorable partition coefficient). To explain this behavior Loftsson et al. [16] have recently suggested that the UWL lining epithelia, where mobility of dissolved molecules is decreased as compared to aqueous solutions, creates a barrier with a higher transport resistance as compared to that of the membrane. On these bases, they suggested that CDs enhance drug flux through mucosa by (i) increasing the concentration gradient over UWL and/or (ii) facilitating drug transport through UWL acting as chaotropes. The fact that J_{SS} and K_p decreased when Dic solubility was constant and only HPβCD concentration increased (in Table 3, compare permeability parameters at 0.5% and 1% HPβCD), which is also in agreement with our previous results [6], prompts us to lean toward the first hypothesized mechanism. Actually, the decrease of both the permeability parameters can be related to a progressive decrease of the apparent lipophilicity of Dic in the presence of HPβCD due to complex formation in UWL. A possible enhancing effect of HPβCD by acting on the properties of mucosa was excluded since K_p values did not increase as the amount of HPβCD increased.

Permeation experiments on PEO tablets stuck to porcine buccal mucosa, where the evolution with time of Dic concentration at receptor side was followed, clearly showed that the effect of HPβCD was strictly related to the dissolution properties of the loaded drug (DicH or DicNa). Actually, PEO/CD/DicH tablets allowed a Dic permeation higher than PEO/DicH tablets, whereas the contrary occurred for DicNa-loaded matrices. The fact that the results obtained on mucosa and silicone membrane followed the same trend lets us exclude that the presence of a UWL in buccal mucosa is a relevant aspect in this specific case. In fact, cumulative flux through a membrane (J) is expressed by Eq. (1):

$$J = P_m \cdot C_v \tag{1}$$

where P_m is the drug permeability coefficient in the membrane and C_v is the drug concentration in the vehicle (donor phase). Since

$$P_m = \frac{\mathcal{D}_m \cdot k_m}{\delta} \tag{2}$$

where k_m is the drug partition coefficient between vehicle and membrane, $\mathcal{D}_m$ is the drug diffusivity in the membrane and δ is the membrane thickness, Eq. (1) can be rearranged as

$$J = \frac{\mathcal{D}_m \cdot k_m}{\delta} \cdot C_v \tag{3}$$

The term $k_m \cdot C_v$ represents the drug amount partitioning in the membrane at the donor side (C_m).

In the case studied, C_v is drug concentration at swollen tablet/membrane interface. Assuming that in the swollen gel layer

(1) HPβCD is freely soluble;
(2) a drug/HPβCD complex is formed;
(3) HPβCD concentration in the swollen gel at membrane interface is constant since it is unable to partition into the membrane;
(4) the only species which can partition in the membrane is free drug ($k_m^{dr} >> k_m^{com}$);

Eq. (3) can be rearranged as

$$J = \frac{\mathcal{D}_m^{dr} \cdot k_m^{dr}}{\delta} \cdot C^* \tag{4}$$

where C^* is the effective drug concentration in the swollen gel as contributed by free (C^{dr}) and complexed (C^{com}) drug molecules.

On this basis, the different behavior experienced for the tablets containing different water soluble forms of Dic can be explained as schematized in Fig. 5. In the case of PEO/CD/DicH tablets, C^* is increased as compared to PEO/DicH tablet due to the formation of

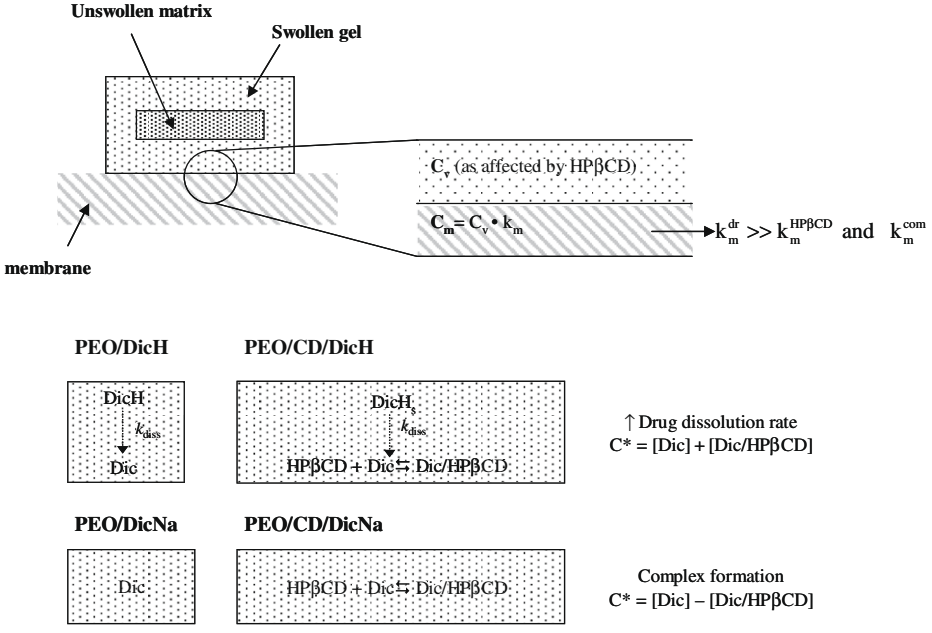

Fig. 5. Schematic representation of drug partitioning into a lipophilic membrane at tablet/membrane interface. Refer to test for abbreviations.

a soluble Dic/HPβCD complex in the swollen layer. If at every position and time, the equilibrium between complexed and free drug molecules exists and is instantaneously attained in the gel, the availability of drug molecules from the complex is faster than the availability of drug molecules from the solid. Although complexation does not alter chemical potential (i.e., the amount of free drug molecule which can partition into the membrane), the presence of a Dic/HPβCD soluble "reservoir" allows a faster transport of solubilized Dic to membrane surface and results in an increase in drug flux. On the other hand, in PEO/CD/DicNa tablets, drug dissolves very rapidly in the swollen gel layer. In this situation, the formation of Dic/HPβCD complexes inside swollen PEO decreases C^*. Since $k_m^{dr} >> k_m^{com}$, that is, the complex is unable to partition into the membrane, an overall decrease of J is attained. It is expected that in both cases, the stability constant of drug/CD complexes affects C^*.

The results of this study highlight that the effect of HPβCD addition in erodible hydrophilic matrices strongly depends on the environment where release occurs. In the case of release in an aqueous medium where all the species solubilized in the swollen matrix (drug, HPβCD, drug/HPβCD complex) diffuse out of the system in the external aqueous medium, HPβCD addition can be suggested to accelerate the release rate of poorly soluble drugs. On the other hand, when considering applications where matrix is applied to a mucosal membrane, HPβCD diffusion out of the system is limited and drug transport is accelerated for poorly soluble drugs and is slowed down for highly soluble drugs. By transposing this situation in vivo, one can infer that different effects can be achieved by administering the same tablets through different routes (i.e., administration as a gastrointestinal or buccal delivery system). Moving to specific properties of PEO tablets containing Dic and considering that this drug holds a great potential also for locally occurring inflammatory processes in the mouth, it could be speculated that one can control its level of action (systemic or local) by simply acting on the solubility of incorporated drug (DicH or DicNa) as well as by adding HPβCD in the polymeric platform.

5. Conclusions

HPβCD can be incorporated as an aid-excipient in hydrophilic erodible tablets to modulate drug-release rate in aqueous media and transport properties through lipophilic barriers. The effect of HPβCD addition in erodible hydrophilic tablets strongly depends on drug solubility in the swollen matrix as well as the environment where drug release occurs (aqueous medium, membrane interface). In the case examined here, HPβCD speeds up drug-release rate in an aqueous environment when Diclofenac is loaded in the PEO matrix as both poorly and highly soluble forms. In the case of permeation through artificial (silicon) and biological (porcine buccal mucosa) barriers, the presence of HPβCD increases Diclofenac cumulative flux in PEO/CD/DicH tablets, whereas it decreases drug flux in PEO/CD/DicNa tablets. Thus, for a more rational use of CDs as release and permeation modulators, drug solubility inside the hydrated matrix as well as characteristics of the biological environment should be taken into account as key fundamentals to attain specific delivery requirements.

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