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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.