Release of Ketoprofen from Dermal Bases in Presence of Cyclodextrins: Effect of the Affinity Constant Determined in Semisolid Vehicles

I. Orienti, V. Zecchi*, V. Bertasi, and A. Fini

Dipartimento di Scienze Farmaceutiche Universita' di Bologna, Via Belmeloro 6 - 40126 Bologna, Italy

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We describe a method to determine the affinity constant values between Ketoprofen and β-cyclodextrin and hydroxypropyl-β-cyclodextrin in semisolid vehicles. The method is based on the diffusion of the drug, released from semisolid vehicles, through a lipidic non porous membrane. The affinity constants of Ketoprofen towards cyclodextrins as determined in semisolid media better represent the release of the drug from dermal bases than the corresponding values in aqueous systems.

Freisetzung von Ketoprofen aus dermalen Trägersubstanzen in Anwesenheit von Cyclodextrin: Wirkung der Affinitätskonstante, bestimmt in halbfesten Vehikeln

Wir beschreiben ein Verfahren zur Bestimmung der Affinitätskonstante zwischen einem Arzneimittel und einem Komplexbildner in einer halbfesten Trägersubstanz zwecks Untersuchung der Freisetzung von Ketoprofen aus physikalischen Mischungen mit β-Cyclodextrin und Hydroxypropyl-β-Cyclodextrin. Zur Darstellung der Diffusion des Arzneimittels aus dermalen Trägern durch eine Lipidmembrane sind die in halbfesten Medien bestimmten Affinitätskonstanten von Ketoprofen gegenüber Cyclodextrin aussagekräftiger als die entsprechenden Werte im wäßrigen System.

Interest in the use of cyclodextrins to improve the solubility and availability of poorly soluble drugs has largely focussed on the structure of the solid complexes or behaviour in aqueous solution[1-8]. Very few data have been reported for semisolid hydrophylic or hydrophobic media like those commonly employed in topical systems[9,10]. In particular these systems offer no data on the drug-complexing agent affinity constants commonly related to those determined in aqueous systems.

The present work aimed to study the diffusion through a lipidic membrane of Ketoprofen released from dermal bases (Carbopol gel and Petrolatum:Lanolin 9:1) in presence of increasing amounts of β-cyclodextrin and hydroxypropyl-β-cyclodextrin in drug:cyclodextrin molar ratios varying from 1:0.25 to 1:2. Our main object was to detect the affinity constant drug-complexing agent values in these systems and to evaluate their role in the control of drug availability.

Experimental Part

Materials

Ketoprofen (KET, ICS I-Milan) was milled in an analytical mill, sieved and the fraction between 25 and 15 μm was employed. The distribution of the powder particles was assessed to be similar and homogeneous by the microscopic method. The mean geometric diameter was 20 ± 2 μm. β-cyclodextrin (BCD) and hydroxypropyl-β-cyclodextrin (HPBCD) (Janseen B-Beerse and Pharmatec FL-Alachua) were employed without further purification. Carbopol 940 was supplied by Biochim I-Milan. All the other materials for the dermal bases were commercial samples.

Physical mixtures

The physical mixtures of KET with BCD (KET-BCD) and HPBCD (KET-HPBCD) in acid:cyclodextrin ratios varying from 1:0.25 to 1:2 were thoroughly ground and kneaded with small portions of a water:methanol solution (1:1, v:v) for 1 h. The creamy product was thereafter dried at 90°C to a constant weight.

Preparation of dermal forms

The hydrophylic gel (CBP) was prepared by adding 1 g of Carbopol 940 portionwise to 100 ml of an aqueous dispersion at 30°C of KET or the physical mixture at concentrations of KET varying from 0.1% to 4.0% w:v. The gel was semi-neutralized with triethanolamine. The petrolatum:lanolin fatty ointment 9:1 w:w (PL) was prepared incorporating KET or the physical mixture in the lanolin. The dermal forms were used 1 week after preparation; their homogeneity and the physical form of the active principle (solution or suspension) were controlled microscopically beforehand.

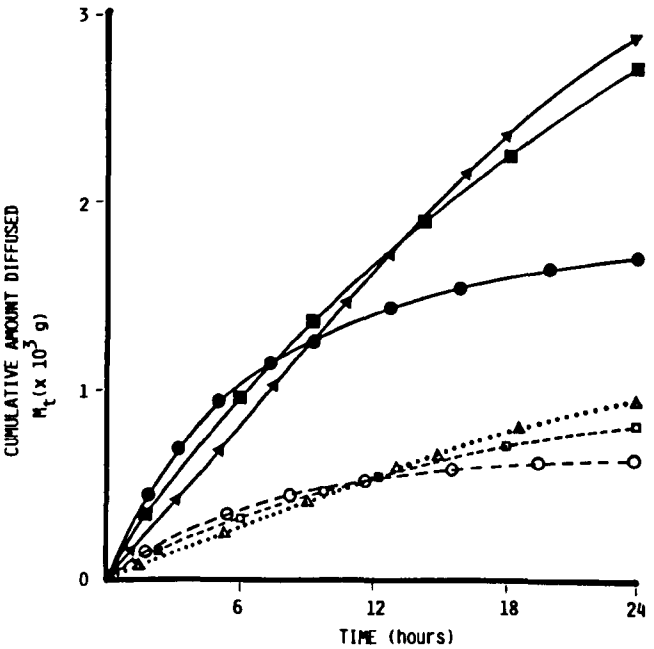

Fig. 1: Cumulative amount vs time of Ketoprofen recovered in the receiving phase from vehicles containing 0.25% of the active principle Carbopol gel: ● KET; ■ KET-βCD 1:1; ▲ KET-HPβCD 1:1.
Petrolatum:lanolin: ○ KET; □ KET-βCD 1:1; △ KET-HPβCD 1:1.

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Determination of the properties in aqueous phase of the inclusion products

The presence of the complex in water solution was confirmed by the solubility method[11]. The solubility isotherms of KET with BCD and HPBCD at pH 2.0 and 37°C had a feature of type B_S and A_L, respectively, according 9 to *Higuchi* and *Connors*[11]; the affinity constants (Kf) were 650 M^{-1} for KET-BCD and 930 M^{-1} for KET-HPBCD.

Release studies

KET release from the different vehicles was performed in a diffusion cell previously described[12], consisting of a donor and a receptor compartment separated by a medical grade dimethylpolysiloxan (PDMS) membrane, whose lipoidal nature allows diffusion only to the uncomplexed drug. The receptor compartment consisted of an aqueous solution buffered at pH 7.4. At pH 7.4 of the receptor phase, sink conditions were assured, the active principle being in its ionized form. This compartment was connected through a peristaltic pump with a spectrophotometer where the diffused KET was analyzed. The unit was kept at 37°C. For each dermal base-lipoidal membrane system, the release behaviour was followed for 24 h; throughout the work we discussed the cumulative amount diffused after 2 h (M2) and 24 h (M24). The results represent the average value of at least 4 runs.

Table 1: Cumulative amounts of Ketoprofen recovered in the receiving phase after 2 h M2 ($x10^3$ g) and 24 h M24 ($x10^3$ g) at different concentrations of the active principle in the vehicle and at different Ketoprofen: complexing agent molar ratios

		CBP				PL			
%KET	KET:CD	KET-BCD		KET-HPBCD		KET-BCD		KET-HPBCD	
		M2	M24	M2	M24	M2	M24	M2	M24
0.25	1:0	0.48	1.60	-	-	0.23	0.68	-	-
	1:0.25	0.42	1.68	0.41	1.75	0.18	0.71	0.17	0.74
	1:0.50	0.38	2.01	0.36	2.12	0.13	0.82	0.11	0.92
	1:1	0.32	2.76	0.30	2.80	0.09	0.84	0.08	1.04
	1:2	0.24	3.03	0.22	3.18	0.06	1.02	0.04	1.11
0.50	1:0	0.60	1.67	-	-	0.32	0.70	-	-
	1:0.25	0.56	1.82	0.54	1.85	0.27	0.72	0.25	0.96
	1:0.50	0.50	2.21	0.49	2.34	0.21	1.06	0.18	1.23
	1:1	0.47	2.82	0.46	3.08	0.18	1.10	0.16	1.30
	1:2	0.39	3.06	0.38	3.20	0.14	1.29	0.13	1.53
1.0	1:0	0.70	5.01	-	-	0.42	0.72	-	-
	1:0.25	0.69	4.85	0.69	4.86	0.41	0.76	0.39	1.70
	1:0.50	0.67	4.86	0.66	4.88	0.36	2.07	0.34	2.10
	1:1	0.63	4.86	0.62	4.89	0.32	2.23	0.30	2.25
	1:2	0.57	4.88	0.56	4.89	0.29	2.45	0.26	2.48
4.0	1:0	0.72	5.15	-	-	0.48	3.05	-	-
	1:0.25	0.72	5.02	0.71	5.01	0.46	3.71	0.44	3.88
	1:0.50	0.71	4.98	0.70	5.00	0.45	3.72	0.44	3.89
	1:1	0.71	4.98	0.70	4.99	0.43	3.76	0.43	4.37
	1:2	0.70	4.97	0.69	4.98	0.43	3.80	0.42	4.46

Results and discussion

Effect of complexation on the release of Ketoprofen from dermal bases

Fig. 1 reports the 24 h diffusion profiles of KET at the concentration of 0.25% respectively in CBP and PL, both in absence and in presence of complexing agents. The diffusion rate is always higher for CBP than for PL and in presence of BCD and HPBCD the diffusion profiles are significantly modified. In fact, in presence of a complexing agent (CD) in the vehicle, the following complexation equilibrium must be taken into account:

$$KET + CD \rightleftarrows KET\text{-}CD$$

When the concentration of the diffusable species decreases with time as it permeates to the receptor solution, the complexed drug may serve as a reservoir. Loss of uncomplexed drug from the donor phase is probably compensated for by dissociation of the complex, thus maintaining a pseudo steady-state diffusion across the membrane. The presence of the complexing agent decreases the concentration of the free drug in solution and, as a consequence, the corresponding diffusion profiles observed for the physical mixtures, are lowered with respect to the profiles of pure Ketoprofen. This effect is observed for about 8-10 h while for longer periods the loss of the diffusable drug lowers the release rate more significantly in the case of pure Ketoprofen than the physical mixtures where the complexation equilibrium maintains a fairly constant release rate. This different diffusional behaviour observed for the physical mixtures with respect to pure Ketoprofen progressively disappears as the formulative concentration increases: in fact, the increase in the diffusable amount sustains a pseudo steady state diffusion even for pure Ketoprofen in the period examined.

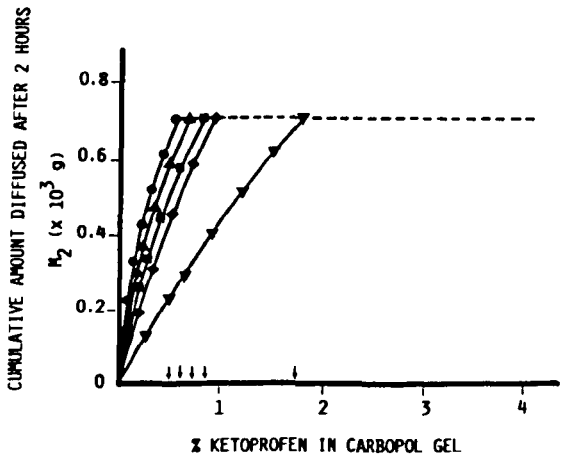

Fig. 2: Cumulative amount of Ketoprofen recovered in the receiving phase after 2 h (M_2) as a function of the percentage of the active principle (% KET) in Carbopol gel: ● KET; ▲ KET-βCD 1:0.25; ■ KET-βCD 1:0.50; ◆ KET-BCD 1:1; ▼ KET-βCD 1:2. (↓) solubility values of KET (% KETs) for each KET:βCD molar ratio.

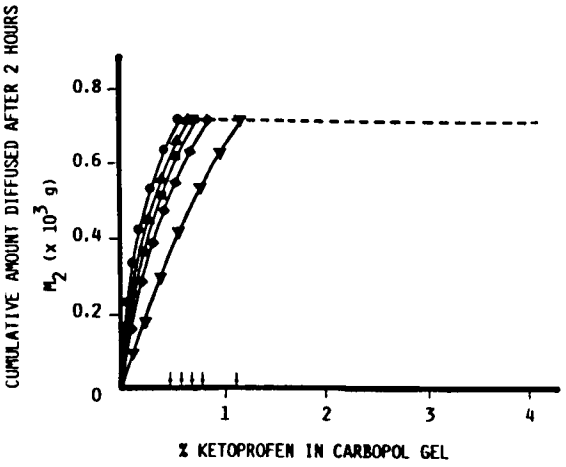

Fig. 3: Cumulative amount of Ketoprofen recovered in the receiving phase after 2 h (M_2) as a function of the percentage of the active principle (% KET) in Carbopol gel: ● KET; ▲ KET-HPβCD 1:0.25; ■ KET-HPβCD 1:0.50; ◆ KET-HPβCD 1:1; ▼ KET-HPβCD 1:2. (↓) solubility values of KET (% KETs) for each KET:HPβCD molar ratio.

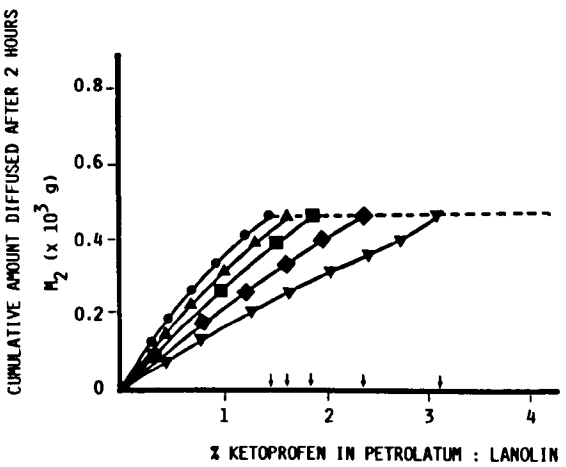

Fig. 4: Cumulative amount of Ketoprofen recovered in the receiving phase after 2 h (M_2) as a function of the percentage of the active principle (% KET) in Petrolatum:lanolin: ● KET; ▲ KET-βCD 1:0.25; ■ KET-βCD 1:0.50; ◆ KET-βCD 1:1; ▼ KET-βCD 1:2. (↓) solubility values of KET (% KETs) for each KET:BCD molar ratio.

Properties of the inclusion products in semisolid phases

In a semisolid phase, the method reported[11] for the determination of the affinity constant between the drug and the cyclodextrins in liquid phases cannot be applied owing to analytical difficulties in determination of drug solubility in the semisolid phase in presence of complexing agents. These solubility values were here determined from the intersection between the two parts of the diagrams obtained by plotting the cumulative amount diffused after a representative time (*e.g.* 2 h) as a function of the formulative concentration (Figs. 2-5). These diagrams show a first ascending portion corresponding to the diffusable drug in solution, and a subsequent portion, similar to a plateau region, where the diffused amount does not appreciably change

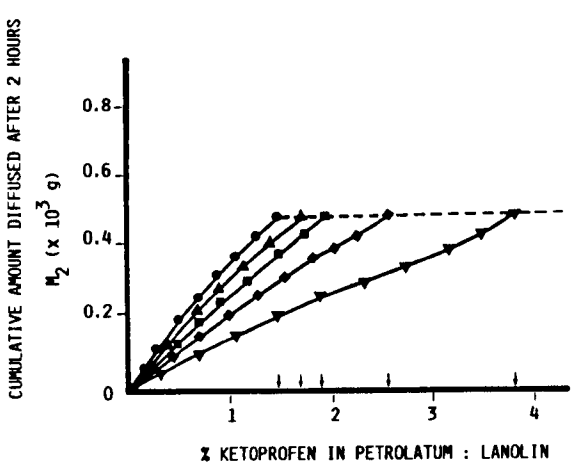

Fig. 5: Cumulative amount of Ketoprofen recovered in the receiving phase after 2 h (M_2) as a function of the percentage of the active principle (% KET) in Petrolatum:lanolin: ● KET; ▲ KET-HPβCD 1:0.25; ■ KET-HPβCD 1:0.50; ◆ KET-HPβCD 1:1; ▼ KET-HPβCD 1:2. (↓) solubility values of KET (% KETs) for each KET:HPβCD molar ratio.

with the formulative concentration, corresponding to the diffusable drug in suspension. The formulative concentration corresponding to these intersections (% KETs) corresponds to the saturation of the vehicle with respect to the diffusable form of the drug and was taken as the solubility value of Ketoprofen in the vehicle both in presence or in absence of complexing agents. Figs. 2 and 3 report the M2 values vs the formulative concentrations both for the pure Ketoprofen and in presence of cyclodextrins at decreasing molar ratios KET:CD varying from 1:0.25 to 1:2. For the same formulative concentration, the M2 values are lowered as the molar ratio decreases. As expected, the % KETs values (Table 2) are a function of the KET:CD molar ratio and depend on both the affinity constant values and the concentration of the complexing agent in the vehicle.

Table 2: Percentages of Ketoprofen incorporated in the vehicles corresponding to saturation (% KETs) in presence of complexing agents at different Ketoprofen:complexing agent molar ratios

	CBP		PL	
KET:CD	BCD	HPBCD	BCD	HPBCD
1:0	0.51	-	1.50	-
1:0.25	0.54	0.56	1.65	1.67
1:0.50	0.58	0.62	1.84	1.90
1:1	0.69	0.78	2.38	2.54
1:2	1.06	1.70	3.12	3.80

Determination of the affinity constant values between the drug and the complexing agent in semisolid vehicles

The solubility concentrations of the drug in presence of complexing agents, when plotted as a function of the corresponding concentrations of the complexing agents (Fig. 6),

show profiles which can be considered representative of the phase solubility diagrams in the semisolid vehicles studied. From the initial ascending portion of these diagrams, the affinity constant values for KET with BCD and HPBCD both in CBP and PL, were determined according to *Higuchi* and *Connors*[1] and are reported in Table 3 in comparison with those previously determined in water. As observed in Table 3, the affinity constant values obtained in semisolid vehicles are significantly lowered with respect to those obtained in water. This behaviour can be explained by considering the different affinity of the drug between the hydrophobic ring of the CD and the vehicles where the drug is dissolved or dispersed: CBP, PL or water. The higher solubility of KET in PL (1.50%) and CBP (0.51%) than in water (0.016%) indicates a lower affinity of KET for the hydrophobic ring and consequently a weaker tendency towards complexation in these semisolid vehicles. As regards the diffusion through the membrane, M2 values are higher for

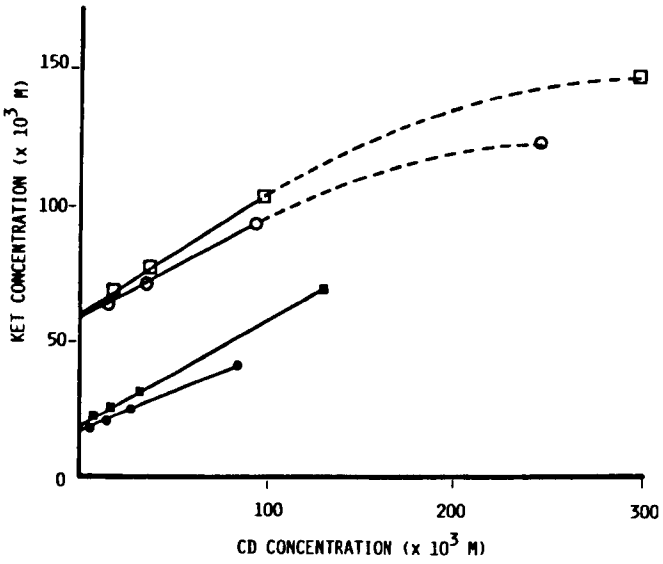

Fig. 6: Phase solubility diagrams of ● KET-βCD; ■ KET-HPBCD in Carbopol gel. ○ KET-βCD; □ KET-HPβCD in Petrolatum:lanolin at 37°C.

Table 3: Affinity constant values (M^{-1}) determined at 37°C in semisolid vehicles and in water

	CBP	PL	Water
KET-BCD	18±1	10±1	650
KET-HPBCD	27±1	12±1	930

BCD than HPBCD, when all other parameters are the same. This can be attributed to the greater affinity of KET for HPBCD than BCD, as indicated by the Kf values. In order to evaluate quantitatively the effect of the Kf on the diffusion of KET through the membrane for the formulation examined, the decrease in the cumulative amount diffused in presence of complexing agents with respect to pure KET (Δ M2) was reported in Fig. 7 as a function of Kf for the 1:1 physical mixtures in each vehicle. A linear relationship was found, indicating that complexation controls the diffusive gradient according to the Kf values determined in each vehicle. Despite the experimental uncertainty of the method the affinity constant values determined in this way fit the release data in these semisolid media much more reliably than those obtained in water. This is because they account for the real equilibria present in the system which derive from the different interactions between the species involved in the equilibrium and the dermal base.

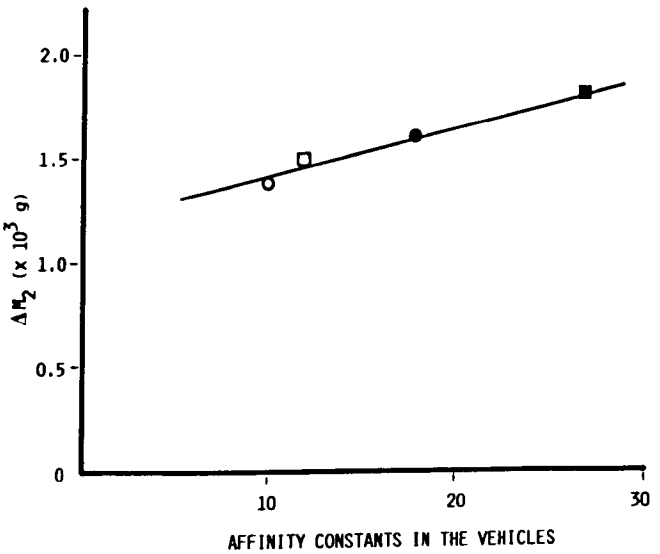

Fig. 7: Differences between the M_2 values of pure KET and the 1:1 physical mixtures (ΔM_2) vs the stability constants in the vehicles. The M_2 values are referred to vehicles containing 0.25% KET.
PL: ○ KET-βCD; □ KET-HPβCD. CBP: ● KET-HPβCD; ■ KET-HPβCD.

Conclusion

Inclusion complexes between KET and BCD or HPBCD are weaker in a semisolid medium than in water and differences between the two β-cyclodextrins almost disappear. Kf in water cannot be suitably applied to fit experimental data in semisolid media. The corresponding values determined directly in the two vehicles are much more representative of the drug:complexing agent interactions and of its subsequent control of drug release. KET release in topic systems can be controlled with increasing amounts of BCDs (at least up to 1:2 molar ratio) necessary to influence complex formation and thus adjust the concentration gradient of the diffusable form.

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