Available online at www.sciencedirect.com
SCIENCE DIRECT
International Journal of Pharmaceutics 319 (2006) 63–70
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Cyclodextrin-containing poly(ethyleneoxide) tablets for the delivery of poorly soluble drugs: Potential as buccal delivery system

Brunella Cappello [a], Giuseppe De Rosa [a], Lucia Giannini [a], Maria Immacolata La Rotonda [a,*], Giuseppe Mensitieri [b], Agnese Miro [a], Fabiana Quaglia [a], Roberto Russo [c]

[a] *Dipartimento di Chimica Farmaceutica e Tossicologica, Università degli Studi di Napoli Federico II, Via D. Montesano 49, 80131 Napoli, Italy*
[b] *Dipartimento di Ingegneria dei Materiali e della Produzione, Università degli Studi di Napoli Federico II, Piazzale Tecchio, Napoli, Italy*
[c] *Istituito di Chimica e Tecnologia dei Polimeri, Consiglio Nazionale delle Ricerche, Via Campi Flegrei 34, 80078 Pozzuoli, Italy*

Received 10 June 2005; received in revised form 23 March 2006; accepted 28 March 2006
Available online 25 April 2006

Abstract

The aim of this work was to develop a tablet for the buccal delivery of the poorly soluble drug carvedilol (CAR), based on poly(ethyleneoxide) (PEO) as bioadhesive sustained-release platform and hydroxypropyl-β-cyclodextrin (HPβCD) as modulator of drug release. As first, PEO tablets loaded with CAR/HPβCD binary systems with different dissolution properties were tested for CAR and HPβCD release features and compared to PEO tablets containing only CAR. When the drug was incorporated as CAR/HPβCD freeze-dried product, all CAR content was released from the tablet in about 10 h, displaying a constant release regimen after a transient. The effect of HPβCD incorporation on the release mechanism, was rationalized on the basis of the interplay of different physical phenomena: erosion and swelling of the tablet, drug dissolution, drug counter-diffusion and complex formation. In the second part of the study, the potential of HPβCD-containing PEO tablets as buccal delivery system for CAR was tested. It was found that the incorporation of HPβCD in the tablet did not alter significantly its good adhesion properties. The feasibility of buccal administration of CAR was assessed by permeation experiments on pig excised mucosa. The amount of CAR permeated from PEO tablet was higher in the case of HPβCD-containing tablets, the maximum value being obtained for CAR/HPβCD freeze-dried system. Our results demonstrate that, when the tablet is employed as transmucosal system, the role of drug dissolution enhancement in the hydrated tablet is much more relevant than in solution for increasing the delivery rate.

Keywords: Carvedilol; Hydroxypropyl-β-cyclodextrin; Mucoadhesion; Buccal delivery

1. Introduction

The buccal administration of drugs is attracting considerable attention since it has the advantage to give high blood levels, circumvent first-pass metabolism and avoid degradation in the gastrointestinal tract by enzymes and bacteria (Rathbone et al., 1996). Buccal patches are generally based on bioadhesive polymers which, once hydrated, adhere to the buccal mucosa and withstand salivation, tongue movements and swallowing for a significant period of time. Poly(ethyleneoxide) (PEO) is a biocompatible eroding polymer available in a number of molecular weights, which is receiving growing attention as sustained-release bioadhesive platform due to its safety, ease of processing (direct compression is feasible) and possibility to control drug release. Depending on the molecular weight of PEO, different dissolution and water swelling rates, viscoelastic behaviour of the swollen gel as well as extent and duration of bioadhesion can be achieved. PEO has been used in oral sustained-release tablets (Apicella et al., 1993; Cappello et al., 1994; Kim, 1995; Kim, 1998), ocular inserts (Di Colo et al., 2001) and buccal delivery systems (Bottenberg et al., 1991; Tiwari et al., 1999). Proper modulation of drug release rate has been attained by tailoring molecular weight and its distribution (Apicella et al., 1993; Cappello et al., 1994). However, the design of buccal systems for poorly water-soluble drugs is a challenging issue. Lipophilic drugs, although being well absorbed through oral epithelia, exhibit too low fluxes due to a low chemical potential gradient, which is the driving force for transport. In this regard, cyclodextrins (CD) have emerged as an effective tool to increase drug release rate of sparingly sol-

* Corresponding author. Tel.: +39 081 678647; fax: +39 081 678647.
E-mail address: larotond@unina.it (M.I. La Rotonda).

0378-5173/$ – see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2006.03.031

uble drugs once incorporated in sustained-release matrix-type systems made of different polymers (Rao et al., 2001; Sangalli et al., 2001; Jain et al., 2002; Chowdary and Kamalakara, 2003; Koester et al., 2003; Pose-Vilarnovo et al., 2004). CD can affect some relevant properties of the drug delivery system that in turn are strictly related to drug release rate. Actually, CD can promote changes in erosion rate and hydrophilicity of the matrix (Giunchedi et al., 1994; Rao et al., 2001), induce osmotic effects (observed in the case of polyionic CD) (Okimoto et al., 1999) and pore formation (Villar-Lopez et al., 1999), as well as modify drug effective mobility in the hydrated polymer (Quaglia et al., 2001).

In an attempt to develop a buccal tablet for the delivery of a poorly water-soluble drug, we designed a matrix based on a blend of poly(ethyleneoxide)s (PEO) as bioadhesive sustained-release platform and hydroxypropyl-β-cyclodextrin (HPβCD) as modulator of drug release. Carvedilol (CAR), a non-selective β-adrenergic blocking agent with α_1-blocking activity, which is sparingly soluble in water and shows limited bioavailability after oral administration, was selected for the study. In the first part of the study, we rationalized the effect of HPβCD on the release features of the system whereas in the second part we assessed the potential of CAR-loaded PEO/HPβCD tablets as buccal delivery system.

1.1. Drug release from erodible/soluble matrices containing CD: some considerations

The effects of CD addition on drug release features of a polymeric system can be different depending on drug loading of the matrix (Bibby et al., 2000) and diffusivities of drug, CD and their complexes in the hydrated polymer. When drug concentration in the hydrated polymeric matrix is above the saturation level, an equilibrium is attained between solid and dissolved drug in the hydrated matrix. Upon addition of CD, the amount of drug molecules solubilized in the hydrated polymer increases. If diffusivity of CD and its complex is comparable to drug diffusivity, an increase in the concentration of mobile drug molecules occurs, resulting in an increase of drug release rate. On the other hand, if diffusivity of CD and its complex is lower than drug diffusivity, the effective drug mobility is depressed due to complexation and the release rate can be speeded up or slowed down depending on the relative values of diffusion coefficient, on the ratio between drug loading and CD concentration and on the stability constant of the complex. In the case drug concentration in the polymeric matrix is below the saturation level, no change in drug release rate is expected if all the species have comparable diffusivities, whereas the formation of a drug-CD complex in the hydrated matrix results in a decrease of drug mobility, and in turn of release rate, if drug diffusivity is higher than CD diffusivity.

The mechanism of release from monolithic devices made of swellable and erodible polymers loaded with poorly water-soluble drugs and CDs as release modulator is rather complex in view of several physical phenomena involved. In fact, reliable predictive models of drug delivery from these systems entail the solution of moving boundary problems which should take into account penetration of water into the tablet with concurrent swelling and solubilization/erosion of the matrix, dissolution of both the drug and CD in the swollen layer, CD/drug complex formation, counterdiffusion of drug, CD and complex in the swollen layer. In this section we depict a qualitative view of the delivery process which, without loosing the relevant physical aspects involved, could supply a simplified approach for the interpretation of the behaviour observed experimentally. We are assuming that there are three relevant moving fronts which are established in a hydrophilic tablet in contact with a water solution: (1) the swelling front, S, which separates the unpenetrated core from the swollen and dissolving shell; (2) the erosion or solubilization front, E, which separates the swollen polymer layer from the external medium; (3) the eventual drug dissolution front, D, which separates an inner oversaturated region where both dispersed and solubilized drugs are present from an outer water-swollen polymer layer where only solubilized drug is present (this layer is superimposed to the S front in the case of water-soluble species, as is the case of CD). The relevant assumption of fronts sharpness has been made here to attain a simplified treatment of the problem. Actually in many real situations this is not the case and more complex treatments have to be introduced (Narasimhan and Peppas, 1997; Narasimhan, 2001). The fronts are schematised in Fig. 1 for the case of a poorly soluble drug and CD dispersed uniformly in a hydrophilic matrix. The moving rates of these fronts are substantially dependent upon the nature of the components and their concentration in the tablet. After a transient, if the thickness of the tablet is large enough, a pseudo-steady state is established when a synchronization of S and E fronts occurs and a constant drug profile is established in the swollen layer. If the characteristic times of diffusion of drug, CD and complex are all smaller than the tablet swelling time, it can be assumed that their profile in the swollen outer shell is linear and the drug and CD

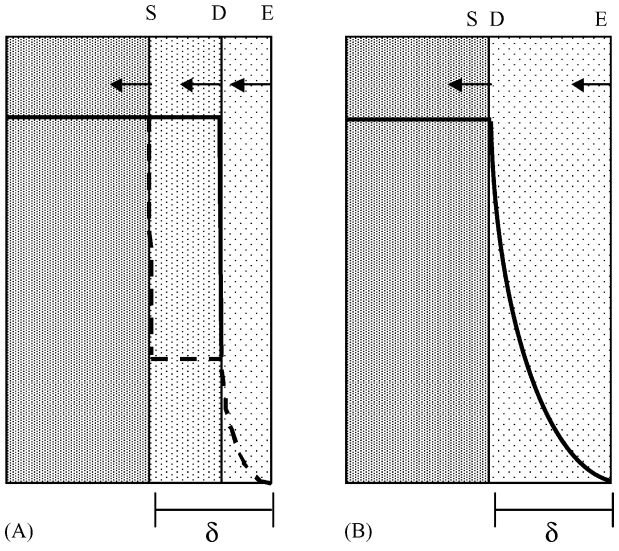

Fig. 1. (A) Drug profiles in CD-loaded tablets. (—) Total drug profile (dissolved and undissolved); (- - -) dissolved drug profile. (B) CD profile in the tablet (CD has been assumed as completely soluble in the water swollen layer). δ represents the thickness of the swollen layer.

profiles at pseudo-steady state can be envisaged as reported in Fig. 1.

2. Materials and methods

2.1. Materials

Carvedilol (CAR) was kindly supplied by Roche Pharmaceuticals (Segrate, Italy), hydroxypropyl-β-cyclodextrin (HPβCD, DS 0.97) was donated by Roquette Freres (Lestrem, France), whereas NF grade poly(ethyleneoxide) (PEO, 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.

2.2. CAR and HPβCD quantitative analysis

For dissolution/release studies, CAR was quantified spectrophometrically at 243 nm on a model 1204 spectrophotometer (Shimadzu, Japan) fitted out with 1-cm quartz cell. For diffusion studies, CAR was quantified by HPLC on a chromatograph (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 243 nm and a C-R6 integrator. The column was a Sphereclone 5 μm ODS(2) (250 mm × 4.6 mm) equipped with a precolumn (ODS, 4 mm × 3 mm) (both from Phenomenex, Torrance, CA). The mobile phase was a mixture acetonitrile/phosphate buffer (0.05 M KH_2PO_4 at pH 4.5) (60:40, v/v) run at 0.8 ml/min. This HPLC method was used also to evaluate CAR stability.

HPβCD was quantified by spectrophotometric analysis of the fading of a phenolphthalein alkaline solution in the presence of the complexing agent. The phenomenon, due to the formation of the colourless stable inclusion complex phenolphthalein/HPβCD (molar ratio 1:1), is directly related to the amount of cyclodextrin added to the solution (Zarzycki and Lamparczyk, 1998). A stock phenolphthalein solution 3 mM in methanol was diluted 1:100 in 0.05 M carbonate buffer at pH 10.5 just prior to use. Into a test tube phenolphthalein working solution was added to a HPβCD sample. The absorbance at 553 nm (phenolphthalein λ_{max}) of the resulting solution was measured just after mixing. Preliminary experiments were carried out in order to establish the optimal conditions for phenolphthalein/HPβCD complexation in phosphate buffer. Maximum ΔABS was obtained using a sample to reagent ratio 1:3 (v/v). All measurements were performed in triplicate at room temperature against a reagent blank. Standard solutions within the range 5–125 μg/ml were prepared in the release medium and calibration curves were obtained plotting the decrease in absorbance versus HPβCD concentration. Beer's law was verified over this concentration range ($r^2 > 0.99$). The limit of quantitation (QOD) was 5 μg/ml. To validate daily the performance of the analytical method, the absorbance values of HPβCD standards were evaluated.

2.3. Preparation of CAR/HPβCD powders

Binary systems were prepared from CAR and HPβCD powders screened through a #170 sieve. The stoichiometric ratio employed to prepare CAR/HPβCD solid systems was 1/2 (mol/mol). For the preparation of the physical mixture, CAR and HPβCD powders were placed in a mixing jar. Mixing was performed in a Turbula apparatus (W.A. Bachofen, Switzerland) at a speed of 90 g/min, for 30 min. The freeze-dried product was prepared from a solution obtained dissolving 1 g of physical mixture in 1 l of ethanol/0.2 mM HCl solution (1/9, v/v). The aqueous portion was acidified to increase CAR solubility via salt formation. The solution was freeze-dried in a Modulyo Edwards apparatus. CAR was stable to the procedure used to prepare freeze-dried product as assessed by the HPLC method reported in the Section 2.2. The residual moisture of freeze-dried product (about 2%, w/w) was evaluated by the "loss on drying" method at 40 °C for 3 h (Ph. Eur. par. 2.2.32).

2.4. Preparation of PEO tablets

Tablets were prepared by direct compression of CAR (4 mg) or CAR/HPβCD binary systems (29 mg of binary system containing 4 mg of CAR), Polyox WSR 205 (10.5 mg), Polyox WSR 301 (10.5 mg) and magnesium stearate (1% of the total tablet weight). 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., UK) at 1000 kg/cm^2 for 5 s using a flat-faced die (diameter 5 mm). Tablets loaded with CAR had a thickness of 1.1 ± 0.03 mm and a resistance to crushing of 93 ± 2 N. Tablets loaded with CAR/HPβCD binary systems had a thickness of 2.7 ± 0.04 mm and a resistance to crushing of 95 ± 3 N.

2.5. In vitro release studies

Dissolution profiles of CAR from HPβCD-containing powders (all containing an amount of CAR equivalent to 10 mg) were evaluated according to USP 26, apparatus 2 method in a Sotax AT7 system (Sotax, Italy). CAR and CAR/HPβCD powders were placed in 1 l of phosphate buffer saline (PBS, 2.38 g Na_2HPO_4, 0.19 g KH_2PO_4, 8 g NaCl per liter adjusted at pH 6.8 with ortophosphoric acid) at 37.0 ± 0.1 °C and with a paddle rotation speed of 30 rpm. Results are reported as dissolved CAR fraction (ratio of dissolved CAR to the total amount of CAR added to the medium) ± S.D. of four replicates.

Release profiles of CAR and HPβCD from tablets were evaluated according to USP 26, apparatus 1 method. The tablet was placed in the basket and immersed in 400 ml of PBS at 37 °C and basket rotation speed of 30 rpm. At predetermined times, 3 ml were withdrawn and analysed for CAR and HPβCD contents. The concentration of CAR in the surrounding medium was always below the saturation concentration (0.018 mg/ml). Results are reported as fractional release (M_t/M_{inf}, where M_t is the amount released at time t and M_{inf} is the total amount present in the tablet) ± S.D. of four replicates.

2.6. Erosion of PEO tablets

The erosion study was performed on tablets prepared from Polyox WSR 205 (10.5 mg), Polyox WSR 301 (10.5 mg), magnesium stearate (1% of the total tablet weight) without or with HPβCD (25 mg) as described in Section 2.3. The tablets were weighed, placed in plastic containers, added with 10 ml of PBS and placed in a thermostatic bath at 37 °C. A sample was prepared for each testing time. At predetermined intervals, the medium was withdrawn, the tablet was lightly blotted with a tissue paper and dried up to constant weight at 40 °C under vacuum. The fractional weight loss (WL) of the tablet was calculated using the following equation:

$$\mathrm{WL} = \frac{W_\mathrm{i} - W_\mathrm{t}}{W_\mathrm{i}}$$

where W_i is the initial weight of the matrix and W_t is the weight of the matrix at time t. The results are expressed as mean ± S.D. of four replicates.

2.7. Porcine buccal tissue preparation

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 (composition as for the release studies and referred in the following as simulated saliva) at 4 °C and used within 2 h. The buccal mucosa was separated from the underlying tissue using surgical scissors.

2.8. Mucoadhesion of the tablets on porcine buccal mucosa

The composition of the tablets tested for mucoadhesion is reported in Table 1. The bioadhesive parameters were determined using a dynamometer Instron Mod. 4301 (Instron corp., Canton, MA) equipped with a computer integrated data acquisition system. To the upper and the bottom support of the tensile apparatus two 15 mm diameter aluminium discs were secured. The tablet was fixed to the upper support while the porcine buccal mucosa was fixed to the bottom support by using a cyanoacrylate adhesive. The tablet was wetted with 0.1 ml of simulated saliva by using a micropipette. Then, the upper support was moved down at 30 mm/min and stopped when the force between the tablet and the mucosa was 2 N. After 10 min of contact, the crosshead moved upward at a speed of 10 mm/min with an acquisition rate of 20 points/s. The temperature during the experiment was 23 °C and relative humidity 46–50%. Results are the mean of six force–elongation experiments.

Table 1
Composition and work of adhesion for PEO tablets

CODE	CAR (mg)	PEO blend (mg)	HPβCD (mg)	Work of adhesion (mJ)
PEO	–	21	–	0.98 ± 0.11
PM10[a]	4	10	25	0.26 ± 0.03
PM21[a]	4	21	25	0.56 ± 0.07
FD10[b]	4	10	25	0.13 ± 0.01
FD21[b]	4	21	25	0.45 ± 0.07

[a] PM is a CAR/HPβCD physical mixture.
[b] FD is a CAR/HPβCD binary system prepared by freeze-drying.

2.9. Permeation of CAR through porcine buccal mucosa

Buccal mucosa with an approximate area of 1.5 cm^2 was mounted between the donor and receiver chambers of Franz-type diffusion cells (diffusional area of 0.785 cm^2). The donor chamber was filled with 1 ml of CAR saturated solutions in either PBS or PBS containing an 8% (w/v) of HPβCD (CAR concentration in the solutions was 18 and 70 μg/ml, respectively). To study the effect of HPβCD on CAR permeability, CAR solutions (6 μg/ml) containing increasing amounts of HPβCD (37, 94 and 188 μg/ml corresponding to CAR/HPβCD molar ratios of 1/2, 1/5 and 1/10, respectively) were tested. CAR permeation from PEO tablets was measured by sticking the tablet wetted with 300 μl of PBS to the mucosa in the donor side. Receiver medium was a mixture ethanol/PBS at pH 6.8 (2:3, v/v) maintained at 37 ± 1 °C under gentle stirring. The presence of ethanol to promote drug solubilization in the receiver did not alter barrier permeability as demonstrated by Veuillez et al. (2002). Two hundred microliters of receiver medium were collected at predetermined intervals and replaced by an equivalent volume of fresh medium. The results are reported as μg/cm^2 or μg of permeated CAR ± S.D. of five permeation experiments. The steady state flux was derived from the slope of the linear part of the cumulative amount of drug permeated versus time plot and is expressed as μg/cm^2/h.

3. Results and discussion

3.1. Effect of HPβCD addition on carvedilol release from PEO tablets

CAR and CAR/HPβCD binary systems characterized by different dissolution rates were prepared by simple mixing (PM) or freeze-drying (FD) and incorporated into PEO tablets. The dissolution profiles of CAR from binary systems and its release profiles from PEO tablets are shown in Figs. 2 and 3, respectively. As it can be seen, the dissolution rate of CAR was significantly enhanced when it was coformulated with HPβCD, the FD product displaying the faster dissolution rate. The incorporation of CAR/HPβCD binary systems in PEO tablets significantly increased the rate of CAR release. In fact, after 10 h, tablets without HPβCD had released only 40% of loaded drug, whereas HPβCD-containing matrices had released a significantly higher CAR fraction. In the same time interval, the tablets loaded with PM had released about 60% of their CAR content whereas those loaded with FD had released roughly all their CAR content. The release profile of CAR-loaded tablets without HPβCD was linear with time whereas in the case of HPβCD-containing tablets, linear behaviour was attained after a transient. The release kinetics of HPβCD from tablets were also followed (Fig. 4). Tablets loaded with both PM and FD displayed similar HPβCD release profiles and a release rate faster than that of CAR. Further-

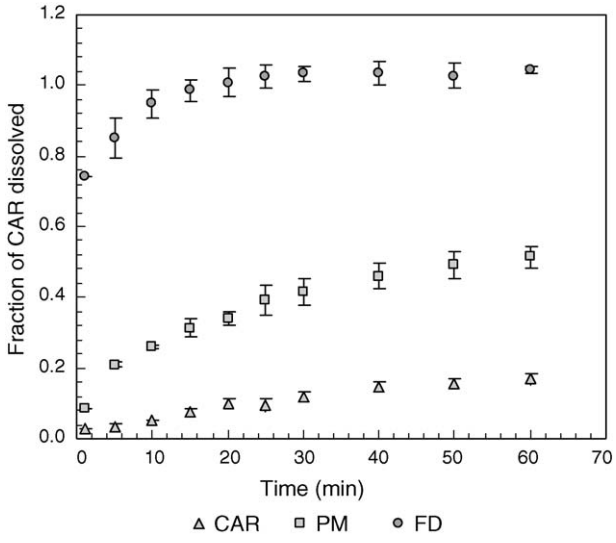

Fig. 2. Dissolution profiles of carvedilol (CAR), CAR/HPβCD physical mixture (PM) or CAR/HPβCD freeze-dried product (FD) in PBS at pH 6.8 and 37 °C. Dissolved CAR fraction is evaluated as the ratio of dissolved CAR at each time to the total amount of CAR added to the medium. Data are the mean ± S.D. of four experiments.

more, an identical HPβCD release profiles for both PM- and FD-loaded systems, indicated that the same boundary conditions are established for both tablets in terms of external HPβCD concentration. As a consequence, the observed differences in CAR release profiles for HPβCD-containing tablets could not be attributed to a different CAR solubility in the release medium. The erosion profiles of the tablets based on PEO or PEO/HPβCD are reported in Fig. 5 as fractional weight loss versus time. It is evident that the presence of HPβCD speeded up the solubilization rate of the matrix as whole, likely due to an increase in polymer hydrophilicity.

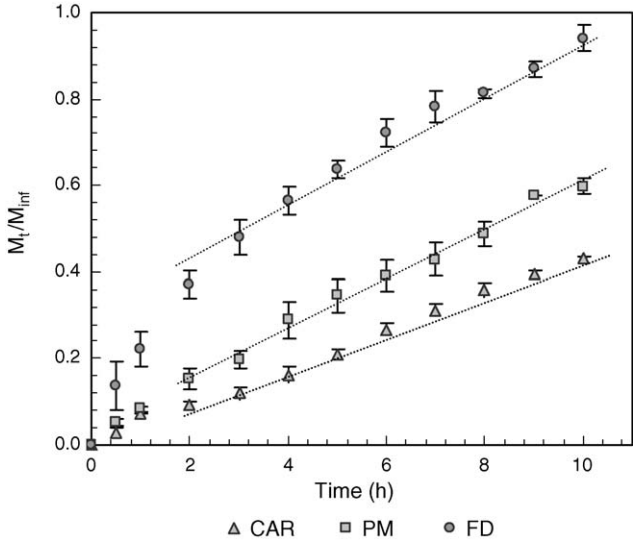

Fig. 3. Release profiles of CAR from PEO tablets incorporating CAR (CAR), CAR/HPβCD physical mixture (PM) or CAR/HPβCD freeze-dried product (FD) in PBS at pH 6.8 and 37 °C. Lines are drawn to guide the eye. Data are the mean ± S.D. of four experiments.

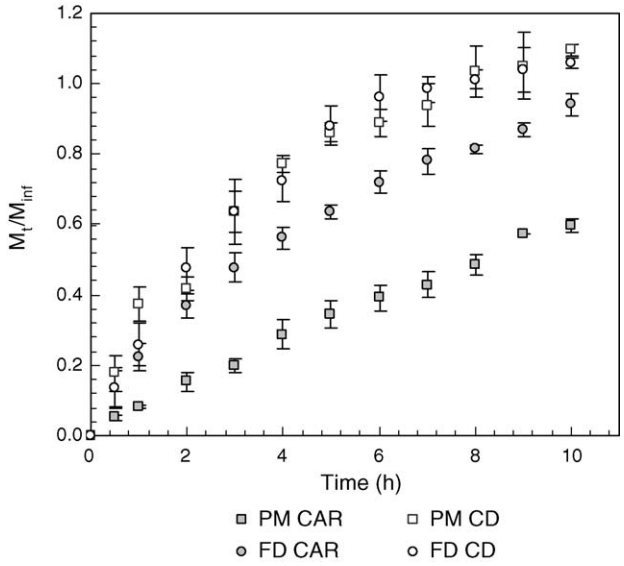

Fig. 4. Release profiles of CAR and HPβCD from PEO tablets incorporating CAR/HPβCD physical mixture (PM) or CAR/HPβCD freeze-dried product (FD) in PBS at pH 6.8 and 37 °C. Data are the mean ± S.D. of four experiments.

3.2. A mechanistic interpretation of release behaviour

The release process can be envisaged as characterized by an initial transient followed by the establishment of a pseudo-steady state regime when fronts E, S and D move in a synchronized way and an external swollen layer of constant thickness is formed. The drug concentration profile that develops in the swollen layer depends upon drug diffusivity, solubility and dissolution rate in the swollen polymer, as well as on the thickness of the developing swollen layer.

CAR release is contributed by both the movement of E front and the diffusive flux related to the drug concentration profile at the E interface. The rate of E front as well as the diffusive

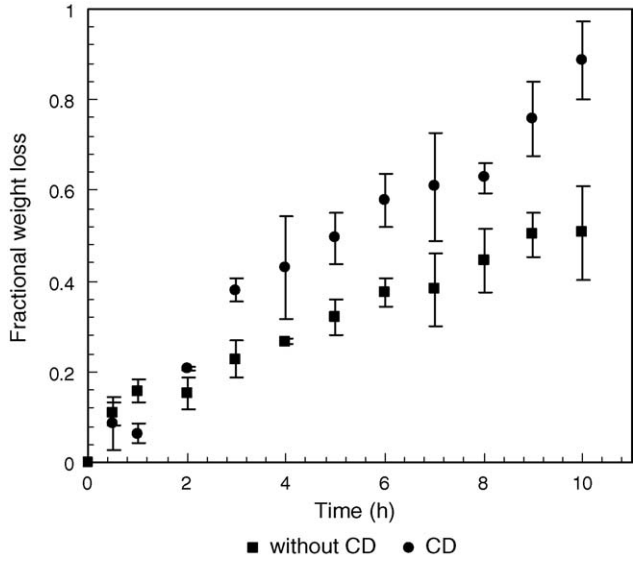

Fig. 5. Fractional weight loss of PEO tablets without and with HPβCD in PBS at pH 6.8 and 37 °C. Data are the mean ± S.D. of four experiments.

flux change with time during the initial transient to attain values constant with time when the pseudo-steady state regimen is established. The presence of HPβCD increases the erosion rate as well as drug concentration at D interface at pseudo-steady state (C^*) and in turn speeds up CAR release rate. The hypothesis is made here that HPβCD does not affect the mobility of the drug in the swollen layer, i.e. HPβCD, CAR and their complex have similar diffusivities in the highly swollen external layers of hydrophilic tablet. In the following we examine in a deeper detail the transient and the pseudo-steady state regimen in view of the effects exerted by the presence of HPβCD in the tablets.

In the initial transient the front rates are not constant, that is E front moves at increasing rate whereas S front moves at decreasing rate up to steady state. As a consequence, the diffusive driving force changes with time due to the increase of the thickness of gel layer proportionally to the square root of time. Hence, the initial non linearity observed in the release profiles of CAR is due to the fact that, before synchronization, both contributions to the release are time dependent. In the case of HPβCD-containing tablets, the movement of E front is faster as compared to tablets without HPβCD (see Fig. 5). Furthermore, a higher diffusive flux develops as a consequence of the higher solubilization rate operated by HPβCD, which increases the amount of mobile species. Both these effects, result in an enhanced release rate of drug as compared to the case of tablets without HPβCD. FD-loaded tablets display the highest release rate due to the fact that they are loaded with the binary system which, on the basis of dissolution rates in water, is expected to dissolve more promptly in the water swollen polymer (Fig. 2).

As mentioned above, if tablet thickness is large enough, after the initial transient a pseudo steady-state regimen can be attained where a synchronization of D, S and E fronts occurs. In this condition, C^* is constant with time and its value is determined by the balance between drug solubilization rate in the swollen polymer and the diffusive flux across the swollen layer. At pseudo-steady state E and D fronts move at the same rate and release is contributed by the movement of E front, which occurs at constant rate, and by the diffusive flux at the E interface, which is constant with time (due to the establishment of a constant drug profile in the swollen layer). This synchronization is expected to occur after a lag time which in general depends upon the molecular weight of the polymer and its physical properties (Cappello et al., 1994; Peppas et al., 1994). In the case of tablets loaded with CAR/HPβCD binary systems it is again expected that a pseudo-steady state is attained where E, S and D fronts are synchronized, although the thickness of the swollen layer is likely smaller than in the case of tablets without HPβCD. In analogy to the transient stage, the presence of HPβCD promotes an increase of both C^* and erosion rate, resulting in an enhanced release rate of drug as compared to the case of the tablets without HPβCD. While the rates of S and E fronts are expected to be similar for FD- and PM-loaded tablets, differences are likely in the drug concentration profiles, in view of a higher C^* for FD-loaded tablets. As far as HPβCD release is concerned, release rate does not vary from PM- to FD-loaded tablets (see Fig. 4), since the evolution of its concentration profile is identical.

This analysis highlights that the introduction of CD in surface eroding controlled release tablets supplies an additive mean to tailor the release by modulating the dissolution rate of the drug in the swollen layer as well as the erosion rate of the matrix. Dissolution rate of CAR/HPβCD powders loaded in the tablets depends upon the physical state of the binary system. Among the systems investigated here, tablets loaded with FD binary system display the highest release rate, in view of its faster dissolution rate features, although differences between FD- and PM-based devices are partially mitigated by the contribution to the release of the matrix erosion, which proceeds at the same rate in both cases. It follows that, when matrix erosion plays a minor role in the release mechanism, as is the case of buccal tablets releasing drug to mucosa, the differences between the two systems are expected to become even higher.

3.3. Potential of PEO tablets as buccal delivery system for carvedilol

A successful design of a buccal delivery system should guarantee both an intimate contact with the mucosa for an adequate time interval and proper release rates. Actually, before a drug passes through the mucosal barrier and reaches blood circulation, it should dissolve in the medium penetrating inside the buccal tablet. This step is generally critical for lipophilic drugs that, although being well absorbed, exhibit a slow dissolution rate in aqueous media. HPβCD-containing PEO tablets could therefore be of interest as a transmucosal delivery system due to their recognized bioadhesive properties and the possibility of improving release features of drugs poorly soluble in aqueous media, which has been illustrated above. However, the incorporation of CAR/HPβCD binary systems in the tablets for such an application should not impair the overall mucoadhesive properties of the system, that is the interdiffusion of polymer chains and mucus components at interface.

An overall evaluation of the mucoadhesive behaviour of different PEO tablets (composition reported in Table 1) on pig buccal mucosa was performed by determining the force of detachment versus elongation. A typical force of detachment-distance curve for the case of PM21 tablet is reported in Fig. 6. The bioadhesive behaviour of the tablets has been character-

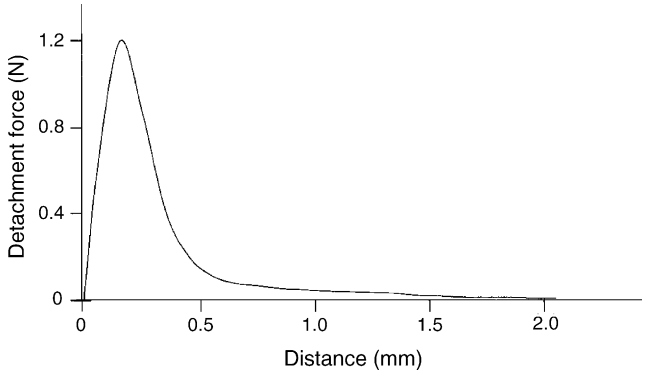

Fig. 6. Detachment force–distance curve for a PM21 tablet adhering to porcine buccal mucosa.

ized by means of the work of adhesion, *W*, i.e. the area under the force–elongation curve (Table 1). As expected, the highest value of *W* was obtained for pure PEO tablet, and a decrease was observed as the PEO content decreased. FD-loaded tablets displayed a slightly higher work of adhesion as compared to PM-loaded tablets with the same composition. Considering the overall properties of HPβCD-containing tablets, it can be concluded that the samples PM21 and FD21 still display good bioadhesive properties, although containing considerable amounts of HPβCD, and are suitable for transmucosal applications.

The feasibility of a buccal delivery for CAR was preliminary assessed by measuring in vitro permeation of CAR through pig buccal mucosa. The results, reported in Fig. 7A, show that CAR permeation through mucosa was quite good and increased in the presence of an 8% (w/v) of HPβCD (J_{SS} were 7 and 22 μg/cm^2/h without and with HPβCD in the donor medium). This effect, in principle, can be attributed to both an increase of driving force for permeation due to the increase of CAR apparent solubility in the presence of HPβCD as well as to a enhancing effect of HPβCD. To highlight this point, permeation experiments on

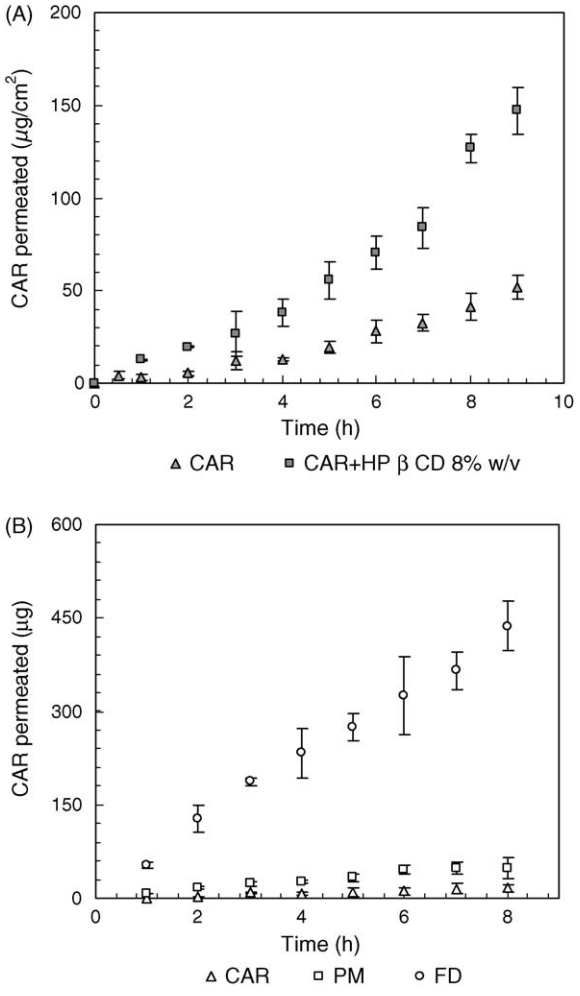

Fig. 7. Permeation through porcine buccal mucosa of CAR. (A) Donor side was a CAR saturated solution in either PBS or PBS with an 8% (w/v) of HPβCD. (B) PEO tablets stuck to mucosa at the donor side incorporating CAR/HPβCD physical mixture (PM) or CAR/HPβCD freeze-dried product (FD). Data are the mean ± S.D. of five permeation experiments.

Table 2
Effect of cyclodextrin addition on CAR permeation through pig buccal mucosa

	CAR/CD molar ratio	$A_{8\,h}$[b] (μg/cm^2)
CAR[a]	–	56
CAR/HPβCD[a]	1/2	58
	1/5	40
	1/10	n.d.

[a] CAR concentration was 6 μg/ml.
[b] Cumulative amount of CAR permeated per unit area over 8 h.

CAR solutions containing increasing amounts of HPβCD were performed. The amount of CAR permeated per unit area through buccal mucosa after 8 h (Table 2) decreased as HPβCD concentration in the donor solution increased, suggesting that HPβCD reduced drug concentration gradient in the mucosa due to the involvement of CAR in a complexation equilibrium ($K_{1:1}$ for complex formation is about 82 M^{-1}, data not shown). Thus, any absorption enhancing effect of HPβCD could be excluded. Subsequently, permeation experiments were performed by sticking PEO tablets on porcine buccal mucosa and assessing the evolution with time of CAR concentration in the receptor side (Fig. 7). The results clearly show that both the HPβCD-containing tablets allowed a CAR permeation higher than that of the tablet containing only CAR, the FD-loaded tablet showing the highest permeated amount after 8 h (9, 48 and 430 μg for tablets containing CAR, CAR/HPβCD physical mixture and CAR/HPβCD freeze-dried, respectively). In the light of the characterization study on tablets, it can be reasonably supposed that the improvement of CAR dissolution features increases the concentration gradient between donor and receptor side and results in a higher CAR permeation through buccal membrane. The role of dissolution enhancement in increasing the rate of delivery is more relevant when the tablet is employed as transmucosal system since, differently from solution conditions, a very limited contribution to delivery derives from matrix erosion.

4. Conclusions

It has been shown that the incorporation of cyclodextrins in a PEO-based hydrophilic matrix intended for the delivery of poorly soluble drugs can be a suitable strategy to optimize the release features of the system while maintaining good bioadhesive properties. Cyclodextrins are responsible for an increase in the erosion rate of the tablet and an improved dissolution of the drug inside the polymeric matrix. This latter effect is the crucial factor, which determines the increase of release rate from the tablets in solution as well as a twenty-fold increase in the amount of carvedilol permeated through porcine buccal mucosa. This systems turns to be of great potential as buccal delivery system in view of the possibility of tailoring release features while maintaining good bioadhesive properties.

Acknowledgment

This work was kindly supported by a grant from MIUR (PRIN 2004).

References

Apicella, A., Cappello, B., Del Nobile, M.A., La Rotonda, M.I., Mensitieri, G., Nicolais, L., 1993. Poly(ethylene oxide) (PEO) and different molecular weight PEO blends monolithic devices for drug release. Biomaterials 14, 83–90.

Bibby, D.C., Davies, N.M., Tucker, I.G., 2000. Mechanisms by which cyclodextrins modify drug release from polymeric drug delivery systems. Int. J. Pharm. 197, 1–11.

Bottenberg, P., Cleymaet, R., de Muynck, C., Remon, J.P., Coomans, D., Michotte, Y., Slop, D., 1991. Development and testing of bioadhesive, fluoride-containing slow-release tablets for oral use. J. Pharm. Pharmacol. 43, 457–464.

Cappello, B., Del Nobile, M.A., La Rotonda, M.I., Mensitieri, G., Miro, A., Nicolais, L., 1994. Water soluble drug delivery systems based on a non-biological bioadhesive polymeric system. Farmaco 49, 809–818.

Chowdary, K.P., Kamalakara, R.G., 2003. Controlled release of nifedipine from mucoadhesive tablets of its inclusion complexes with beta-cyclodextrin. Pharmazie 58, 721–724.

Di Colo, G., Burgalassi, S., Chetoni, P., Fiaschi, M.P., Zambito, Y., Saettone, M.F., 2001. Relevance of polymer molecular weight to the in vitro/in vivo performances of ocular inserts based on poly(ethylene oxide). Int. J. Pharm. 220, 169–177.

Giunchedi, P., Maggi, L., La Manna, A., Conte, U., 1994. Modification of the dissolution behaviour of a water-insoluble drug, naftazone, for zero-order release matrix preparation. J. Pharm. Pharmacol. 46, 476–480.

Jain, A.C., Aungst, B.J., Adeyeye, M.C., 2002. Development and in vivo evaluation of buccal tablets prepared using danazol-sulfobutylether 7 beta-cyclodextrin (SBE 7) complexes. J. Pharm. Sci. 91, 1659–1668.

Kim, C.J., 1995. Drug release from compressed hydrophilic POLYOX-WSR tablets. J. Pharm. Sci. 84, 303–306.

Kim, C.J., 1998. Effects of drug solubility, drug loading, and polymer molecular weight on drug release from Polyox tablets. Drug Dev. Ind. Pharm. 24, 645–651.

Koester, L.S., Xavier, C.R., Mayorga, P., Bassani, V.L., 2003. Influence of beta-cyclodextrin complexation on carbamazepine release from hydroxypropyl methylcellulose matrix tablets. Eur. J. Pharm. Biopharm. 55, 85–91.

Narasimhan, B., 2001. Mathematical models describing polymer dissolution: consequences for drug delivery. Adv. Drug Deliv. Rev. 48, 195–210.

Narasimhan, B., Peppas, N.A., 1997. In: Park, K. (Ed.), The Role of Modeling in the Development of Future Controlled Release Devices. American Chemical Society, Washington, DC, pp. 529–557.

Okimoto, K., Rajewski, R.A., Stella, V.J., 1999. Release of testosterone from an osmotic pump tablet utilizing (SBE)7*m*-beta-cyclodextrin as both a solubilizing and an osmotic pump agent. J. Control Release 58, 29–38.

Peppas, N.A., Wu, J.C., von Meerwall, E.D., 1994. Mathematical modeling and experimental characterization of polymer dissolution. Macromolecules 27, 5626–5638.

Pose-Vilarnovo, B., Rodriguez-Tenreiro, C., Rosa dos Santos, J.F., Vazquez-Doval, J., Concheiro, A., Alvarez-Lorenzo, C., Torres-Labandeira, J.J., 2004. Modulating drug release with cyclodextrins in hydroxypropyl methylcellulose gels and tablets. J. Control Release 94, 351–363.

Quaglia, F., Varricchio, G., Miro, A., La Rotonda, M.I., Larobina, D., Mensitieri, G., 2001. Modulation of drug release from hydrogels by using cyclodextrins: the case of nicardipine/beta-cyclodextrin system in crosslinked polyethylenglycol. J. Control Release 71, 329–337.

Rao, V.M., Haslam, J.L., Stella, V.J., 2001. Controlled and complete release of a model poorly water-soluble drug, prednisolone, from hydroxypropyl methylcellulose matrix tablets using (SBE)(7*m*)-beta-cyclodextrin as a solubilizing agent. J. Pharm. Sci. 90, 807–816.

Rathbone, M.J., Ponchel, G., Chazali, F.A., 1996. In: Rathbone, M.J. (Ed.), Systemic Oral Mucosal Drug Delivery and Delivery Systems. Marcel Dekker, New York.

Sangalli, M.E., Zema, L., Maroni, A., Foppoli, A., Giordano, F., Gazzaniga, A., 2001. Influence of betacyclodextrin on the release of poorly soluble drugs from inert and hydrophilic heterogeneous polymeric matrices. Biomaterials 22, 2647–2651.

Tiwari, D., Goldman, D., Sause, R., Madan, P.L., 1999. Evaluation of polyoxyethylene homopolymers for buccal bioadhesive drug delivery device formulations. AAPS Pharm. Sci. 1, E13.

Veuillez, F., Rieg, F.F., Guy, R.H., Deshusses, J., Buri, P., 2002. Permeation of a myristoylated dipeptide across the buccal mucosa: topological distribution and evaluation of tissue integrity. Int. J. Pharm. 231, 1–9.

Villar-Lopez, M.E., Nieto-Reyes, L., Anguiano-Igea, S., Otero-Espinar, F.J., Blanco-Mendez, J., 1999. Formulation of triamcinolone acetonide pellets suitable for coating and colon targeting. Int. J. Pharm. 179, 229–235.

Zarzycki, P.K., Lamparczyk, H., 1998. The equilibrium constant of beta-cyclodextrin–phenolphtalein complex; influence of temperature and tetrahydrofuran addition. J. Pharm. Biomed. Anal. 18, 165–170.