

Effect of hydroxypropyl- β -cyclodextrin on hydrocortisone dissolution from films intended for ocular drug delivery

M. BEĆIREVIĆ-LAČAN and J. FILIPOVIĆ-GRČIĆ

The formation of an inclusion complex between hydrocortisone and hydroxypropyl- β -cyclodextrin can affect the *in vitro* transfer rate of hydrocortisone from the aqueous to the organic phase. The observed first order transfer rate constants showed that the complexation of hydrocortisone with hydroxypropyl- β -cyclodextrin decreased significantly the transport of the drug depending on the partition coefficient of the drug, and the relative magnitude of the stability constant of the inclusion complex. To optimize the ocular drug delivery, high molecular weight cellulosis and PVA polymeric films were prepared. No unified mathematical model can predict the release profile of drug and complex from films. The drug and complex-polymer interactions in each system could be responsible for the solubility of the drug, and different release behaviours of hydrocortisone and cyclodextrin inclusion complex from the films prepared.

1. Introduction

Absorption of drugs into the eye requires good corneal penetration plus prolonged contact time with corneal tissue. Ideally, the formulation should be able to sustain drug release and to remain in contact with the front of the eye for an extended period of time. Traditional dosage forms for the delivery of drugs and artificial tears to the eye have been solutions and ointments. Several approaches have been used to improve the precorneal residence time and to enhance corneal penetration using polymers for the preparation of films [1]. Some recent reviews summarize the factors which affect corneal penetration of the drugs using cyclodextrins in ophthalmic formulations [2, 3].

Cyclodextrins are said to improve the ocular bioavailability of drugs by keeping water insoluble drug molecules in solution and deliver them to the surface of the corneal barrier where they penetrate into the eye [4]. The relatively lipophilic membrane has low affinity for the hydrophilic cyclodextrin (CD) molecules and therefore they remain in the aqueous membrane exterior, e.g. the tear fluid. It was reported that hydroxypropyl- β -cyclodextrin (HP β CD) did not cause any alterations in the corneal tissues. The large and very hydrophilic HP β CD molecules do not penetrate biological membranes but act as penetration enhancers leading to a constant high concentration of dissolved drug at the membrane surface [5].

The aim of this study was to formulate and evaluate a film of hydrocortisone (HC) using different polymers having different aqueous solubility. Owing to its poor aqueous solubility, HC is usually formulated as topical ophthalmic suspensions. It was claimed that the dissolution rate of the particles must be equal to or greater than their rate of clearance from the precorneal area. To overcome this problem a water soluble CD complex of HC was formulated and used in ocular polymeric systems.

2. Investigations, results and discussion

2.1. Transport experiments

The interfacial model system was employed to measure the transfer rate constants from the aqueous to the organic phase of HC alone or in the complex form. The model system chosen was used to predict the effect of HP β CD on partitioning of HC to the lipoidal membranes of the

eye. The biological activity of a drug depends on its concentration in the receptor compartment, which strongly depends on the transfer rate between both administration and receptor compartments. So the transfer rate studies often use biphasic models, water and organic solvent. The method is based on the fact that polar CD molecules are not expected to partition into the organic phase, and that transfer of HC from an aqueous phase to an organic phase may reflect the ability of the drug to be absorbed into the corneal tissue.

The first order transfer rate constants (k) were obtained from the slope of the linear regression on the logarithm of HC concentrations in the aqueous phase against time (Fig. 1). Table 1 shows first order transfer rate constants for HC alone and its CD complex, k , and half-lives, $t_{1/2}$, determined by interfacial transfer study. The observed first order transfer rate constants clearly show that the complexation of HC with HP β CD decreased significantly the

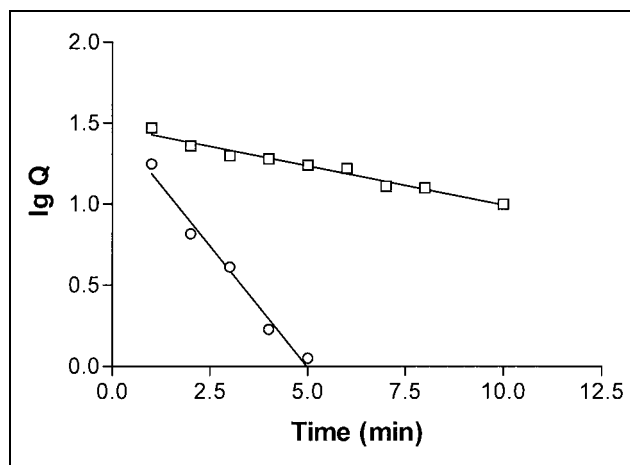


Fig. 1: First order plots (interfacial transfer study) for the decrease of HC concentration in aqueous phase. CD complex (□), HC (○)

Table 1: First order transfer rate constants, k , and half lifes, $t_{1/2}$, of HC and its CD complex determined by interfacial transfer study

Compound	k (min^{-1})	$t_{1/2}$ (min)
HC	0.298 ± 0.023	2.33
HC-HP β CD complex	0.048 ± 0.003	14.34

transport of the drug from the aqueous to the organic phase. A decrease of the first order transfer rate constant from 0.298 min^{-1} (HC alone) to 0.048 min^{-1} (HP β CD complex) was observed, while the half-lives of the transfer increased up to 515%.

When dissociation of the complex occurred in the aqueous phase only the free fraction of HC can diffuse into the organic phase depending on the partition coefficient of the drug and the relative magnitude of the stability constant of the inclusion complex. The stability constant for the 1:1 HC-HP β CD complex was previously determined from a phase solubility diagram [6]. However, the stability constant found for the HC-HP β CD complex was 466 M^{-1} suggesting interaction, and favourable positioning of the drug inside the cavity of the HP β CD molecule. The observed decrease in transport rate was probably due to changes in the partition coefficient upon CD complexation. By altering the apparent solubility and partition coefficient of HC, complexation influenced the transport from the aqueous to the organic phase.

2.2. Dissolution of hydrocortisone and complex from the films

Phase solubility studies indicate the feasibility of obtaining a HC-HP β CD solid inclusion complex by spray drying of solubilized HC in CD solution using ethanol capable of dissolving HC, and giving a clear solution after mixing with an aqueous HP β CD solution. Spray-drying of solubilized HC in CD solution (1:1 molar ratio) yields a product of amorphous appearance with spherical small particles. The particles of about $5 \mu\text{m}$ were distinguished by the formation of aggregates, as observed by the image analysis technique. The content of HC in the complex was determined to be about 25% [6].

An area where cyclodextrins may have a significant therapeutic benefit is the solubilization of drugs intended for ophthalmic use. One way to optimize ocular drug delivery and to prolong precorneal drug residence time is to employ polymers. Ocular delivery films have demonstrated promising improvements in the ocular bioavailability. We used high molecular weight cellulosic and PVA polymers which cannot cross biological membranes and are widely used in ophthalmic preparations as drug delivery vehicles. Plasticizers were added to the formulations mostly to reduce brittleness, impart flexibility and to improve adhesion and removal of the film.

In an attempt to obtain more information on the release kinetics, dissolution data of HC from different films were analysed calculating the expected curves for first order kinetics, biphasic first order kinetics and square root of time kinetic. The curfit computer program which consisted of a least squares fit to a linear or nonlinear function was used.

Table 2 presents the kinetic parameters for dissolution of HC from different films applying different kinetics. The first order kinetics show a deviation from the expected, with low correlation coefficients. The biphasic first order kinetics and diffusion controlled system fit the release patterns better, but the correlation coefficients listed indicate that the release pattern followed better biphasic first order kinetics. The biphasic kinetics included two fairly separate phases. A relatively fast initial release was followed by a slow one. Each of these phases can be characterized by a first order kinetic equation. The concentration of HC in the film did not remain constant after the elapse of a certain period of time because exhaustion of drug was leading to a change in the concentration gradient following first-order release profile. Continual loss of the drug

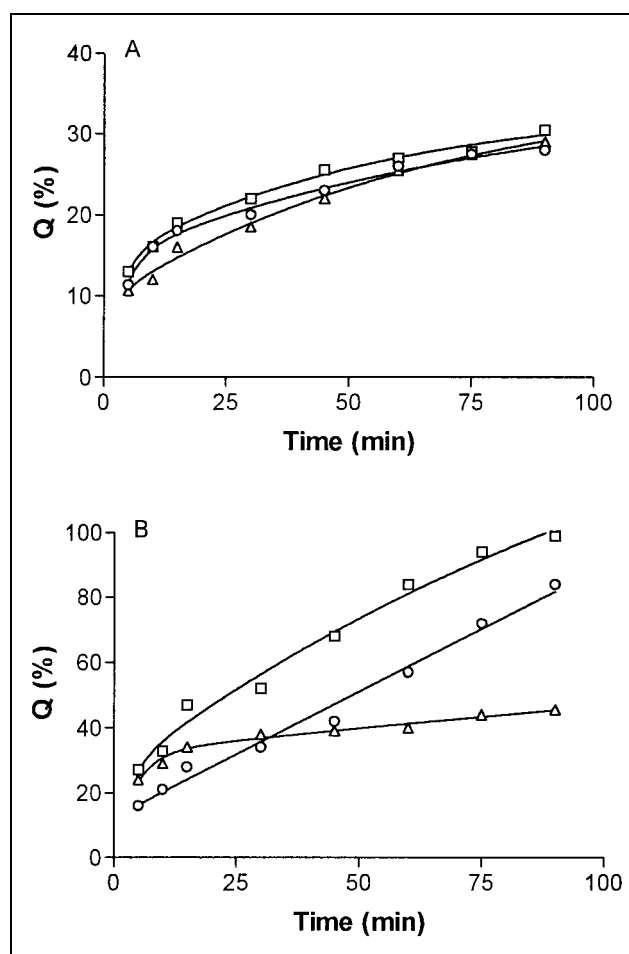


Fig. 2: Release profiles of HC from PVA, HC and EC films as a function of time in the absence (Fig 2A) and presence of CD (Fig 2B). HPC (○), PVA (□), EC (△)

Table 2: Kinetics parameters for dissolution of HC from different films, applying first order kinetic, biphasic release model and Higuchi type matrix kinetic

Film	First order			Biphasic model					Higuchi model	
	k (min ⁻¹)	t _{1/2} (min)	r ²	k ₁ (min ⁻¹)	t _{1/2} (min)	k ₂ (min ⁻¹)	t _{1/2} (min)	r ²	k(mg min ^{-1/2})	r ²
HPC-HC	0.011	62.3	0.9251	0.255	2.7	0.012	60.2	0.9921	0.219	0.9708
HPC-Complex	0.086	8.1	0.8573	4.338	0.2	$9.7 \cdot 10^{-5}$	70.9	0.9865	0.788	0.9484
PVA-HC	0.032	23.4	0.9120	0.321	2.2	0.018	38.6	0.9920	0.229	0.9800
PVA-Complex	0.087	8.0	0.8684	0.326	2.1	0.005	146.7	0.9862	1.061	0.9794
EC-HC	0.055	12.6	0.8743	0.298	2.3	0.014	48.5	0.9985	0.160	0.9905
EC-Complex	0.135	5.1	0.8467	0.726	0.9	0.001	682.5	0.9918	0.266	0.9329

would produce a situation where the rate would fall exponentially in the second phase. Our systems have shown that HC release obeys also Higuchi type matrix kinetics, and the release data may conform to those from matrix devices. So, one should therefore be aware that no unified mathematical model can predict the complete release profile.

To obtain films for ocular administration suitable polymers as ethylcellulose (EC), a typical hydrophobic cellulose derivative, HPC as hydrophilic cellulose derivative, PVA as water soluble and bioerodible polymer, were used. Fig. 2 shows HC release from PVA, HC and EC films as a function of time in the absence (Fig. 2A) and presence of CD (Fig. 2B). The release of HC from the films prepared was expected to be affected by the complexation of the drug with HP β CD. By CD complexation it was possible to increase the aqueous solubility of HC without changing its molecular structure. The HC release from the films in the presence and absence of CD decreased in the order PVA>HPC>EC. Ethylcellulose produced a film which was quite brittle, insoluble in water, and maintained its integrity. PVA and HPC are more hydrophilic than EC. In PVA and HPC films, substantial swelling was noted which would increase water content and channels for diffusion. HPC is water soluble, and no visual dissolution of the film was observed until the end of the experiment. PVA swelled during the time of testing and appreciable film dissolution was noted. PVA and HPC films were subjected to a gelation process and to an erosion process during the release test which was due to the swelling properties of the polymer used.

The complicated drug-polymer interaction in each system could be responsible for the solubility of the drug in the polymer and different release behaviours of the drug in the films prepared. Drug solubility and diffusion coefficient in the film might also affect the release rate. Recent reports have shown that some other water soluble polymers increase the complexation of the drug with cyclodextrins. The addition of polymer to the aqueous complexation medium resulted in an increase in the apparent stability constant of the complex [7].

As a conclusion we can state that in general HC- and CD complex-polymer interactions in different films could be responsible for the different release behaviours of HC. The formation of the inclusion complex can affect the solubility of HC as well as the *in vitro* release characteristics of the drug.

3. Experimental

3.1. Material

Hydrocortisone (HC) was purchased from Sigma (St. Louis, Mo, USA). Hydroxypropyl- β -cyclodextrin MS 0.9 (HP β CD) was a generous gift of Wacker Chemie GmbH (Munich, Germany). Polyvinyl alcohol (PVA) reagent grade with an average mol. wt. of 16,000 was obtained from Aldrich Chemical Co (Milwaukee, Wis, USA). Ethylcellulose (EC) Ethocel (50 cp) was the product of Dow Chemical Co (Midland, Mich, USA). Hydroxypropyl cellulose (HPC) with an average mol. wt. of 100,000, Kluccel LF, was supplied by Hercules Ind. (Wilmington, USA). All other solvents and reagents were of analytical reagent grade.

3.2. Interfacial transfer studies

The interfacial transfer studies were performed by a modification of the method of Dollo et al. [8]. The two phase stirred transfer device which consisted of a beaker thermostated at 37 °C, equipped with the one glass-bladed impeller in the centre of the upper phase with the rotation speed of 100 rev/min, and a magnetized agitator in the bottom phase giving an opposite 100 rev/min rotation was used. The volume of the organic phase (methylene chloride) was 100 ml, equilibrated for 2 h at 37 °C with 150 ml of water. At the beginning of the experiment a solution of water containing 0.02 g HC ("free" or in the complex form) was poured directly into the aqueous phase giving a final volume of 200 ml for the aqueous phase. Samples were collected from the aqueous phase at appropriate times during 90 min and the concentration of the drug was analysed spectrophotometrically at 262 nm after appropriate dilution with ethanol (LKB Ultra-spec Plus Spectrophotometer, Pharmacia, Sweden).

3.3. Preparation of the inclusion complex

HC and HP β CD in a 1 : 1 molar ratio were separately dissolved in 400 ml of 96% (v/v) ethanol and 400 ml of purified water, respectively. The solutions were mixed and sonicated for 15 min to produce a clear solution which was subjected to spray-drying using a Büchi 190 M Mini Spray Dryer (Switzerland). Under these conditions, no spontaneous precipitation of the inclusion did occur. The drying conditions were as follows: flow rate 1000 ml/h, inlet temperature 190 °C, outlet temperature 90 °C and air flow rate 700 NI/h. The content of hydrocortisone incorporated into the complex was determined by UV spectrophotometry.

3.4. Film preparation

Polymer films containing 100 mg of HC "free" or in the complex form were cast from the solutions containing 5% of the polymer. Polymers were added as a dry powder to the vigorously stirred chloroform-ethanol mixture (1 : 1) or purified water in the case of PVA. The solutions were spread on the glass Petri dishes, allowing the films to air dry for 7 days at ambient conditions. The plasticizers polyethylene glycol 400 and acetyltriethyl citrat (Citroflex A2) were added in the concentration corresponding to 20% of the amount of the polymer. The initial drug concentrations in the films prepared were determined spectrophotometrically using samples of the films dissolved in an ethanol-chloroform mixture (1 : 1) or in water.

3.5. Determination of release rate

Rectangular films were obtained by cutting a section of the film. The film was weighed on an analytical balance, and it was placed into a beaker in a 37 °C water bath containing 200 ml of pH 7.4 phosphate buffer solution. The system was agitated with a magnetic stirrer. Samples were withdrawn at time intervals and assayed spectrophotometrically. To maintain a constant volume of the dissolution medium, an amount equal to the volume withdrawn was immediately added after each withdrawal.

References

- 1 Le Boultais, C. A.; Treupel-Acar, L.; Rhodes, C. T.; Sado, P. A.; Le-verge, R.: *Drug Dev. Ind. Pharm.* **21**, 19 (1995)
- 2 Rajewski, R.; Stella, V. J.: *J. Pharm. Sci.* **85**, 1142 (1996)
- 3 Van Doorne, H.: *Eur. J. Pharm. Biopharm.* **39**, 133 (1993)
- 4 Jarho, P.; Järvinen, K.; Urtti, A.; Stella, V. J.; Järvinen, T.: *Int. J. Pharm.* **153**, 225 (1997)
- 5 Loftsson, T.; Fridriksdottir, H.; Stefansson, E.; Thorisdottir, S.; Gudmussun, Ö.; Sigthorsson, M.: *J. Pharm. Pharmacol.* **46**, 503 (1994)
- 6 Filipović-Grčić, J.; Voinovich, D.; Moneghini, M.; Bećirević-Laćan, M.; Magarotto, L.; Jalšenjak, I.: Submitted to *Eur. J. Pharm. Sci.*
- 7 Loftsson, T.; Fridriksdottir, H.; Thorisdottir, S.; Stefansson, E.: *Int. J. Pharm.* **104**, 181 (1994)
- 8 Dollo, G.; Le Carre, P.; Chevanne, F.; Le Verge, R.: *Int. J. Pharm.* **136**, 165 (1996)

Received July 20, 1999

Accepted November 15, 1999

Mira Bećirević-Laćan
Department of Pharmaceutical Technology
Faculty of Pharmacy and Biochemistry
University of Zagreb
10000 Zagreb
A Kovačića 1
Croatia