J Incl Phenom Macrocycl Chem (2007) 57:391–394
DOI 10.1007/s10847-006-9223-x

ORIGINAL ARTICLE

Cyclodextrin derivatives and cyclofructan as ocular permeation enhancers

Results with different model compounds

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Received: 15 May 2006 / Accepted: 20 October 2006 / Published online: 30 January 2007

Abstract The positive influence of specific cyclodextrins and cyclofructan on the permeation of ophthalmic drugs through ocular tissues was demonstrated

Keywords Peranhydro-cyclodextrins · Quaternary ammonium cyclodextrins · Cyclofructan · Permeation enhancement · Ophthalmic drugs

Introduction

Cyclodextrins and other cyclic compounds can have a significant influence on the bioavailability of ocular drugs ([1], and references therein). We have previously demonstrated a significant increase in the amount of diclofenac (from Diclofenac sodium 0.1% eye drops) permeating through an excised pig cornea in presence of HP-γ-CD, as compared to a solution with Cremophor EL (Fig. 1). These results prompted us to test other cyclodextrin derivatives and cyclofructan for their in vitro permeation enhancing effect not only with diclofenac but also with Cox 189 [2] and ketotifen (Scheme 1).

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Materials and methods

The following cyclodextrins were tested: (a) Peranhydro-cyclodextrins [3], namely hexakis(3,6-anhydro)-α-CD and octakis(3,6-anhydro)-γ-CD, and (b) Quaternary ammonium cyclodextrins [3–6], namely (2-hydroxy-3-*N*,*N*,*N*-trimethylamino)propyl-α-CD) and (3-*N*,*N*,*N*-trimethylamino)propyl-β-CD). Additionally, comparisons were made with cyclofructan CFR6 (for formulae see the examples below) (Scheme 2).

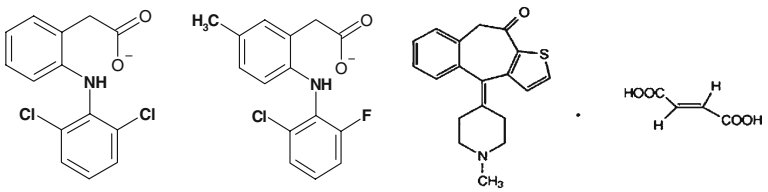
We obtained the cyclodextrins from Cyclolab, Hungary and cyclofructan from Mitsubishi Chemicals, Japan.

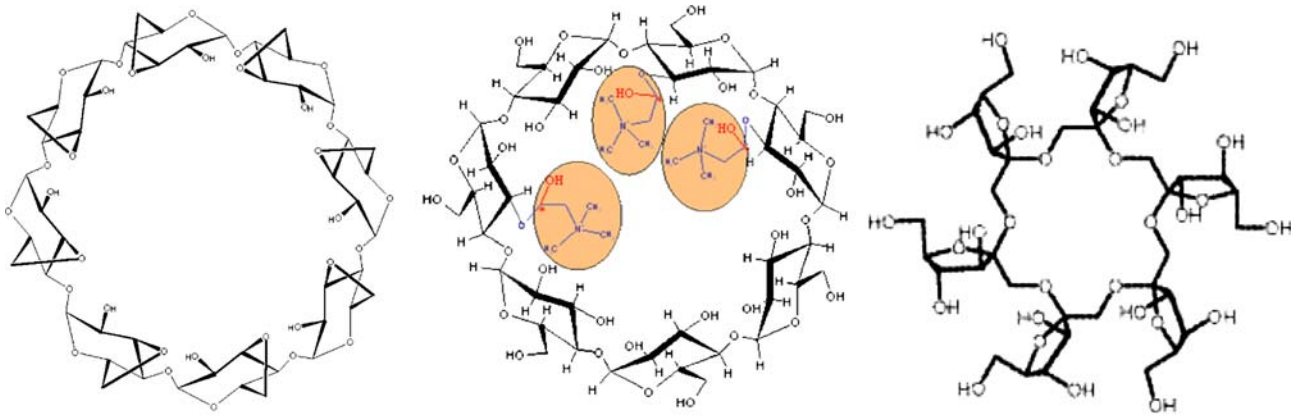
Corneal permeation procedure

Pig eyes were obtained from the local slaughterhouse and used within a few hours after receipt. Permeation

Exploded view of the corneal permeation

Scheme 1 Chemical structure of tested drugs





Scheme 2 Structure of tested cyclic compounds

Diclofenac/Cremophor		Diclofenac/CFR/CDs	
Diclofenac sodium	0.1 g	Diclofenac sodium	0.1 g
Boric acid	1.9 g	Disodium edetate	0.1 g
Trometamol	0.6 g	HP-γ-CD or	
Cremophor EL	5.0 g	Cyclofructan or	
Water ad	100 ml	Peranhydro-γ-CD or	2.0 g
		QA-β-CD	1.0 g
		Propylene glycol	1.9 g
		Trometamol	0.1 g
		Tyloxapol	0.1 g
		Hydochloric acid 1N	0.29 g
		Water ad	100 ml

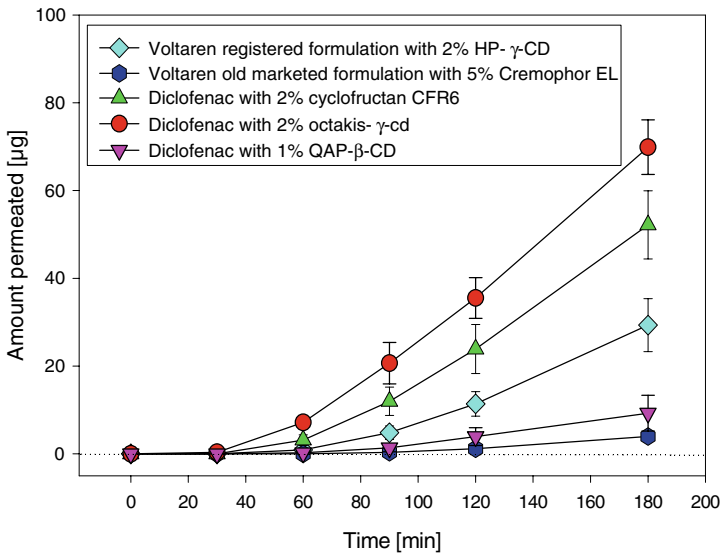


Fig. 1 Corneal permeation of diclofenac

of actives was tested in a modified Franz cell consisting of one donor compartment separated from two acceptor compartments by excised pig corneas (see picture below). Preheated Glutathione Bicarbonate Ringer solution (GBR) with the same salt composition as the tears (''GBR tears'') or as the aqueous humor (''GBR aqueous humor'') was added to the epithelial and endothelial compartments, respectively. The solutions were gassed with a mixture of 95% air–5% CO_2 (about 1–2 bubbles per second) to maintain a pH of

Cox 189/Cremophor		Cox 189/CFR/CDs	
Cox 189	0.1 g	Cox 189	0.1 g
Boric acid	1.9 g	Disodium edetate	0.1 g
Trometamol	0.6 g	HP-γ-CD or	
Cremophor EL	2.0 g	Cyclofructan	2.0 g or
Water ad	100 ml	QA-α-CD	1.0 g
		Propylene glycol	1.9 g
		Trometamol	0.1 g
		Tyloxapol	0.1 g
		Hydochloric acid 1N	0.29 g
		Water ad	100 ml

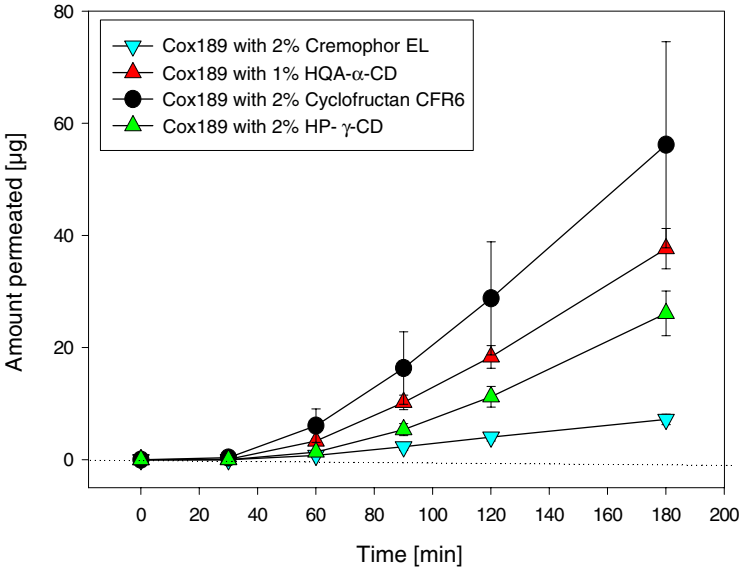


Fig. 2 Corneal permeation of Cox 189

Zaditen		Ketotifen/CFR/CD	
Ketotifen fumarate	0.035 g	Ketotifen fumarate	0.035 g
Glycerin 100%	2.5 g	Glycerin 100%	2.5 g
Sodium hydroxide 1N	0.1 g	Cyclofructan or	
Water ad	100 ml	Peranhydro-α-CD	2.0 g
		Sodium hydroxide 1N	0.1 g
		Water ad	100 ml

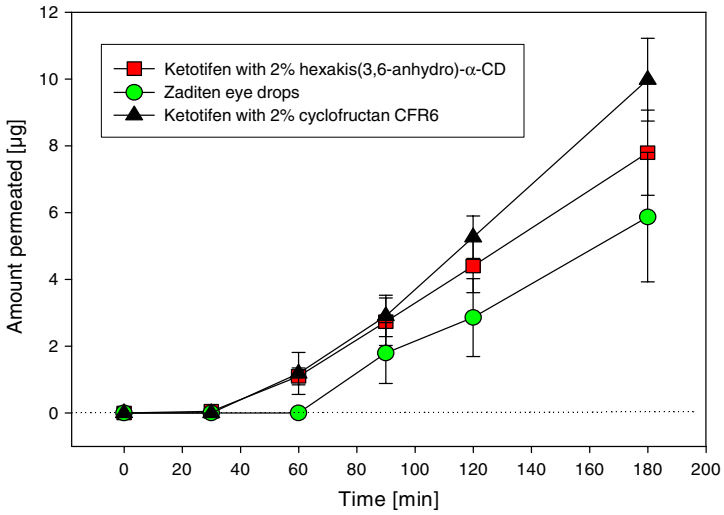


Fig. 3 Corneal permeation of ketotifen

7.4. After 30 min of equilibration, the GBR solution on the epithelial side was substituted for an air/CO_2 saturated GBR solution containing the drug. Samples of 300 (l were taken every hour during a period of 3 h from the endothelial side for further HPLC analysis. Each aliquot was replaced immediately with an equal volume of fresh GBR. The concentration of active in the aliquots was determined by HPLC.

Results and discussion

All the three tested molecules, diclofenac (as sodium), Cox189 and ketotifen (as fumarate), exhibited an enhanced permeability through excised pig corneas in presence of cyclodextrin derivatives. In the case of diclofenac (Fig. 1) the permeated amount of active is almost 20 times higher in presence of 2% octakis(3,6-anhydro)-γ-CD than in the formulation without permeation enhancer (Diclofenac/Cremophor EL). In the case of Cox189 the most powerful permeation enhancer tested so far was HQA-α-CD, which was not significantly different from cyclofructan CFR6. It resulted in about 5–6 times more Cox189 crossing the cornea than in absence of permeation enhancer (Fig. 2). The results with ketotifen fumarate (Fig. 3) showed the same tendency. However, the permeation enhancing factor of the best molecule, hexakis(3,6-anhydro)-α-CD, was relatively small and statistically not significant.

Table 1 Distribution of diclofenac in ocular tissues

Formulation containing:	Aqueous humor	Cornea	Retina	Choroid
Cremophor EL	1.0	1.0	1.0	1.0
HP-γ-CD	1.1	1.1	1.2	2.0
QA-β-CD	2.2	1.8	2.0	2.7
Peranhydro-α-CD	2.4	2.2	2.6	3.8
Cyclofructan	2.3	2.0	4.0	4.4

Several questions arise from these data:

- Is the permeation enhancement a toxic effect? We have evidenced that the permeation enhancement was not the result of tissue damage (histology data not shown). Additionally, the tested formulations exhibited an acceptable acute ocular tolerability in rabbits.
- Can the permeation enhancement also be observed in vivo? Animal pharmacokinetic studies (one 50 µl instillation of diclofenac 0.1% formulations into rabbit eye) demonstrated a statistically significant improvement of diclofenac ocular bioavailability. The values show the bioavailability enhancement factor for the tested formulations (Cremophor EL formulation = 1) (Table 1)
- What is the mechanism of action? The mechanism of action of this class of permeation enhancers is not yet elucidated. Different studies are in preparation to determine whether the effect is the result of an interaction cyclodextrin–drug, or cyclodextrin–tissue (possibly an ion channel activity), or a combination of both.

Conclusion

The observed effect of permeation enhancement is not only interesting for ocular, but certainly also for other topical applications, like delivery through the skin or by inhalation.

Together with the other properties of cyclodextrins (solubilization, stabilization, antimicrobial activity) the permeation enhancing effect observed here is potentially of high interest for the formulator working in drug delivery.

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