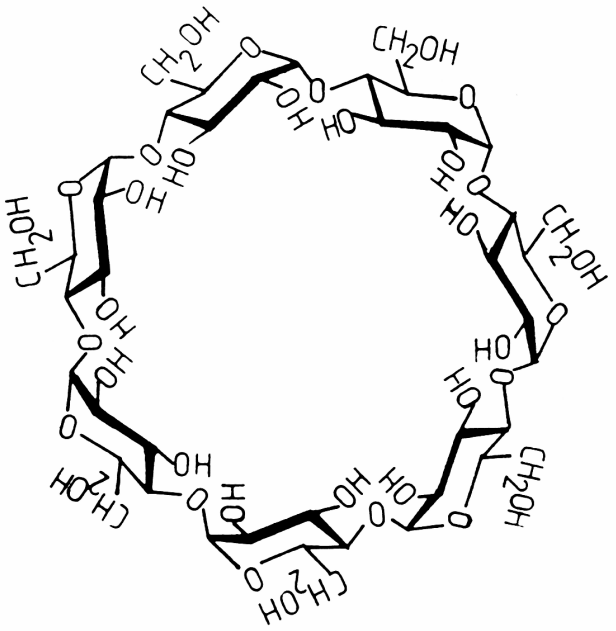
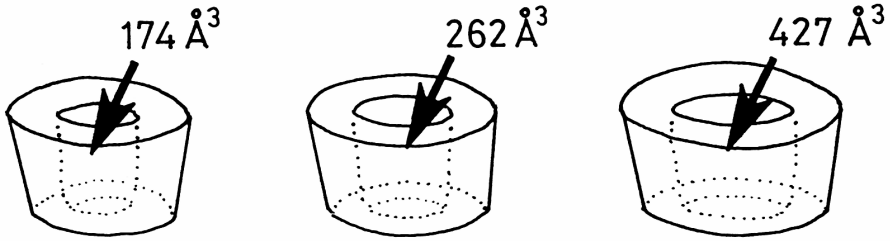
Fig. 1

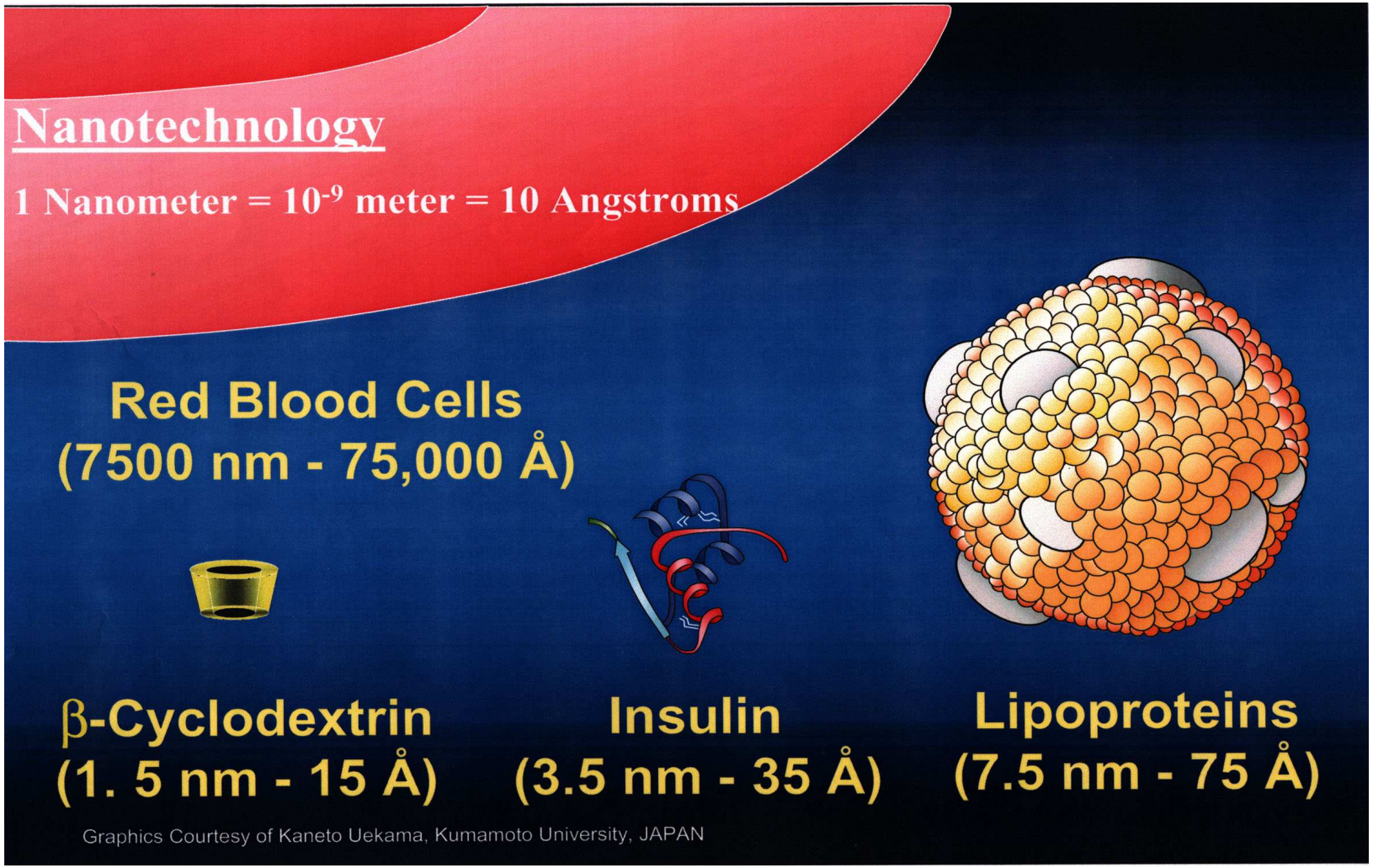


CAVITY VOLUME:

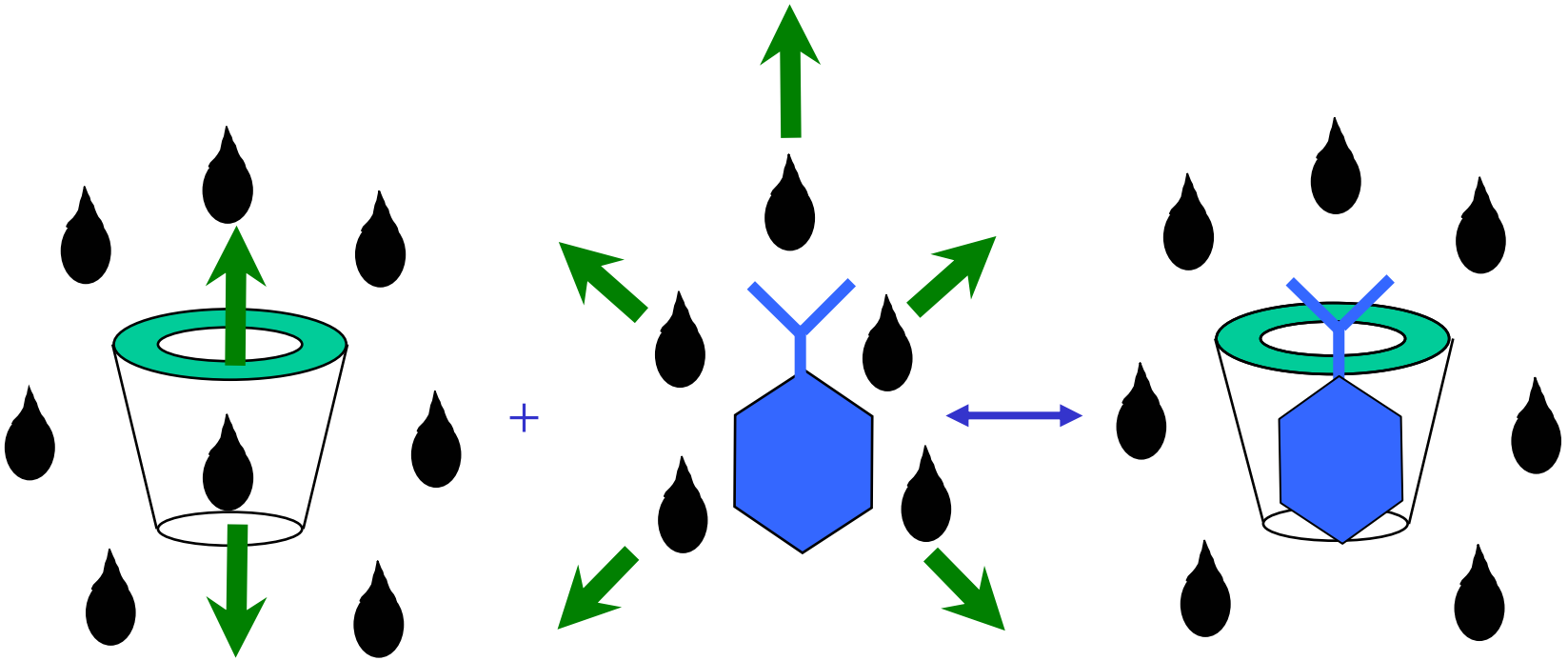


	αCD	βCD	γCD
in one mol:	104 ml	157 ml	256 ml
in one g:	0,10 ml	0,14 ml	0,20 ml

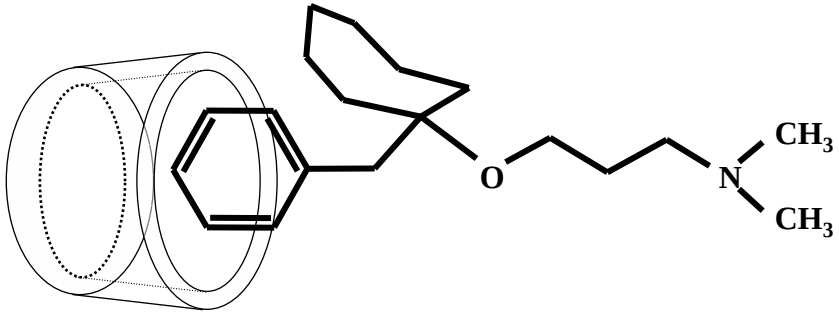
A ciklodextrinek méretük szerint nano-anyagok



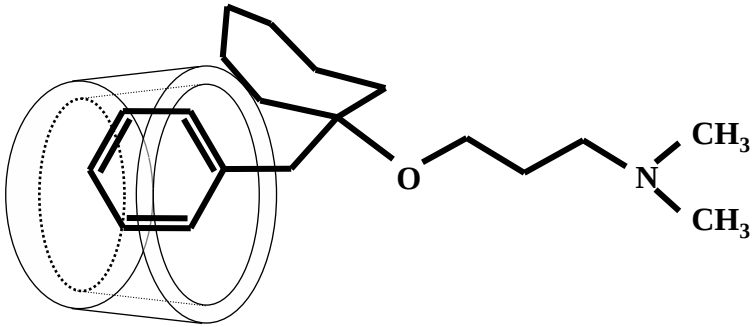
Scheme of inclusion complex formation and dissociation



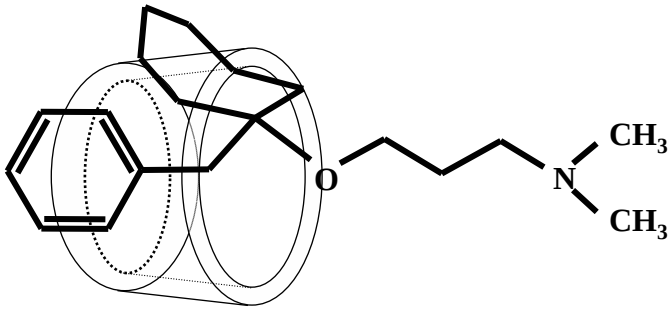
Bencyclan-CD



$K_{\alpha CD}$~3 M^{-1}



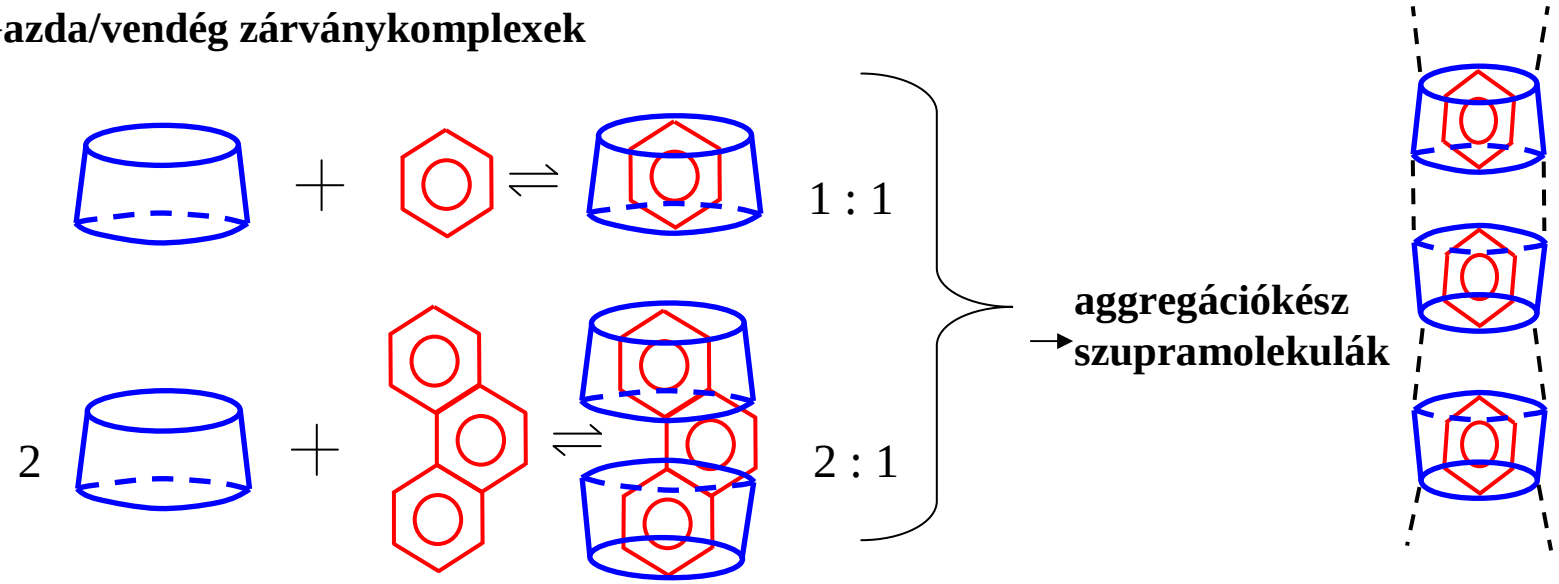
$K_{\beta CD}$~80000 M^{-1}

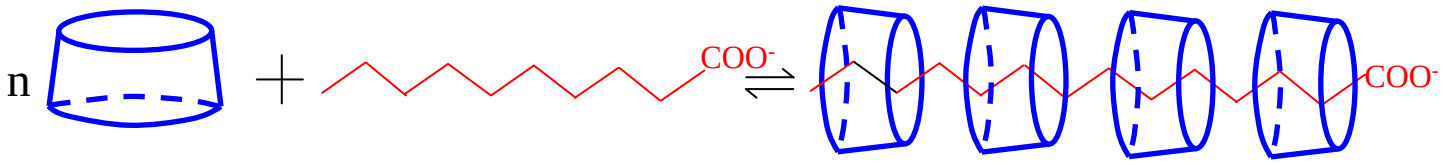


$K_{\gamma CD}$~4000 M^{-1}

CIKLODEXTRIN ALAPÚ MOLEKULÁRIS ÉPÍTMÉNYEK

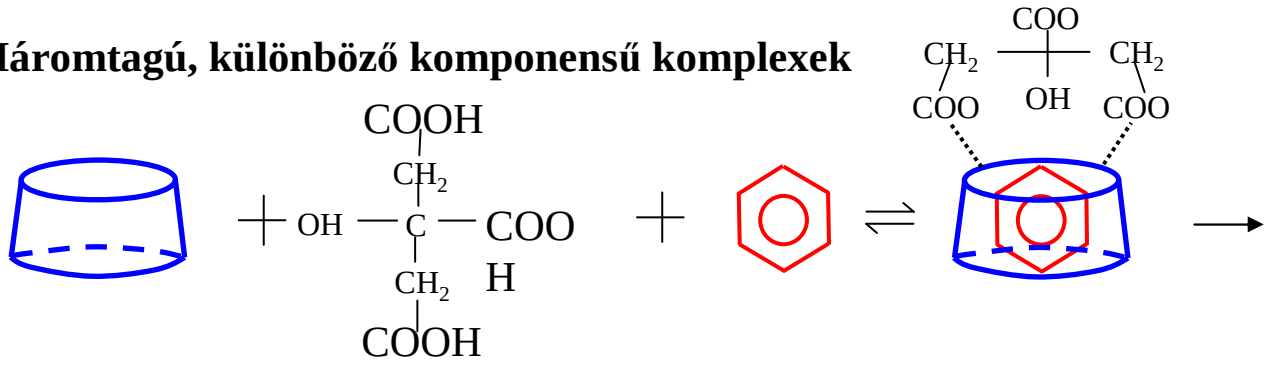
1. Gazda/vendég zárványkomplexek



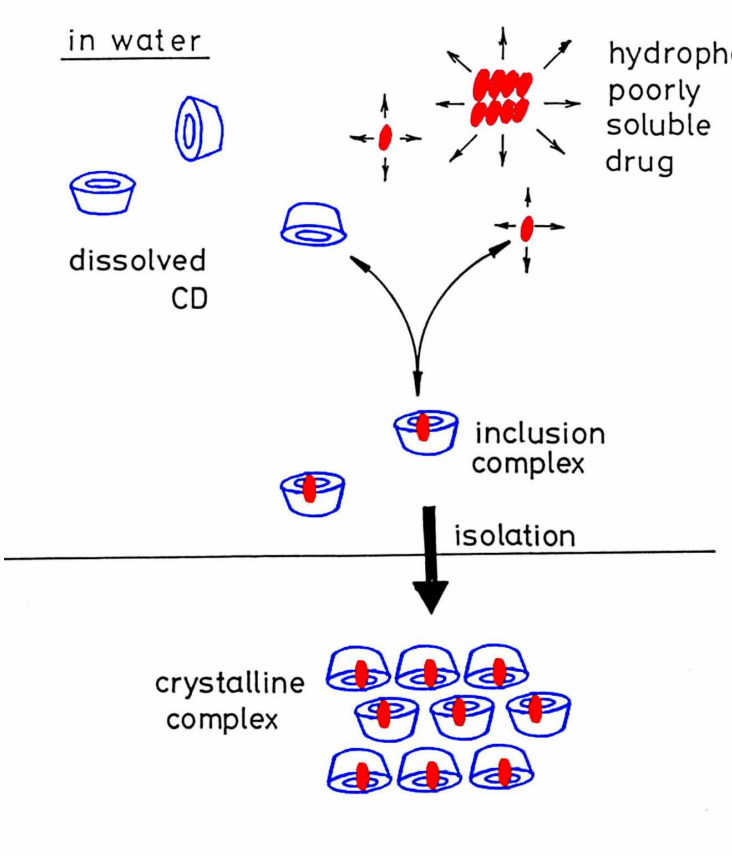


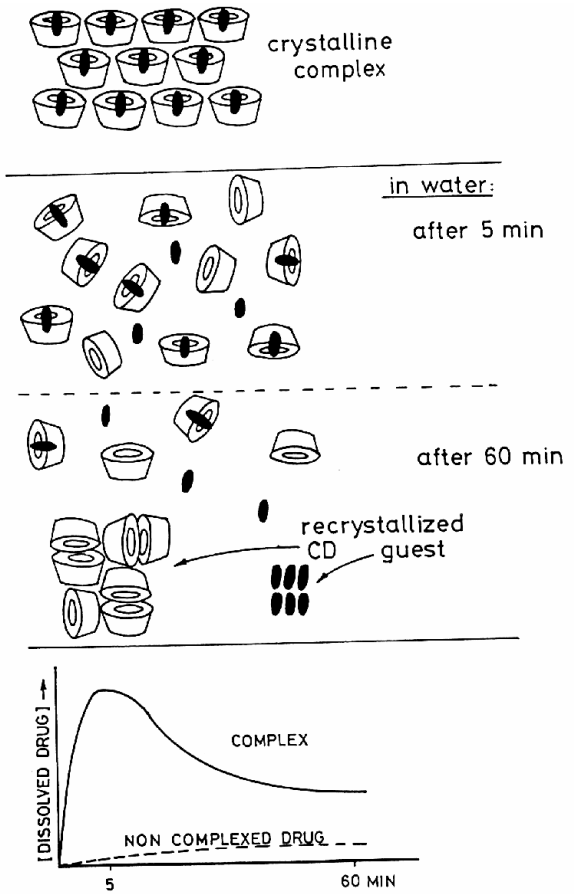
n : 1 molekuláris „nyaklánc”

2. Háromtagú, különböző komponensű komplexek

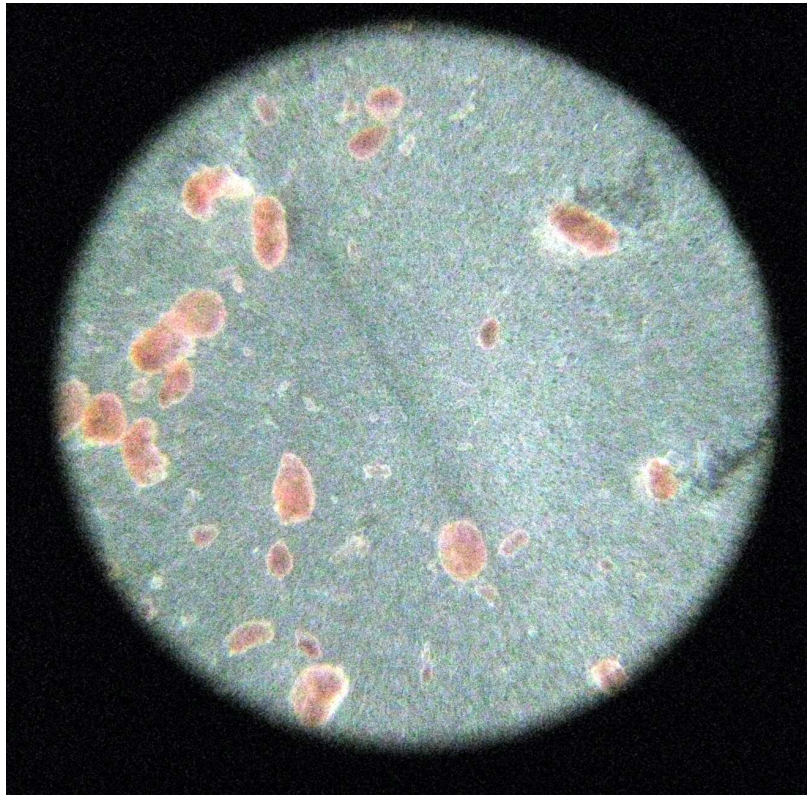


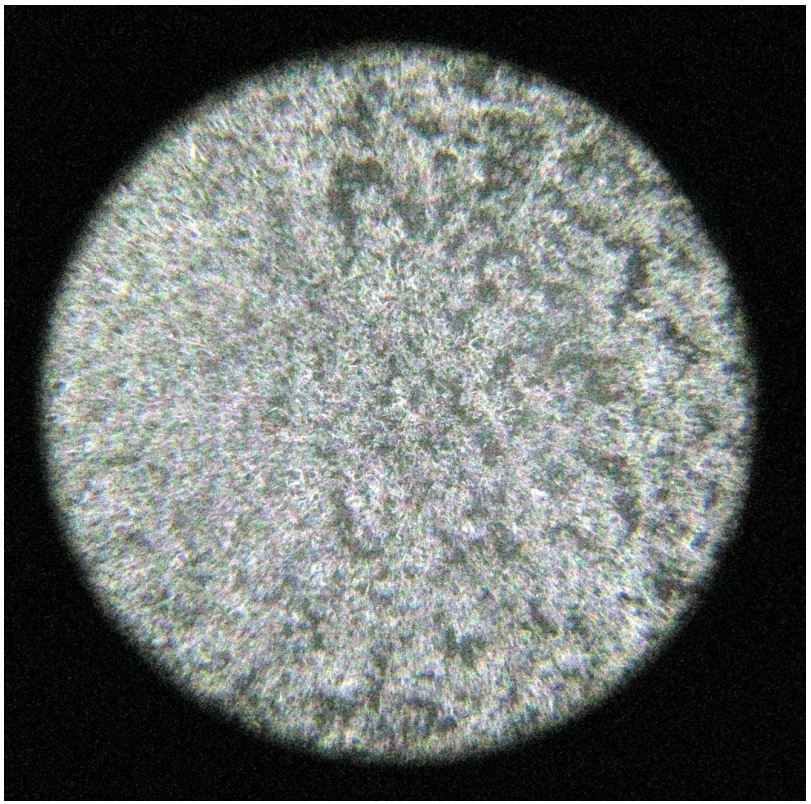
Host – guest interaction
(association and dissociation in aqueous solution)



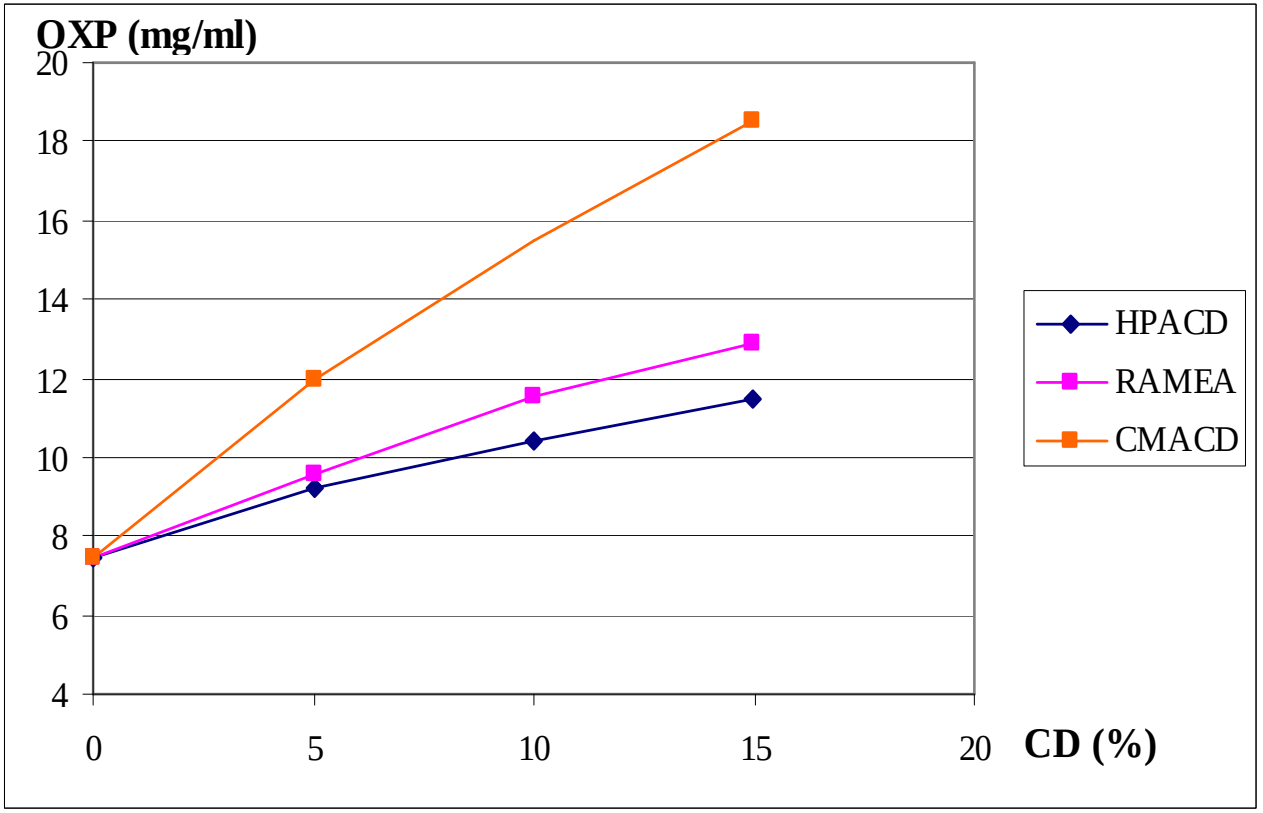


Citromolaj/BCD

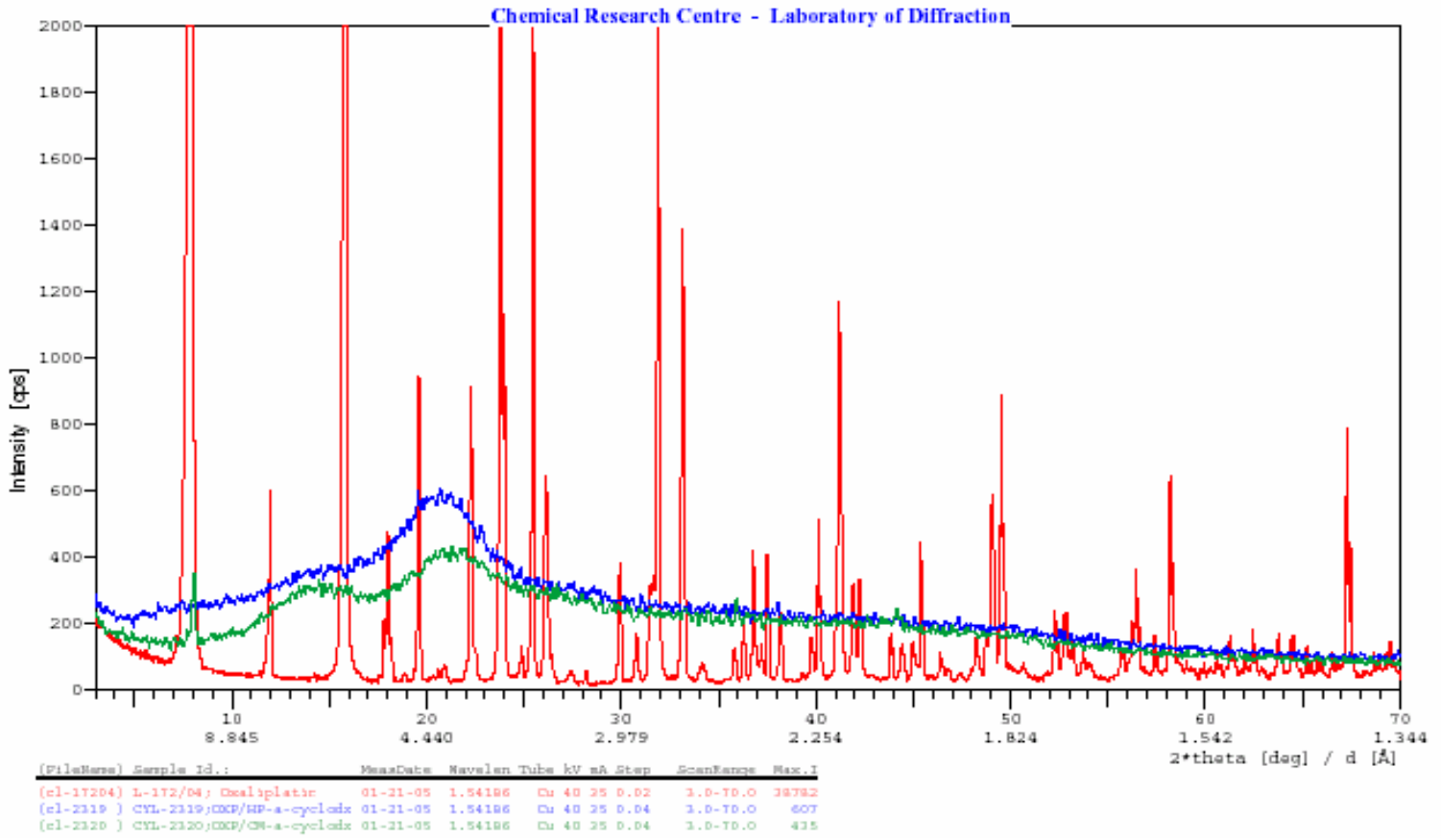




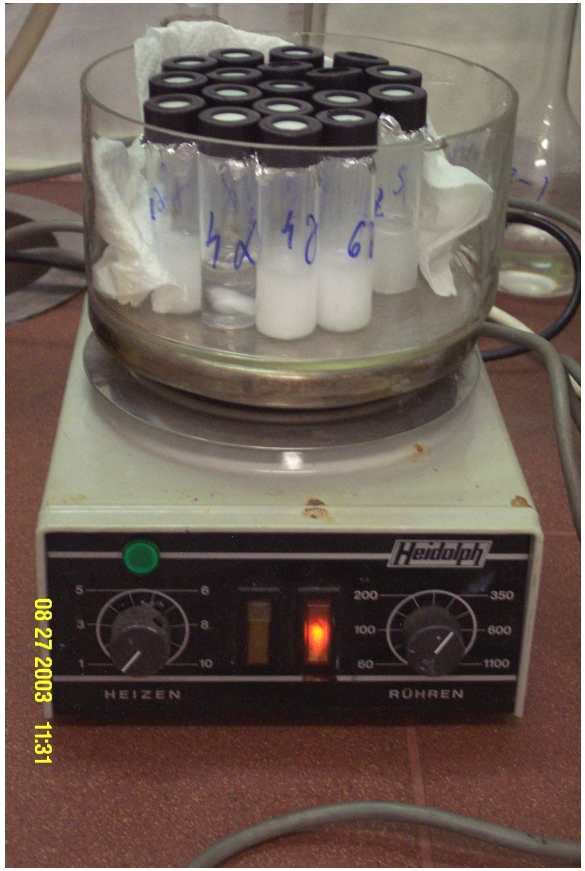
Solubility of OXP in presence of CDs



X-ray powder diffraction properties of OXP (**A**), OXP/HPACD ( ) and OXP/CMACD (**C**)

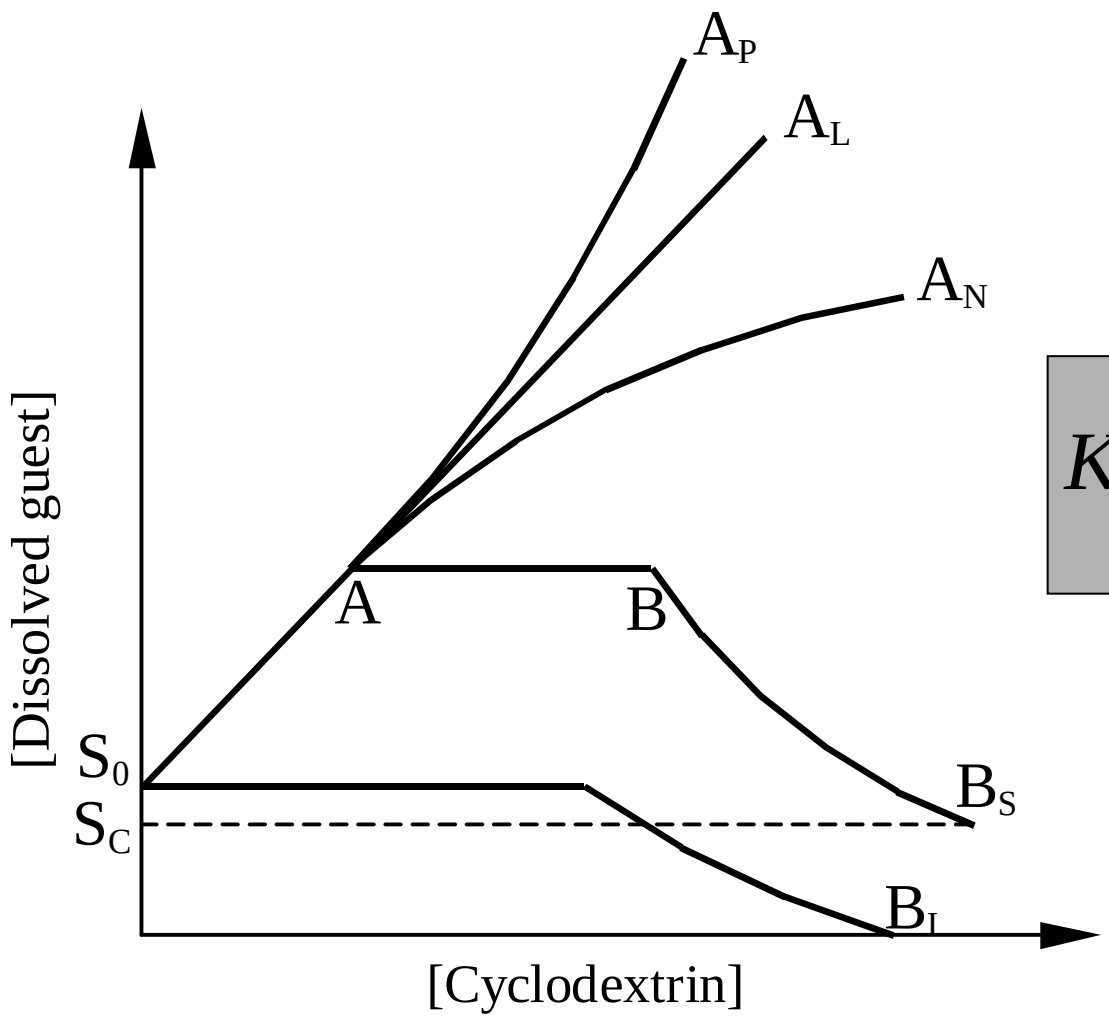


How to measure the solubility isotherms



- Aqueous CD solutions of different concentrations
- Guest in excess
- 24 h stirring
- Centrifuging/filtrating
- Concentration measurement (UV, HPLC)

Types of isotherms



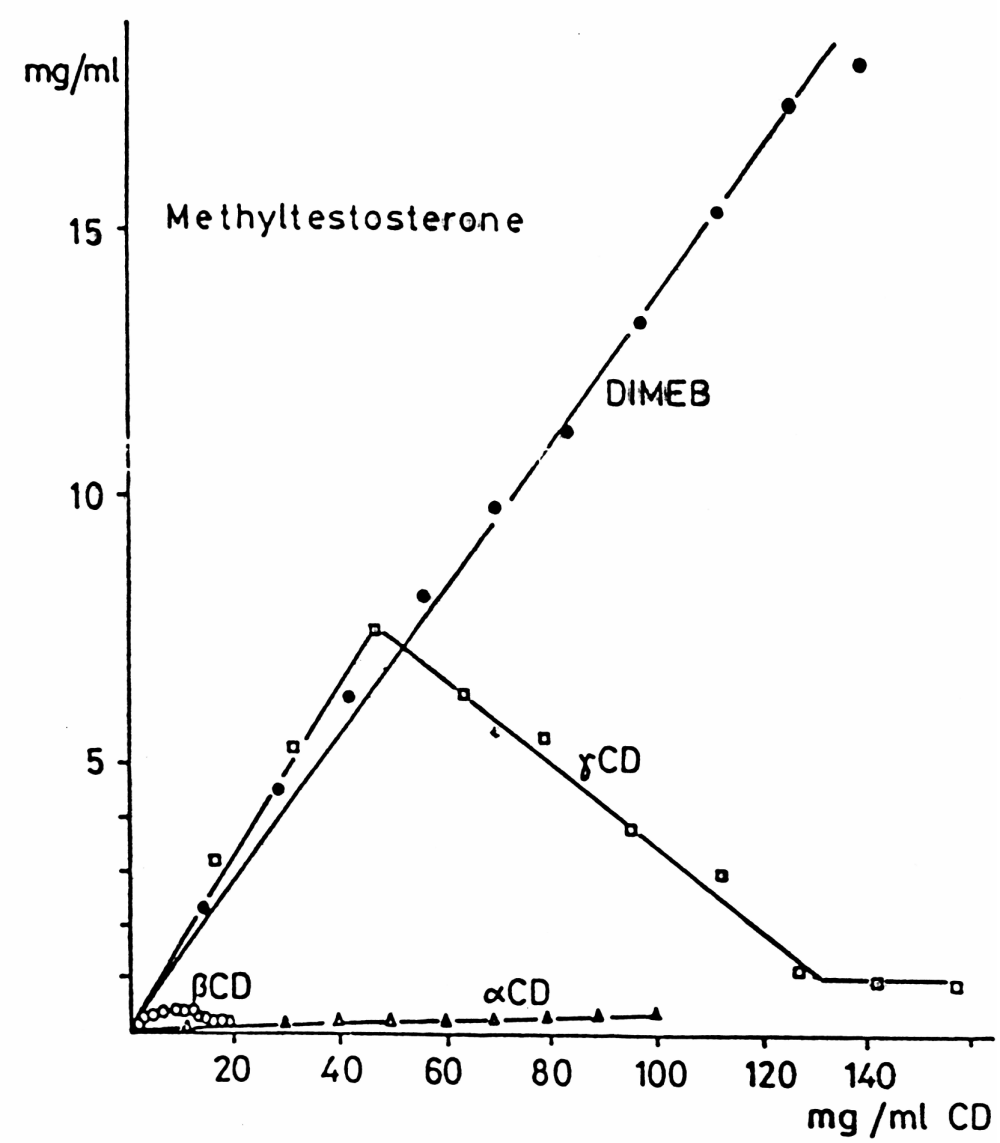
$$K = \frac{tg\alpha}{S_0(1 - tg\alpha)}$$

A legmegfelelőbb ciklodextrin kiválasztása

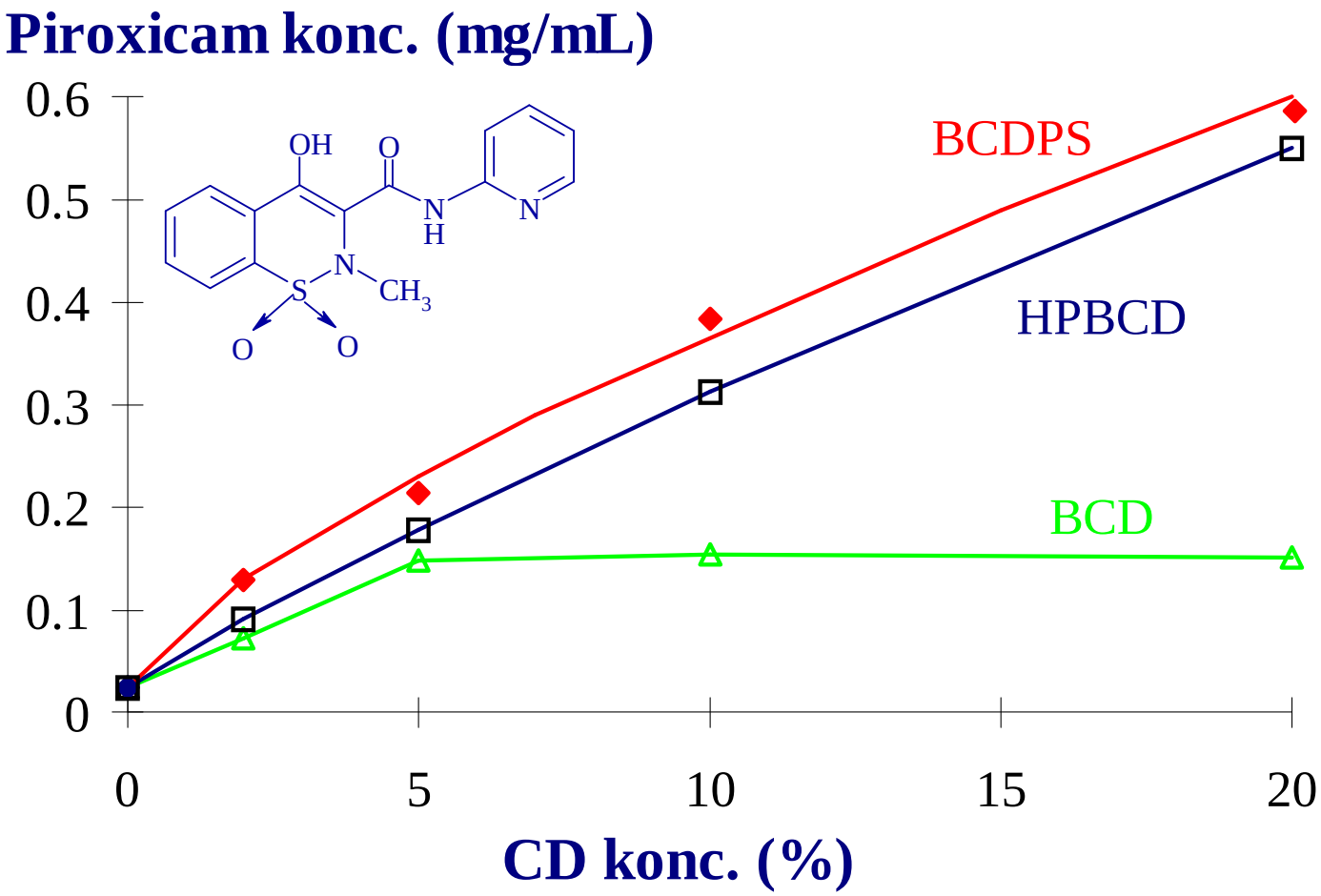
FluoxetineHCl oldékonysága vizes CD oldatokban 25°C-on

CD (%)	dissolved Fluoxetine HCl (mg/mL)				
	α-CD	γ-CD	HPBCD	RAMEB	G_2BCD
0	13.62	13.62	13.62	13.62	13.62
0.5	15.27	15.73	14.80	17.40	14.32
1.0	16.13	18.18	16.61	20.60	15.87
3.0	21.10	26.66	22.42	31.65	18.08
5.0	24.60	33.82	26.11	42.00	21.26
7.0	28.62	42.67	31.60	52.21	23.64
10.0	34.98	55.00	38.20	65.10	27.63

31.001


mg/ml
15
10
5
Methyltestosterone
DIMEB
γCD
βCD
αCD
20
40
60
80
100
120
140
mg /ml CD

Solubility enhancement using different CDs

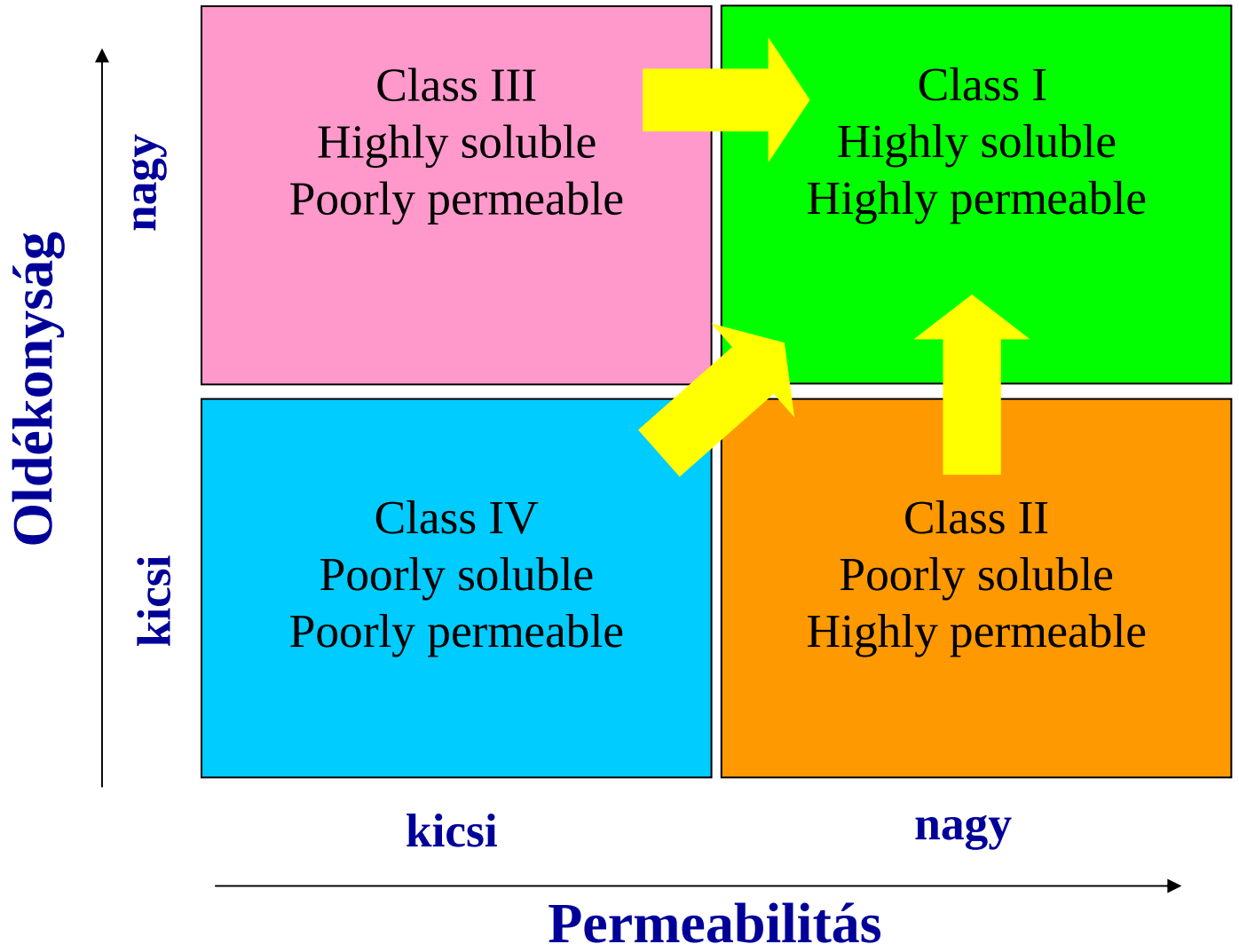


31.41

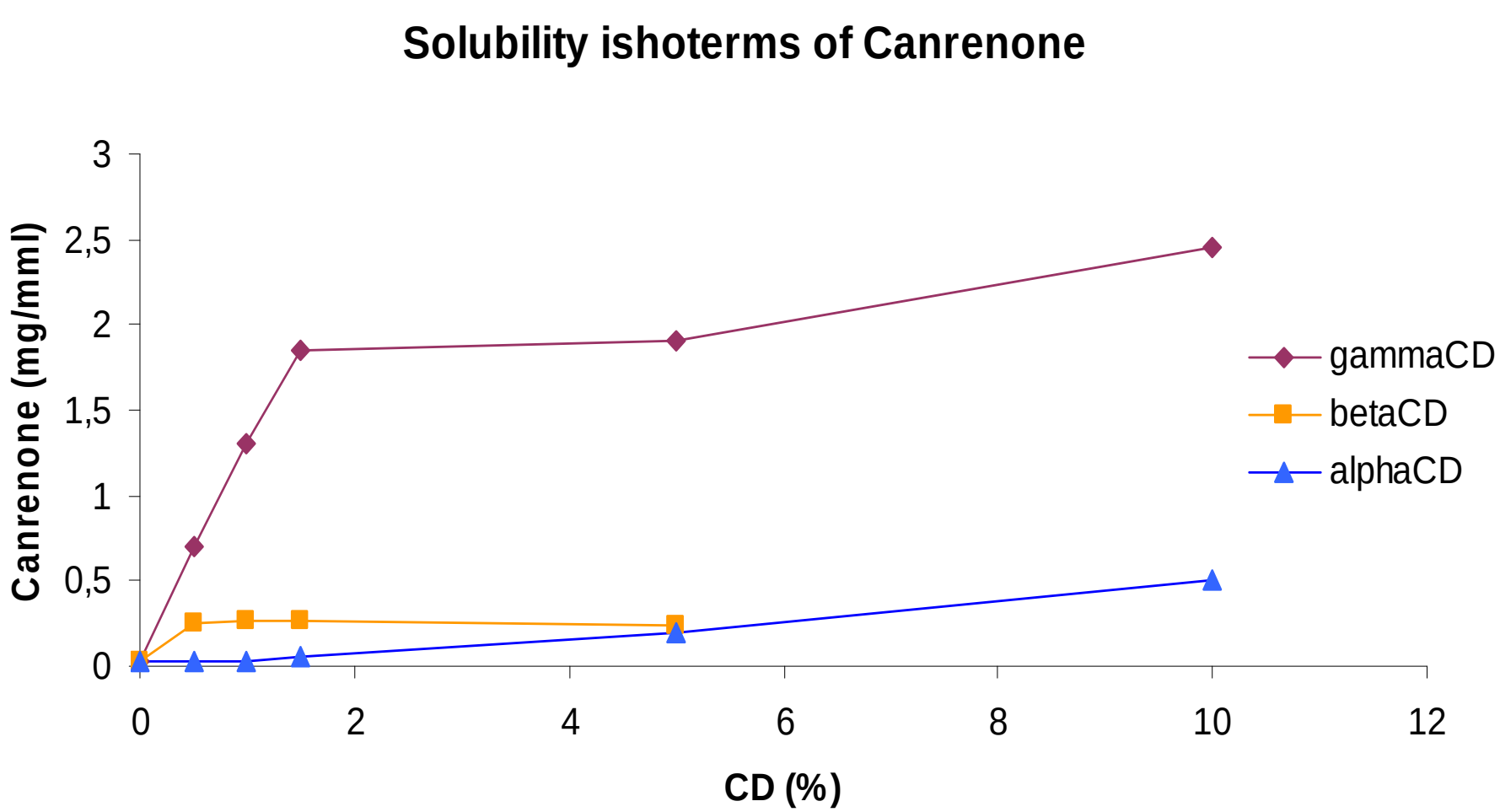
CDs and CD-derivatives are used to modify the following properties of a drug

- wettability
- dissolution rate
- solubility
- bioavailability
- pharmacokinetics
- stability
- smell/taste
- irritating effect
- content uniformity
- polymorphism

A hatóanyagok átsorolása komplexképzéssel

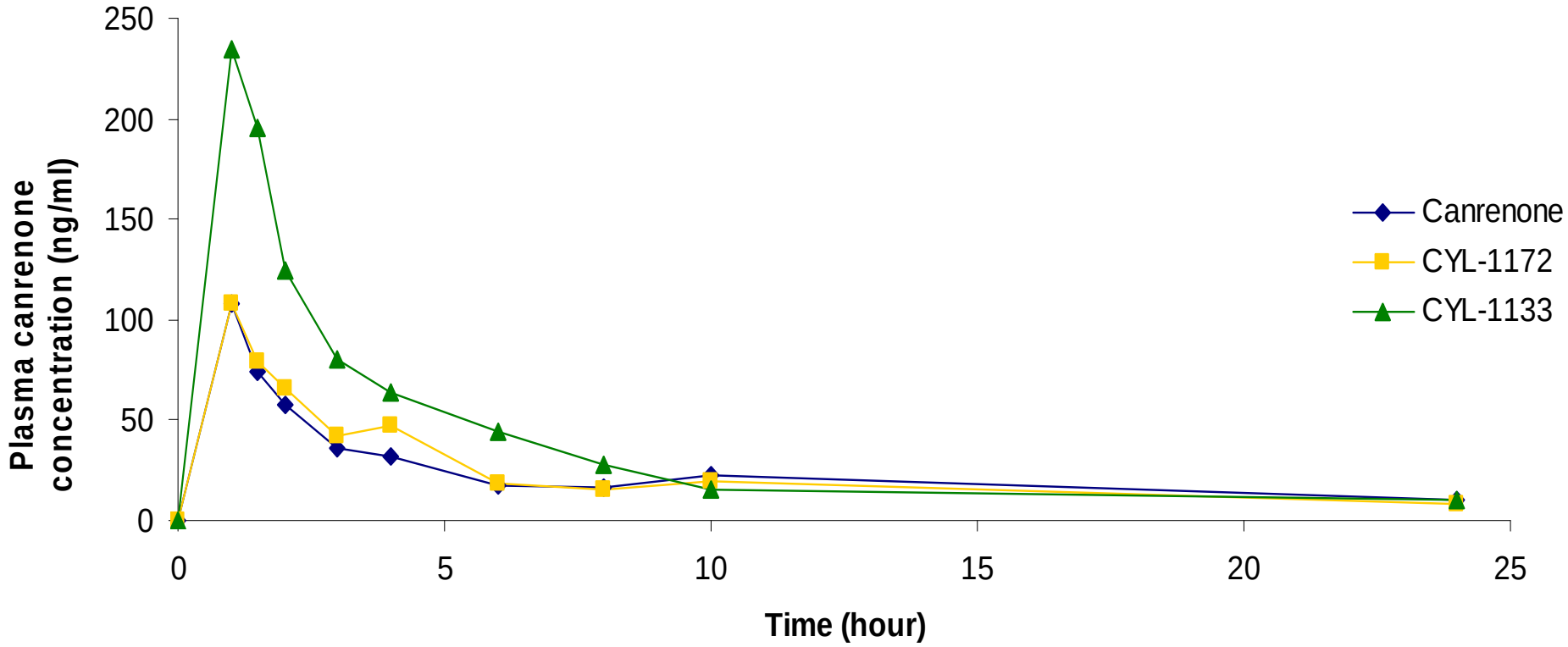


(Amidon et al 1995, Pharm. Res. 12:413-420; T.Loftsson 2002, J.Incl.Phenom. 44:63-67)

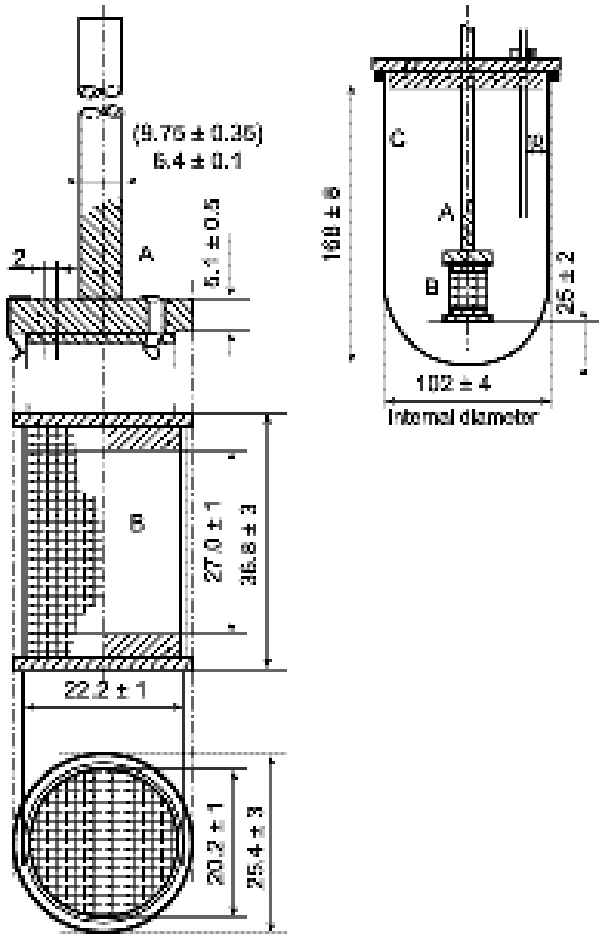

Solubility ishoterms of Canrenone
Canrenone (mg/mml)
3
2,5
2
1,5
1
0,5
0
0
2
4
6
8
10
12
CD (%)
gammaCD
betaCD
alphaCD

In vitro/in vivo korreláció
(reklasszifikálás CD complexálással)

Plasma canrenone levels following oral administration of canrenone and its gammaCD complexes (dose related to canrenone: 3 mg/kg)

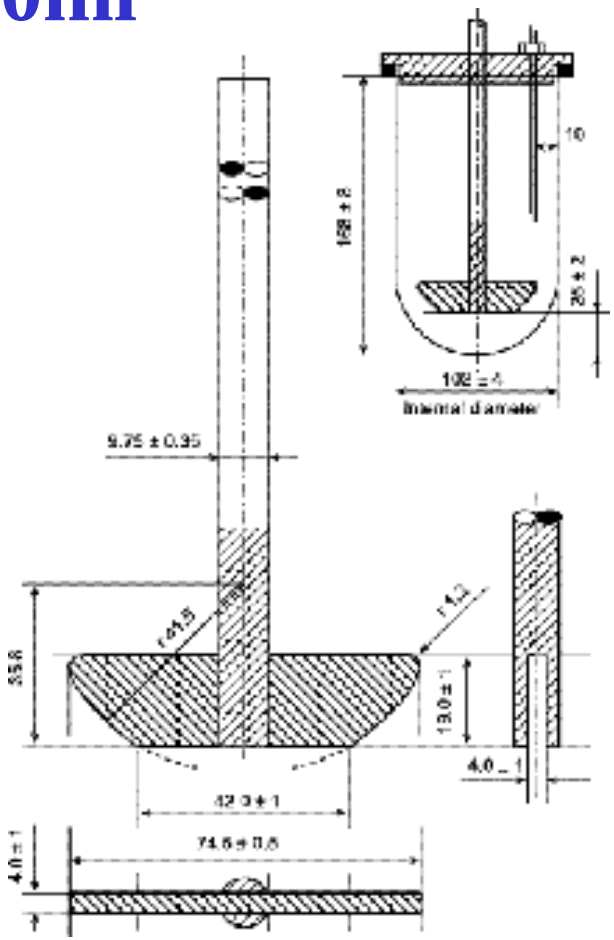


Rotating basket method



Paddle method

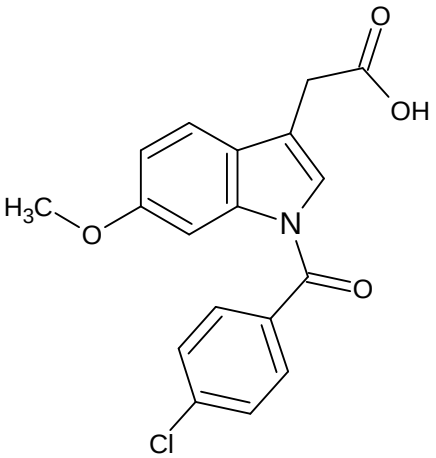
V=900ml

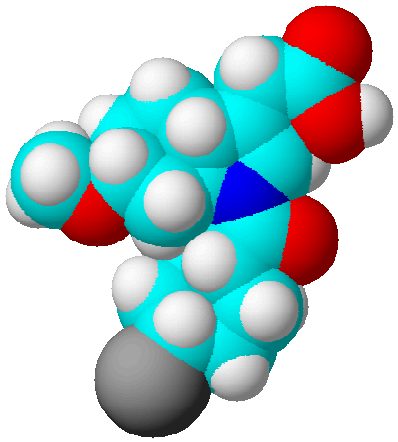


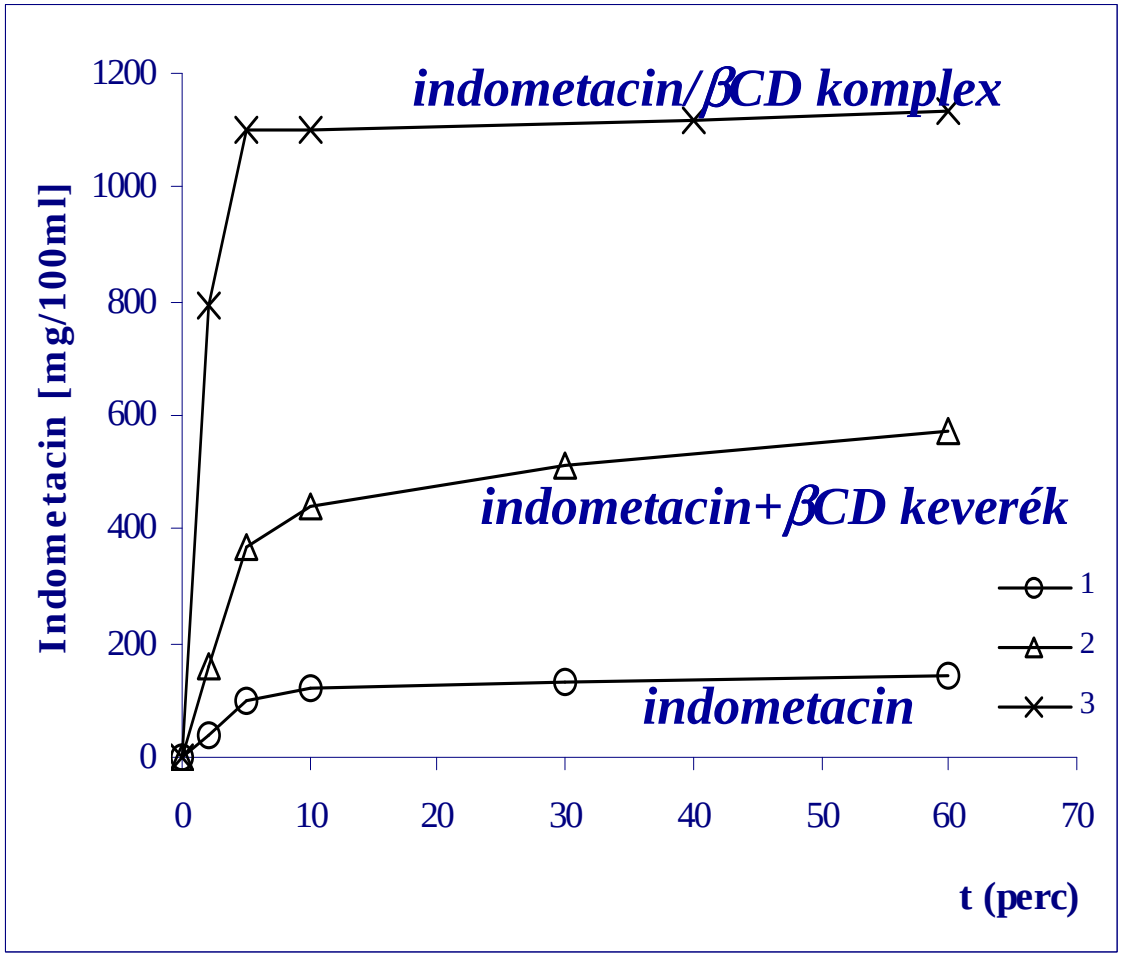
Orális gyógyszerformulációk

Az indometacin *in vitro* oldódássebessége pH 7 pufferben

„Corpora non agunt nisi soluta” (*Paracelsus*)

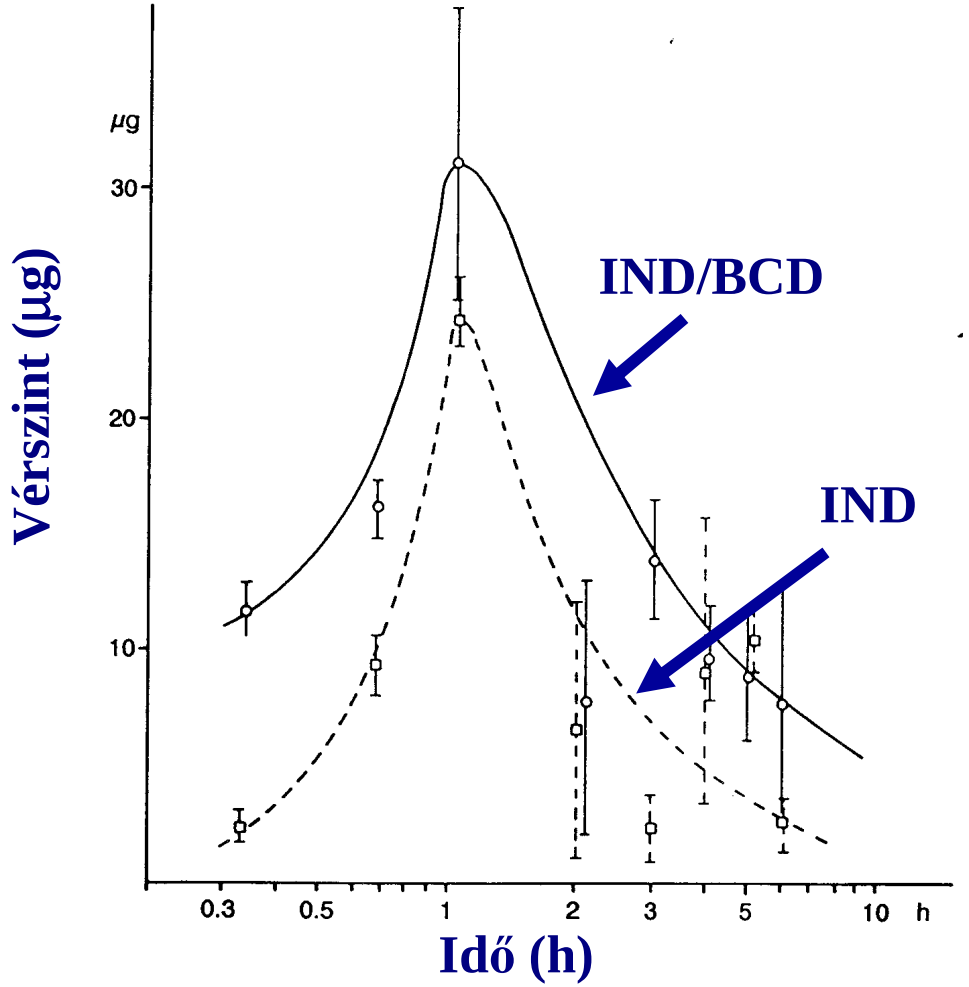




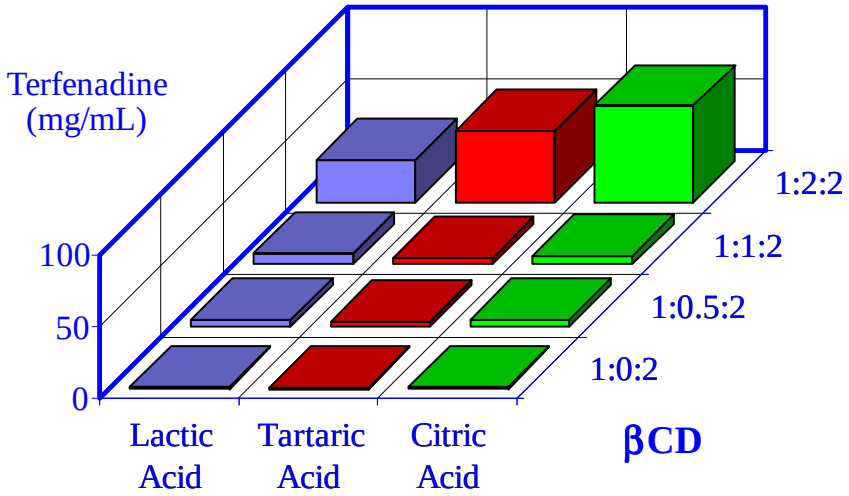


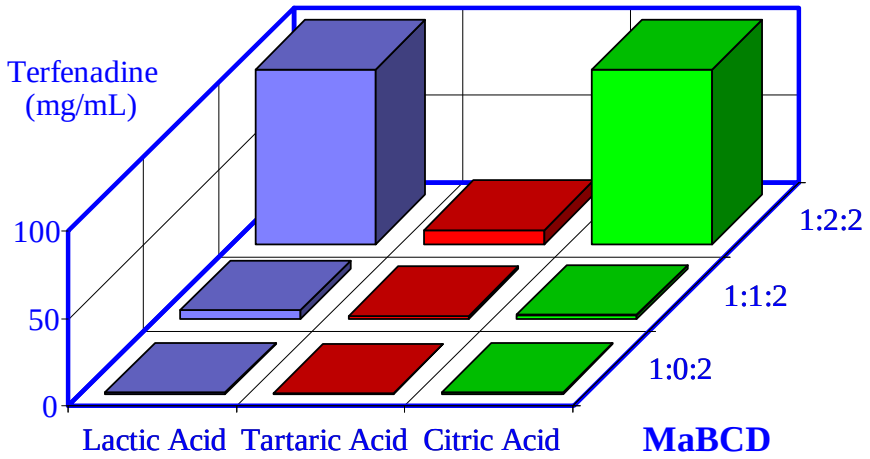
In vitro - in vivo korreláció

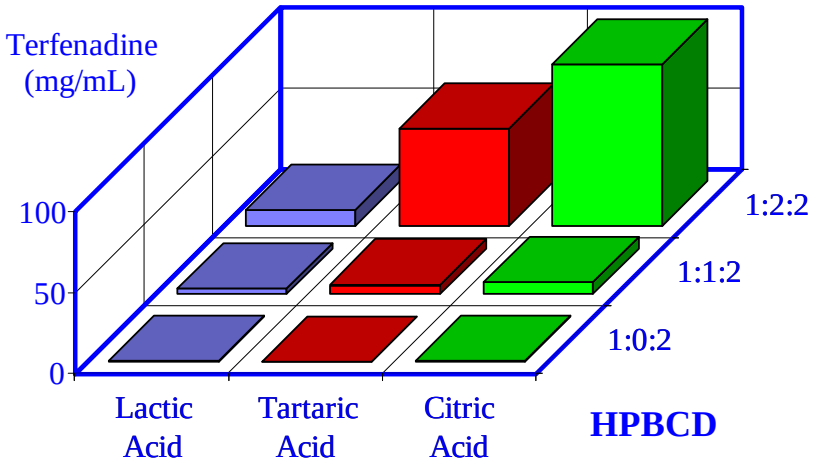
A szabad (IND) és a β-ciklodextrinnel komplexált indometacin (IND/BCD) vérszint görbéje orális adagolás után patkányokon

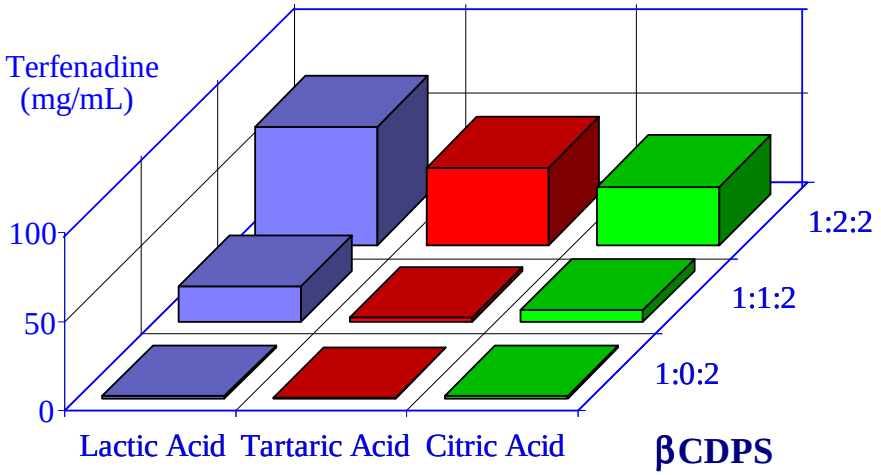


Solubility of Terfenadine in aqueous CD-solutions in the presence of hydroxyacids

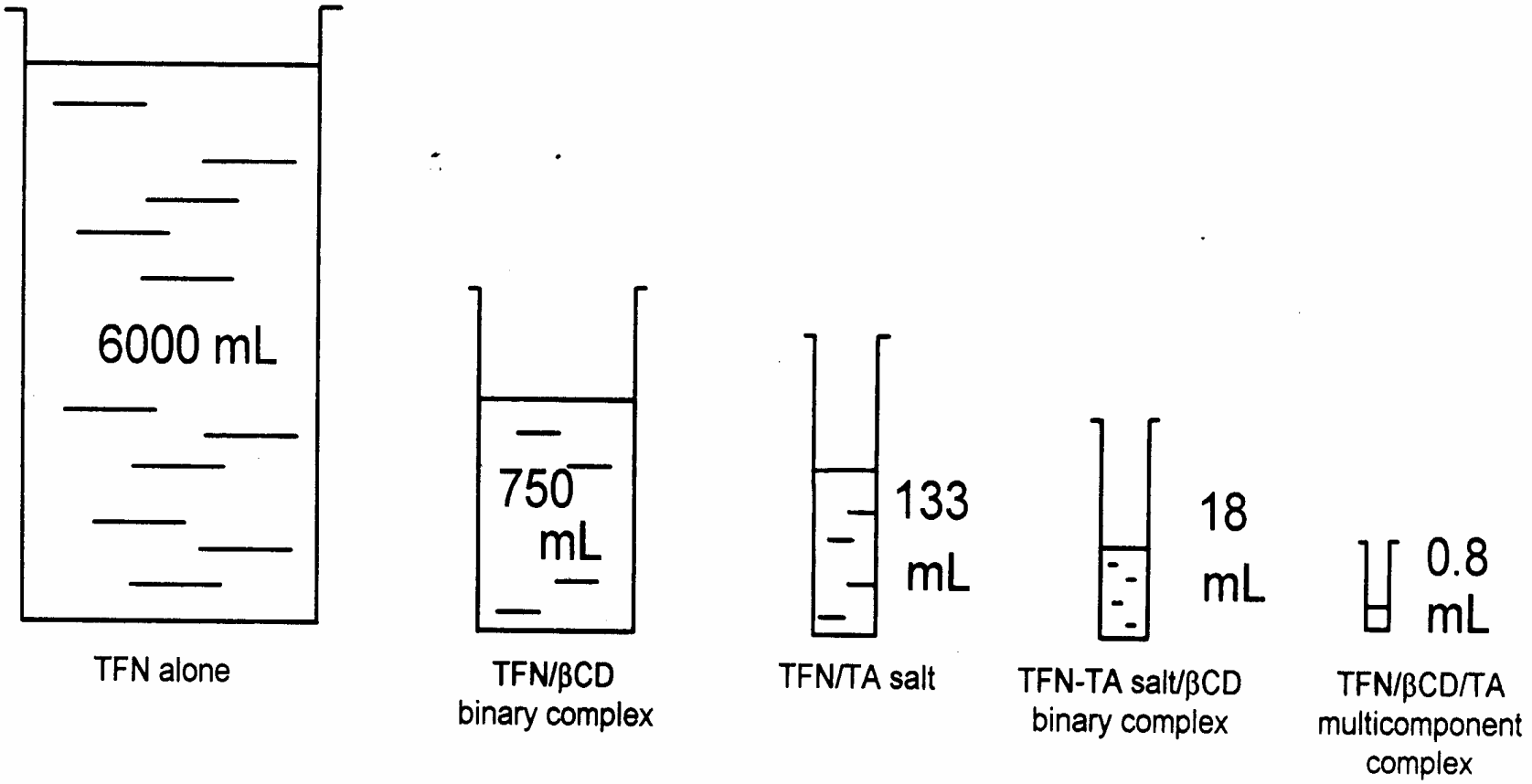




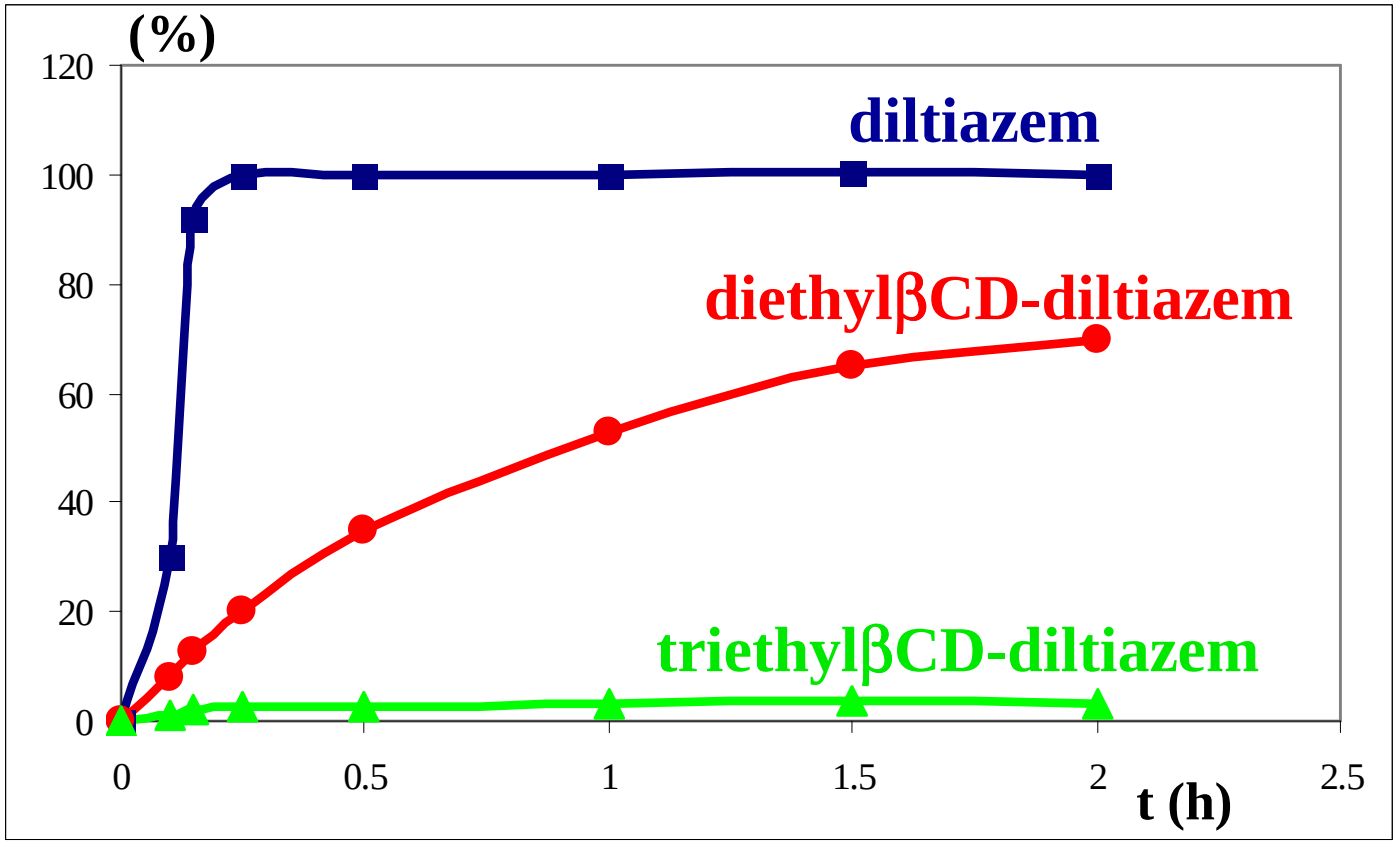




Volume of water for dissolution of 60 mg oral dose of Terfenadine in different forms

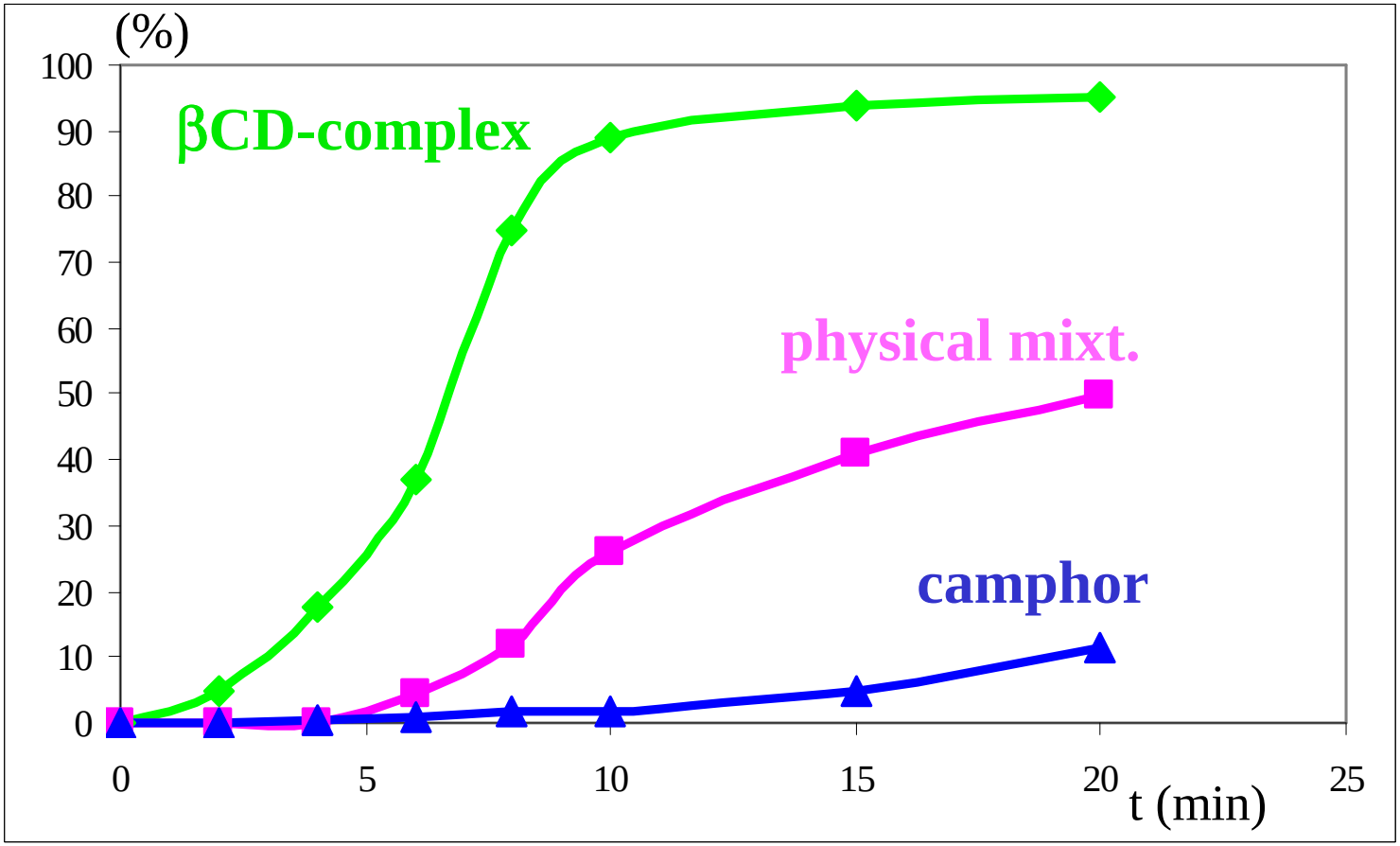


Release profile of diltiazem from tablets

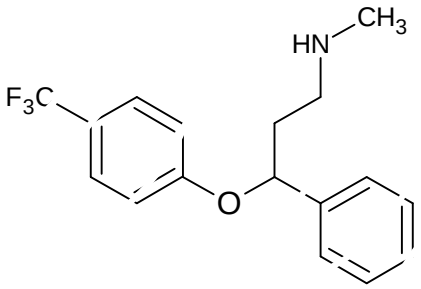


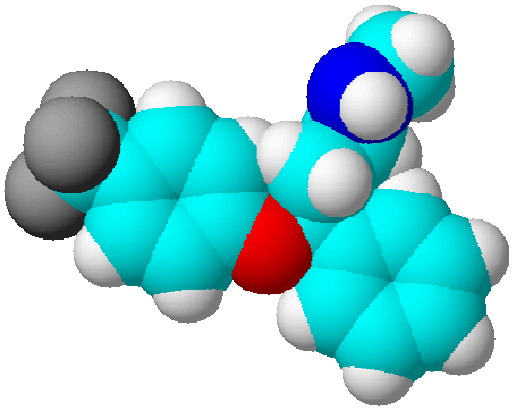
Uekama, 1987

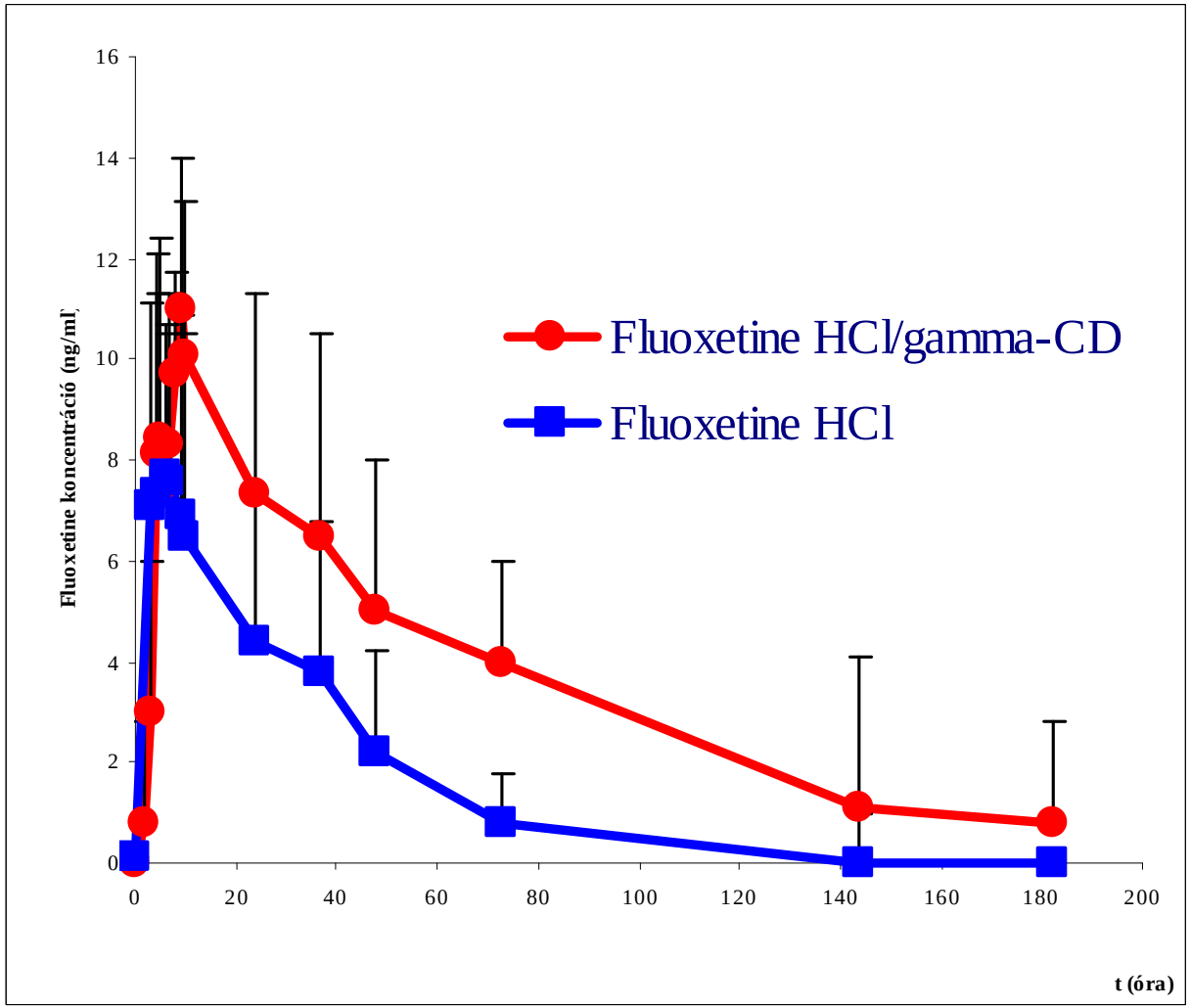
Wettability of free and βCD-complexed camphor



A Fluoxetin humán vérszint azonos dózisú, szabad hatóanyagot (Prozac®) és a Fluoxetin/γ-CD komplexet tartalmazó formulációk orális adása után





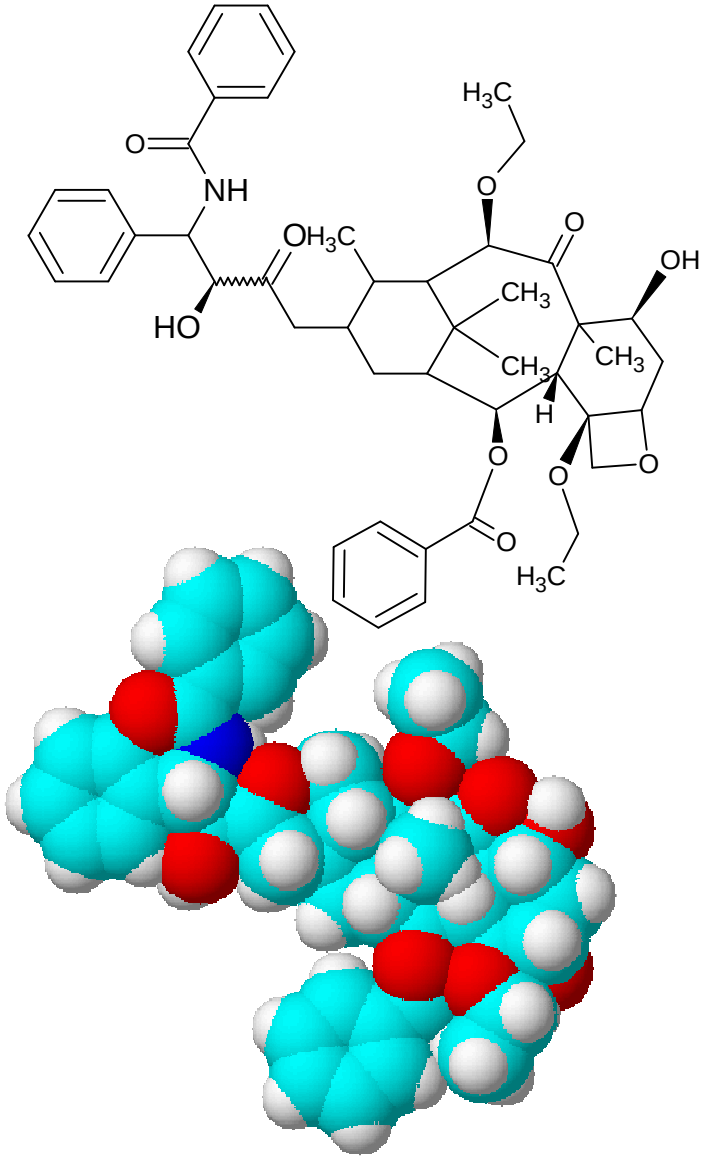


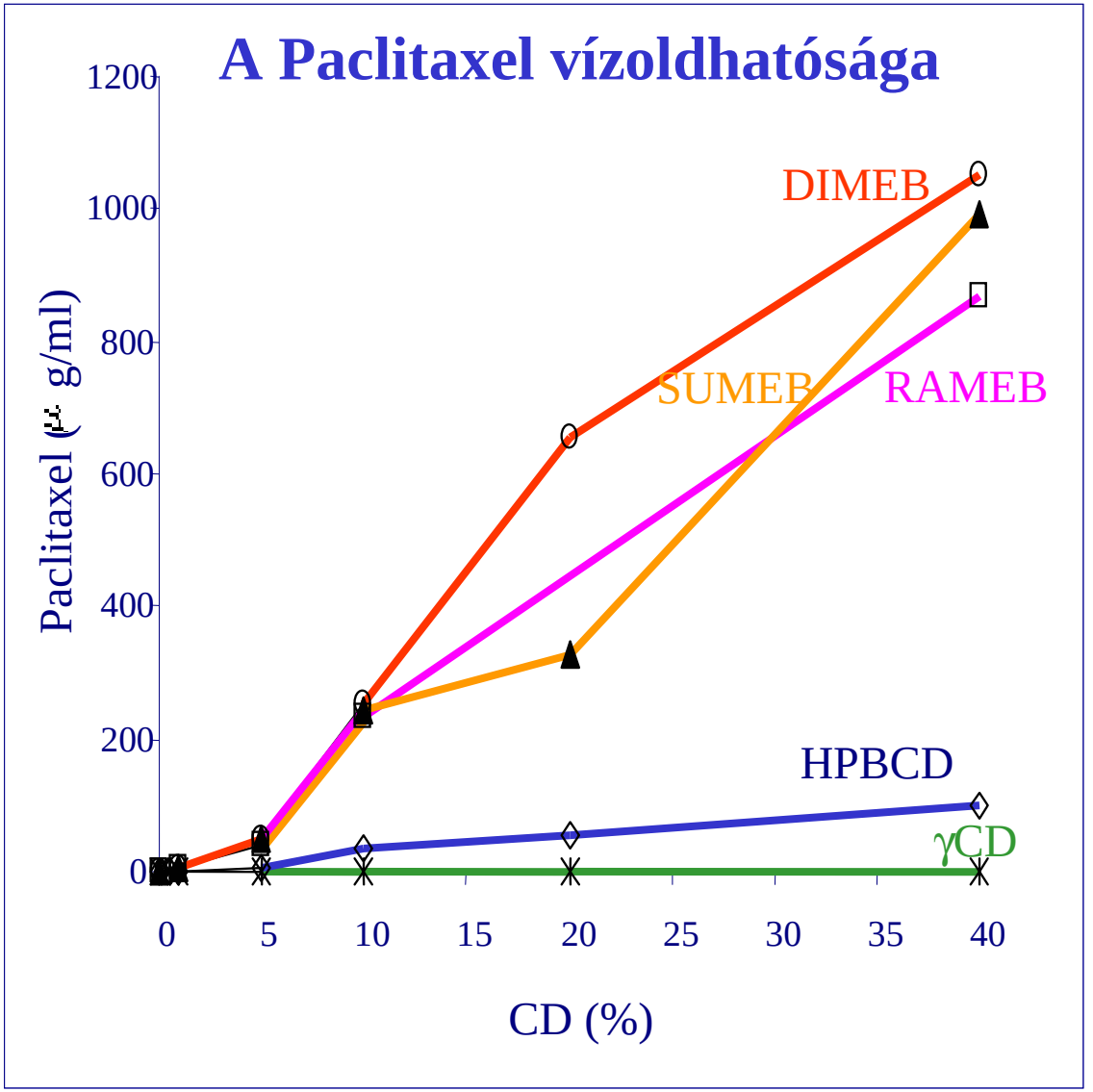
Humán farmakokinetikai eredmények

parameters	Prozac®	FluoxetineHCl/γCD complex
Fluoxetine		
C_{max}	8.9 ng/mL	12.6 ng/mL
t_{max}	4.9 hours	6.5 hours
AUC_{0-48h}	218 ngh/mL	343 ngh/mL
AUC_{total}	302 ngh/mL	754 ngh/mL
Mean Res. Time (h)	22.6±3.3	48.2±23.2
t1/2 β (h)	25.6±7.1	44.8±16.9

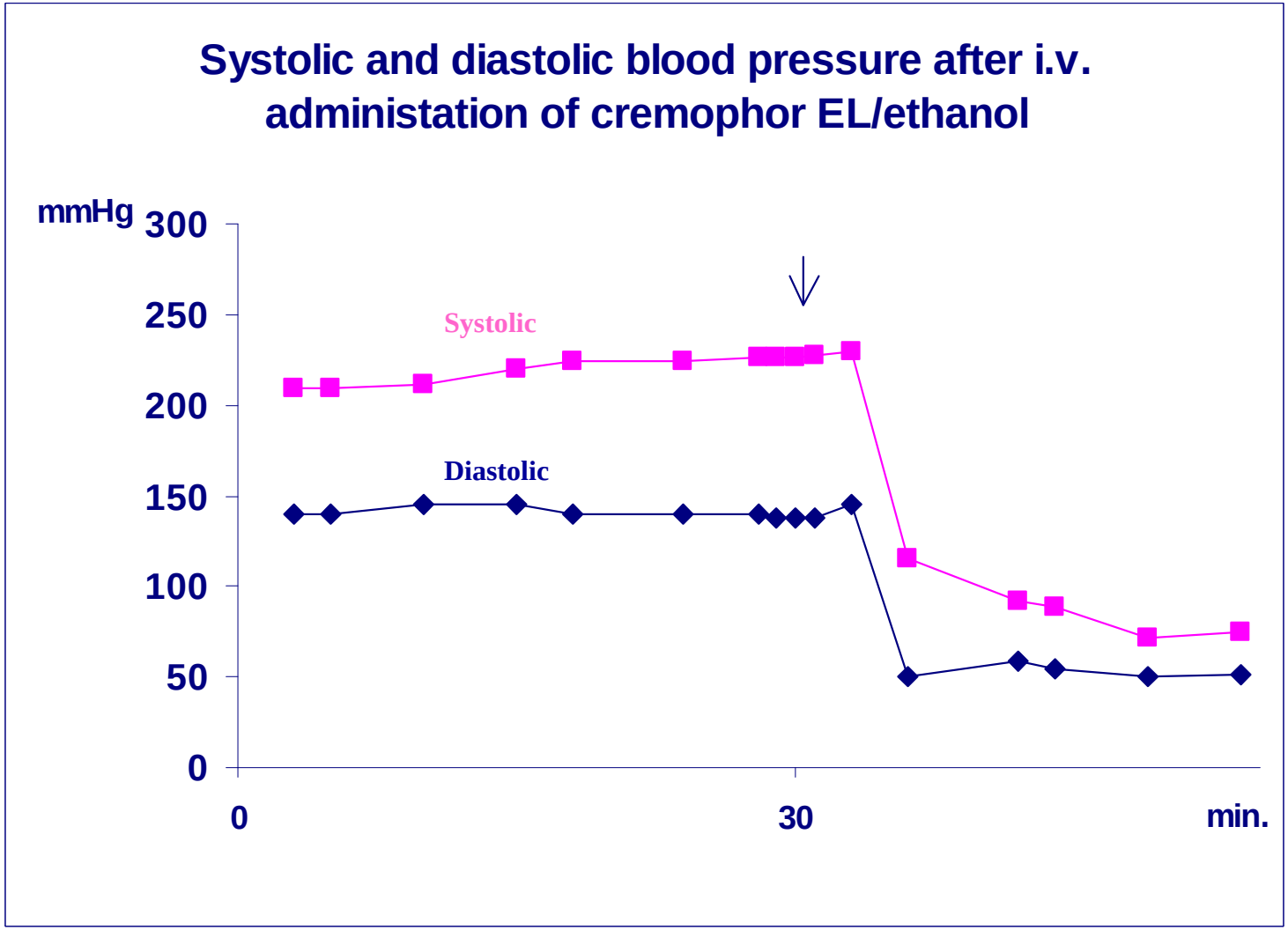
Komplexálás hatására nő a hatóanyag felszívódása orális adagolás esetén

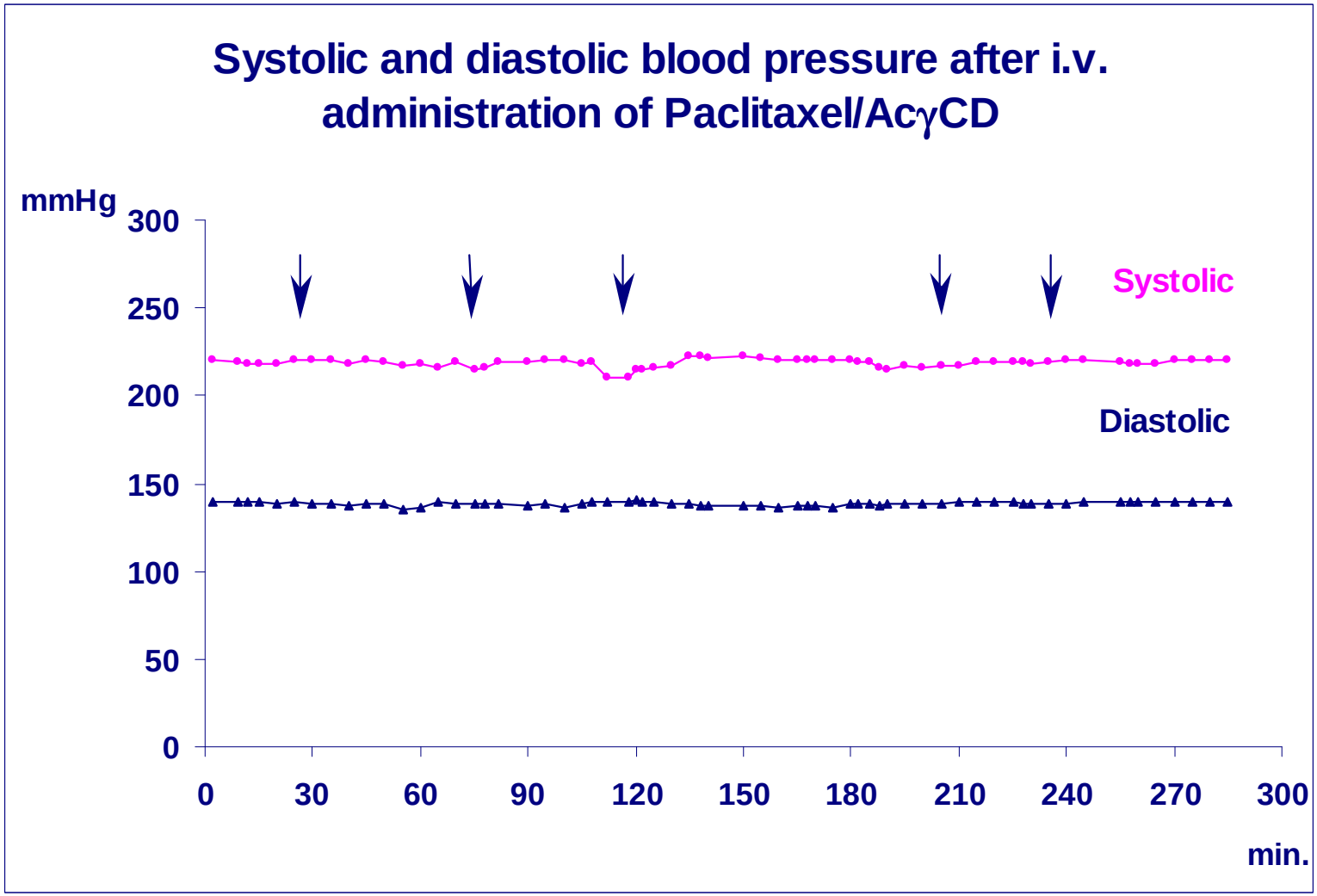
Folyadék gyógyszerformák injekciós célra: Taxánok



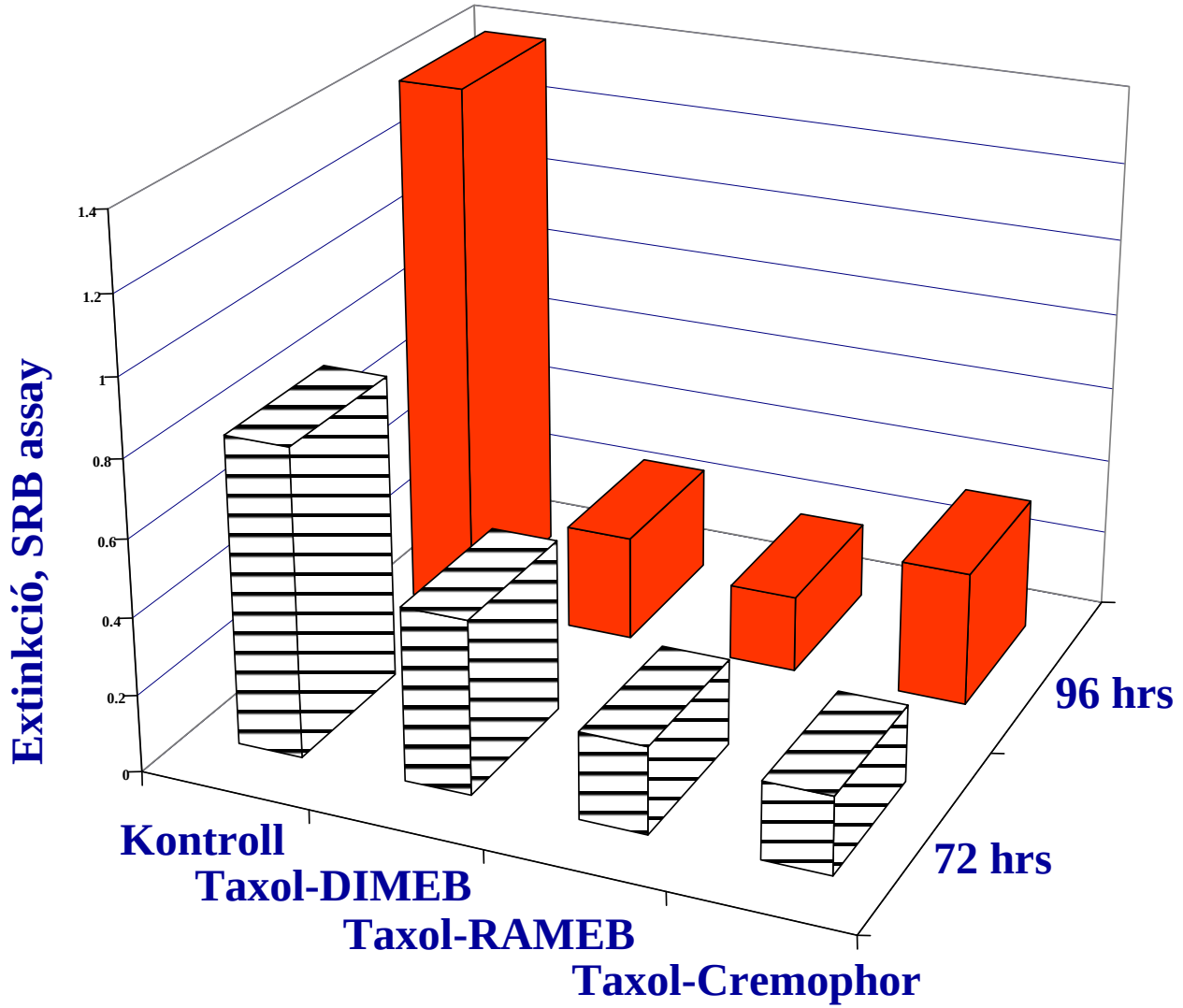


Paclitaxel formuláció kardiotoxicitása iv. kutyán




Systolic and diastolic blood pressure after i.v. administration of Paclitaxel/AcγCD
mmHg
300
250
200
150
100
50
0
Systolic
Diastolic
0
30
60
90
120
150
180
210
240
270
300
min.

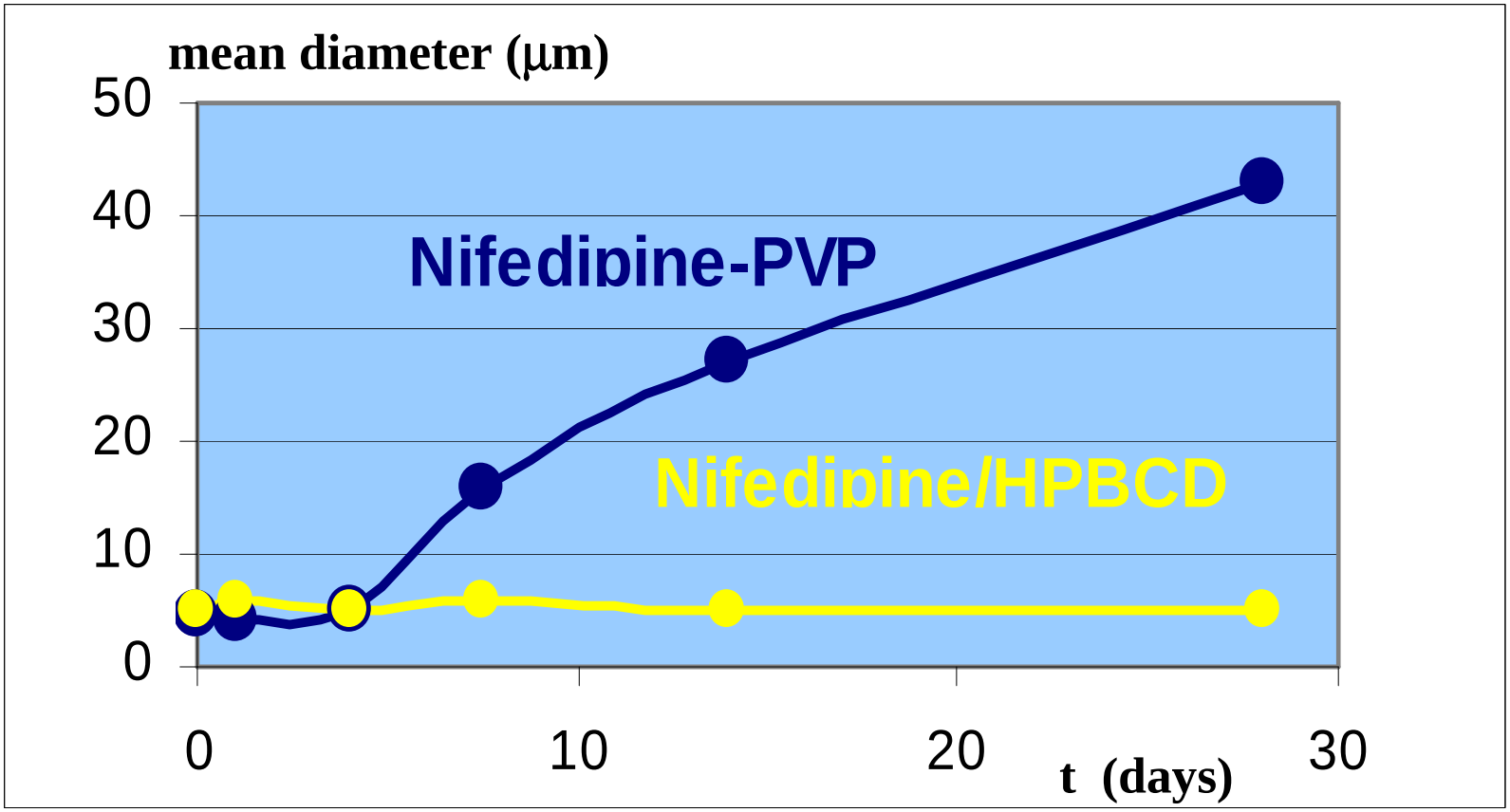
A hagyományos (Taxol-Cremophor-etanol) és a metil-β-ciklodextrinekkel készitett (Taxol/DIMEB, Taxol/RAMEB) paclitaxel oldatok *in vitro* sejtosztódást gátló hatása, PC3 humán sejtvonalon



AUC of Nifedipine after oral admin. of 20mg Nifedipine tabl. for dogs

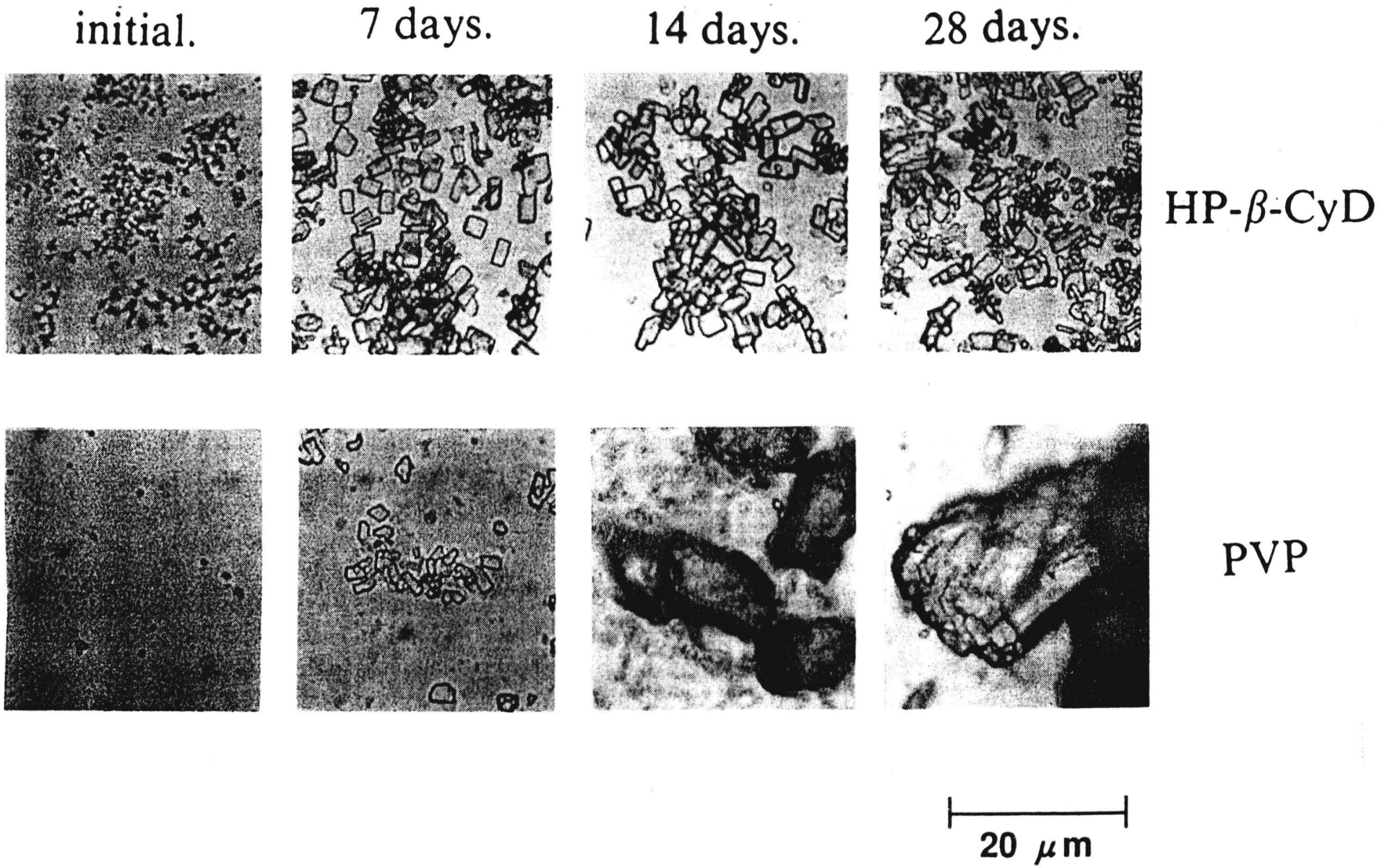
Preformulation	AUC (h x ng / ml)	
	t = 0	t = 14 days
Nifedipine powder	126.85±1.24	-
Nifedipine-PVP	148.39±30.00	103.20±4.56
Nifedipine/ HPBCD	213.22±26.08	211.62±23.59

Size distribution of Nifedipine crystals grown at 60^0C, 75% rH

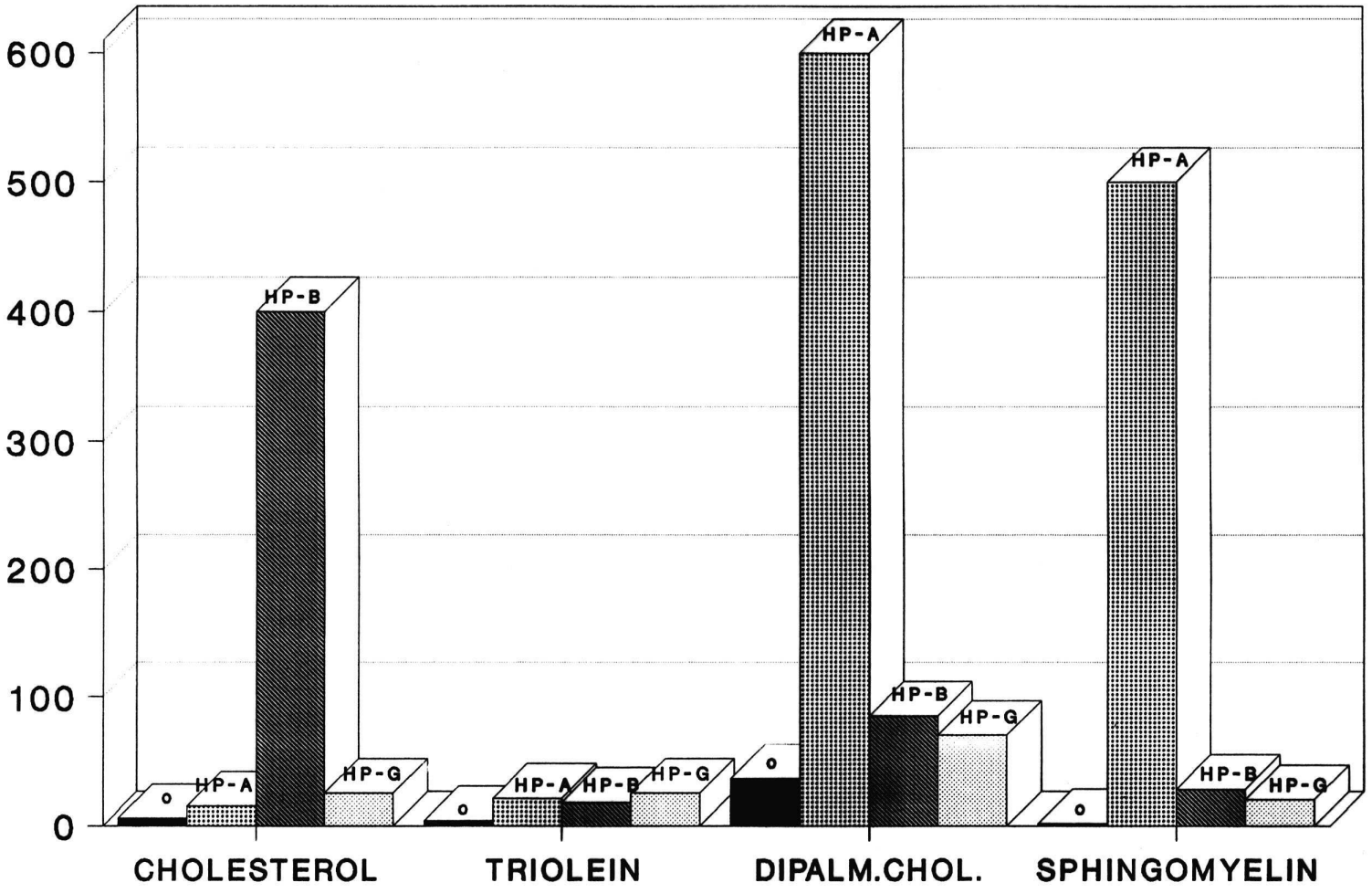


32.21

Photomicrographs of nifedipine crystals



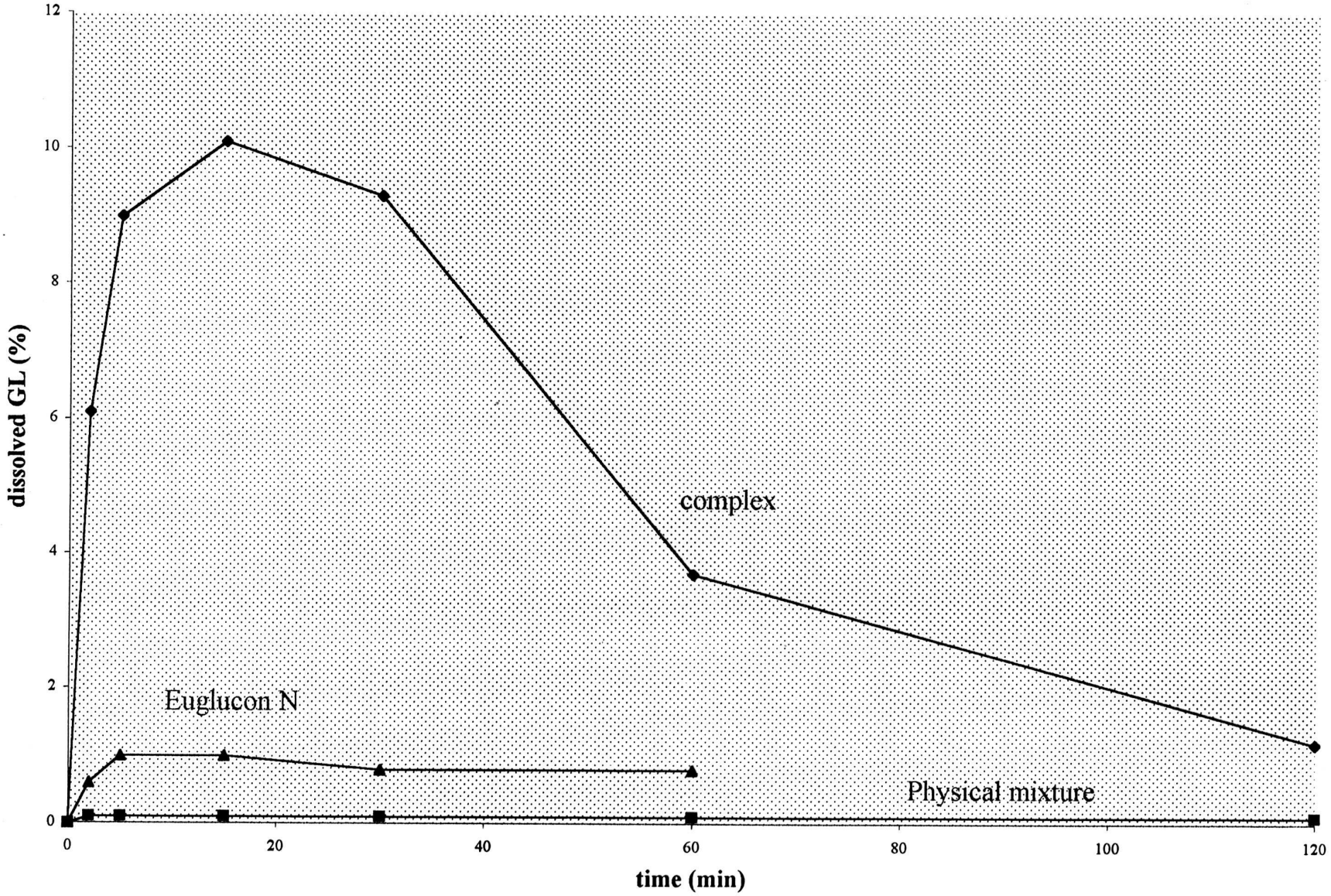
Enhancement of apparent solubilities of lipids by 5% hydroxypropyl-cyclodextrins



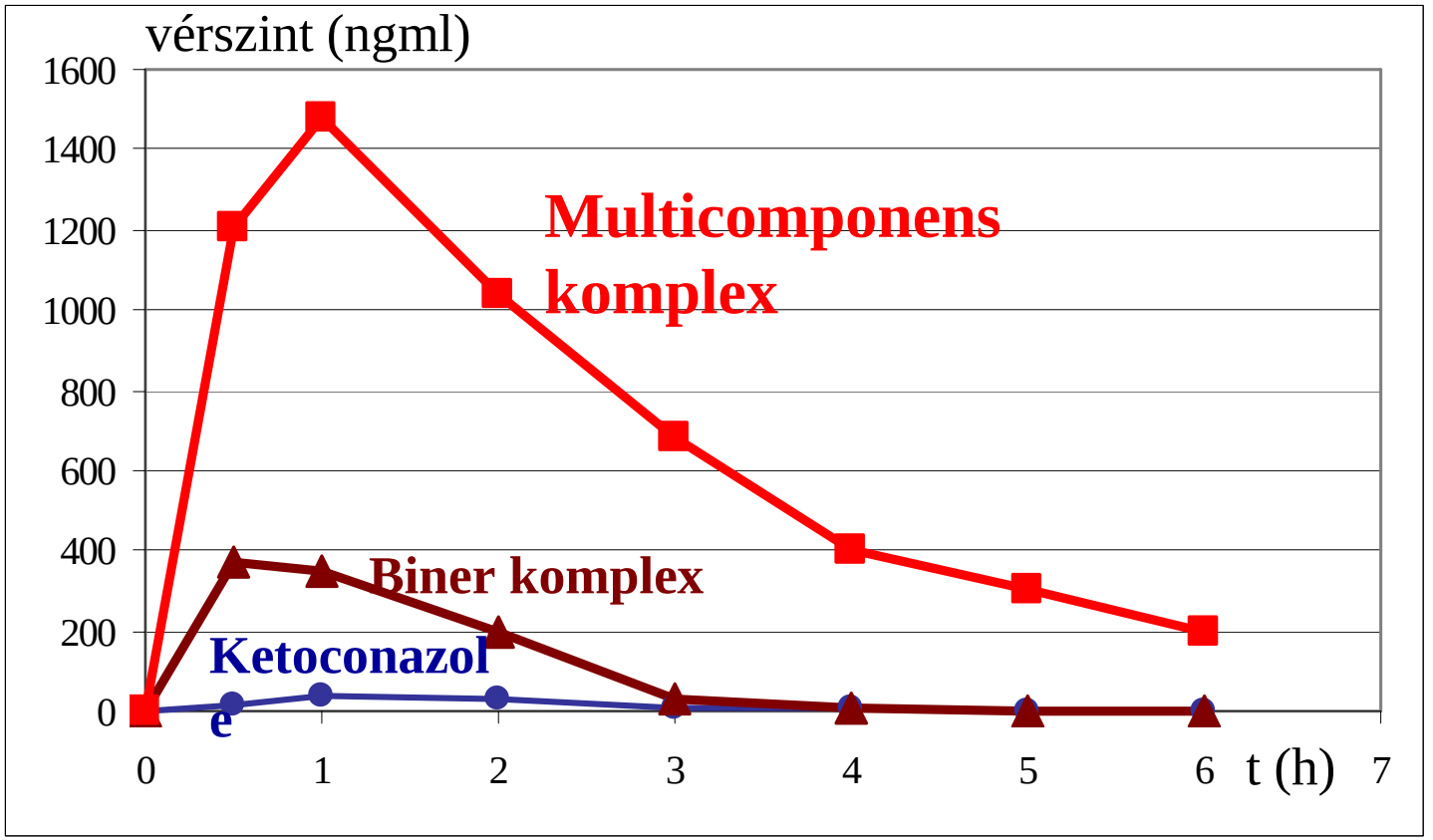
Irie, et.al. 1992

33.6

Fig.4. Dissolution of Glibenclamide at pH 5.0



Ketoconazole felszívódása orális beadagolás után gyomorsav nélküli nyúlon



A biner zárványkomplexek és gyógyszeripari alkalmazásuk

- molekuláris szintű diszperzitás
- nedvesedés- és oldódás fokozás fiziológiás körülmények között
- molekuláris csomagolás stabilizáló hatása (shelf-life)
- a hatóanyag/ciklodextrin komplex nem új kémiai egyed
- a hatóanyag leadása után a CD/membrán kölcsönhatás előnyös
- a ciklodextrin nem hatol át a membránokon
- fokozott biohozzáférhetőség, a dózis csökkentés lehetősége
- páciensbarát készitmények
- életciklus-hosszabitás lehetősége (iparjogi előnyök)

CYCLODEXTRINS IN THE STABILIZATION OF PHARMACEUTICALS

- CHEMICAL STABILITY

HYDROLYSIS

OXIDATION

PHOTODEGRADATION

THERMIC DEGRADATION

CATALYTIC DECOMPOSITION

- PHYSICAL STABILITY

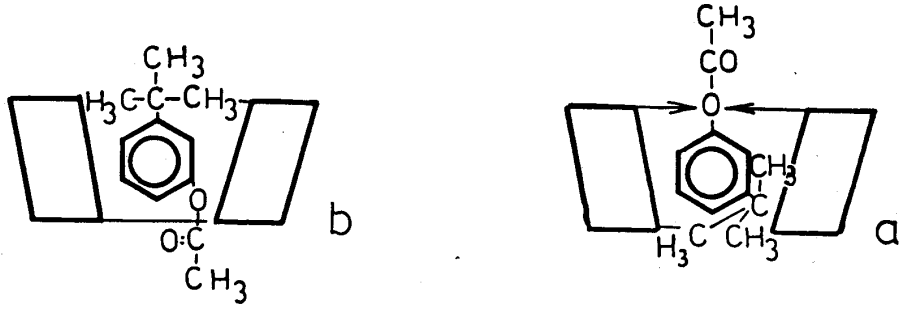
SUBLIMATION

POLYMORPHY

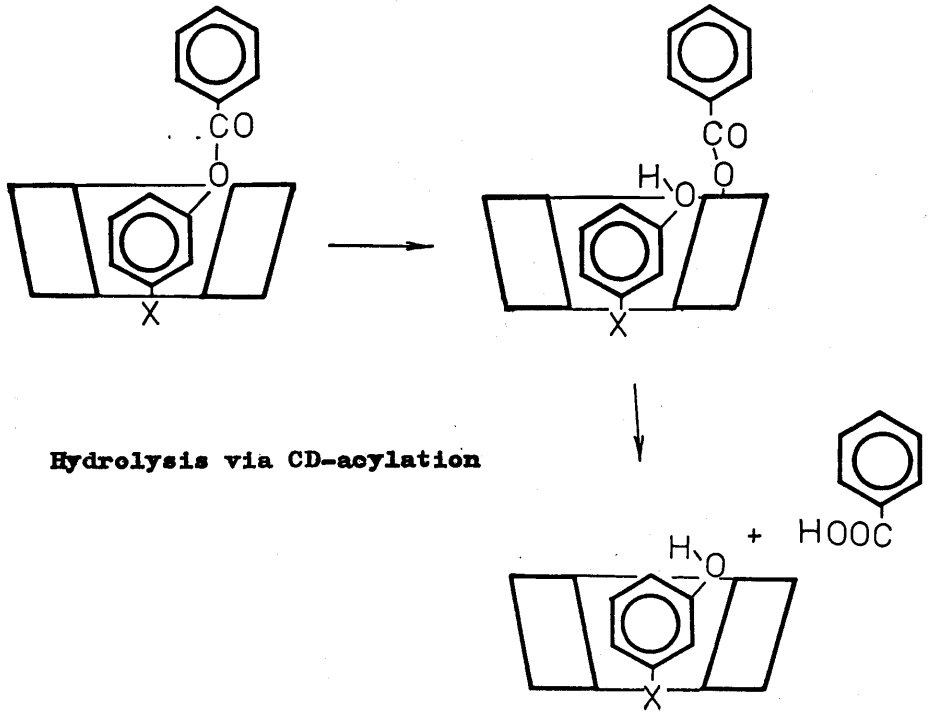
CRYSTALMORPHOLOGY

AGGREGATION

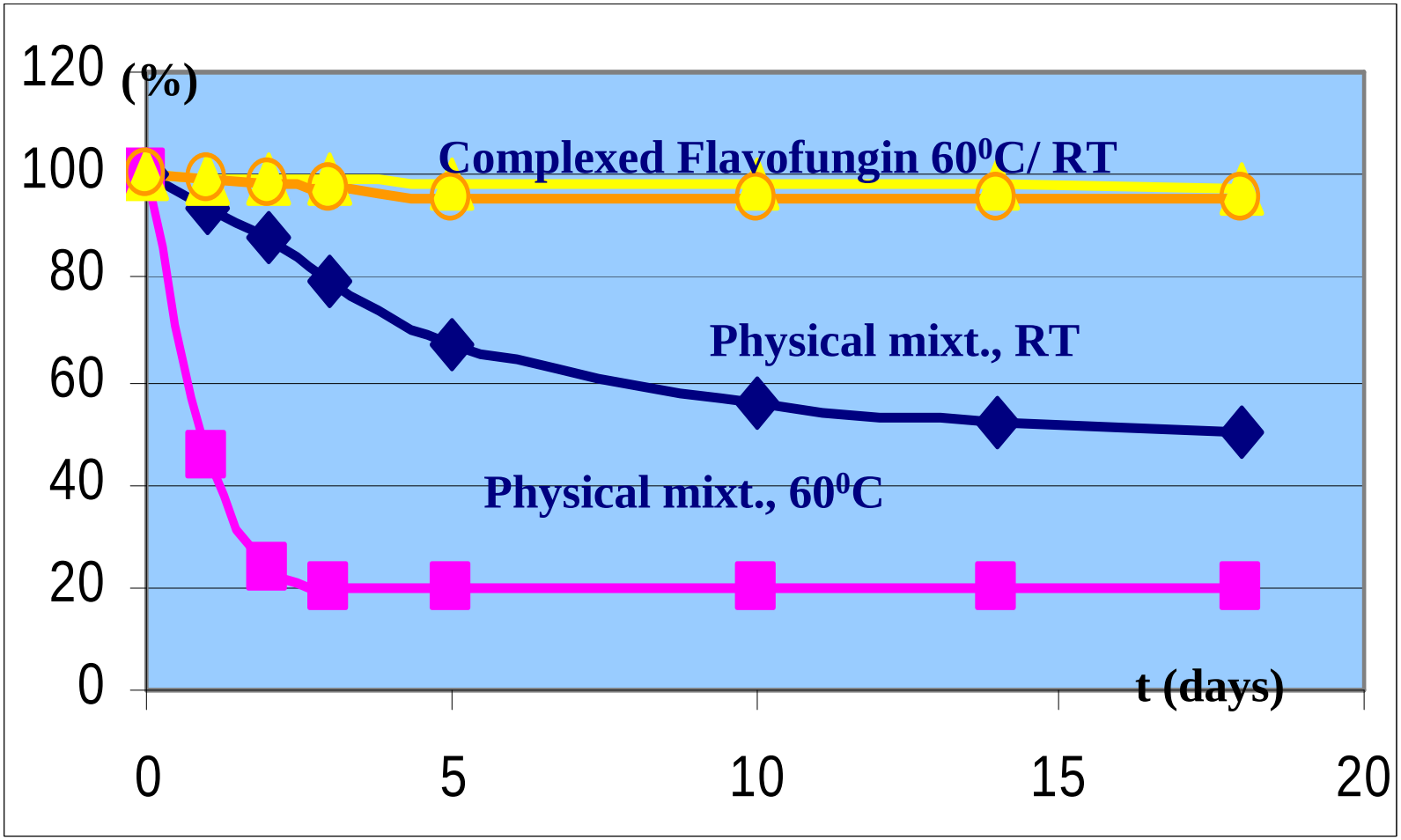
ASSOCIATION

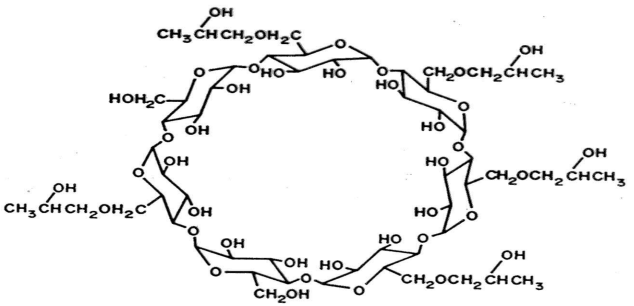


The hydrolysis of m-t-butylphenylacetate is a./ accelerated, b./ decelerated



Thermal decomposition of Flavofungin and Flavofungin/γCD in solution





2 - HYDROXYPROPYL - β - CYCLODEXTRIN
(HP-β-CD)

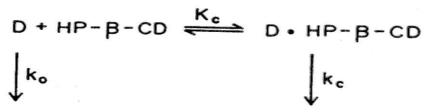
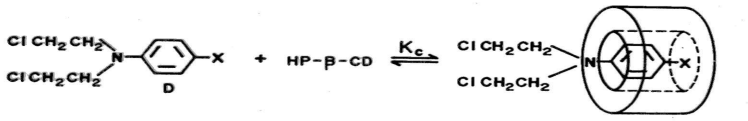
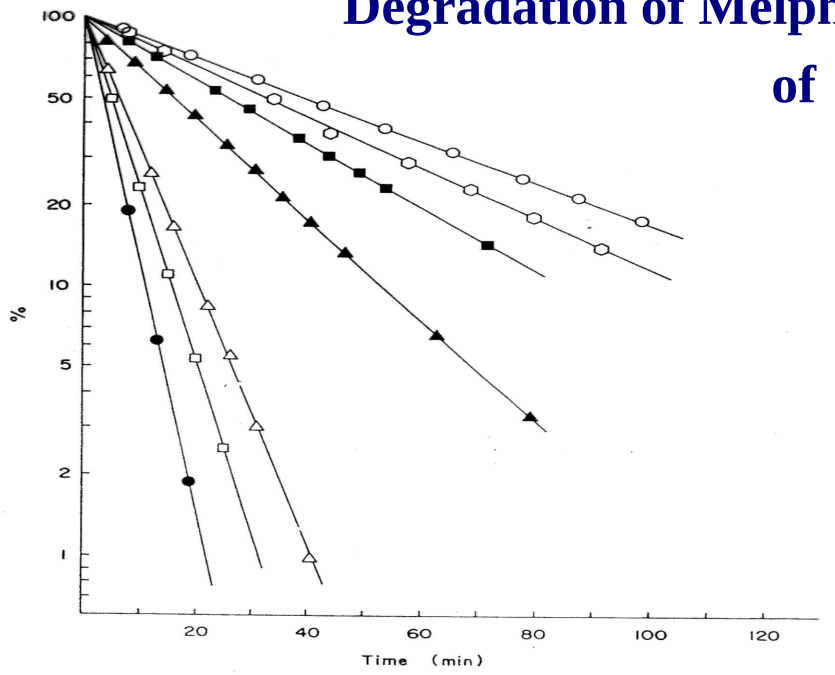


Fig. 1. *Representative structure of 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) and formation of HP-β-CD-melphalan complex (D · HP-β-CD) in aqueous solution.*

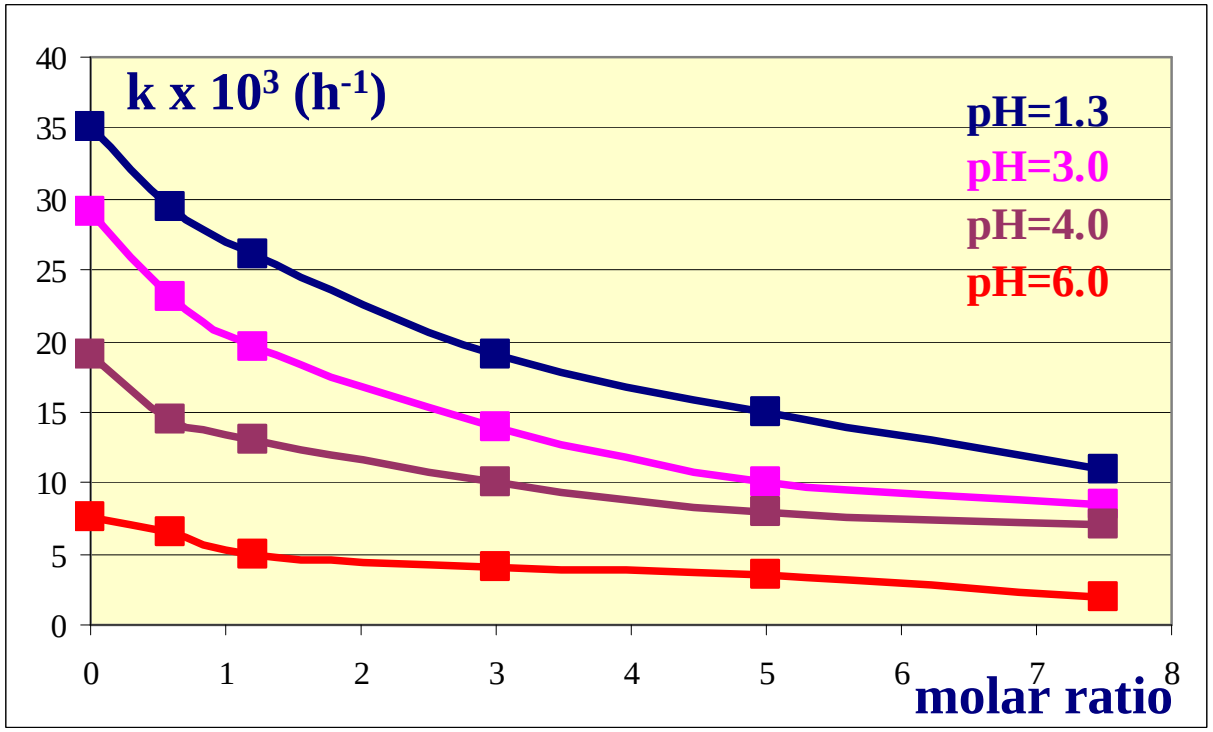


Degradation of Melphalan in presence of 0 – 20% HPBCD



Representative first-order plots (log% remaining against time) for the degradation of melphalan in pH 7.00 aqueous phosphatecitrate (McIlvaine) buffer solutions at 60.0°C. The figure shows the effect of HP-β-CD on the rate of degradation: ●, 0.0% w/v; □, 0.5% w/v; △ 1.0% w/v; ▲, 5.0% w/v; ■, 10% w/v; ○, 15% w/v; ○, 20% w/v HP-β-CD

Effect of HPBCD content on hydrolysis rate constant (k) of ASA at 40^0C

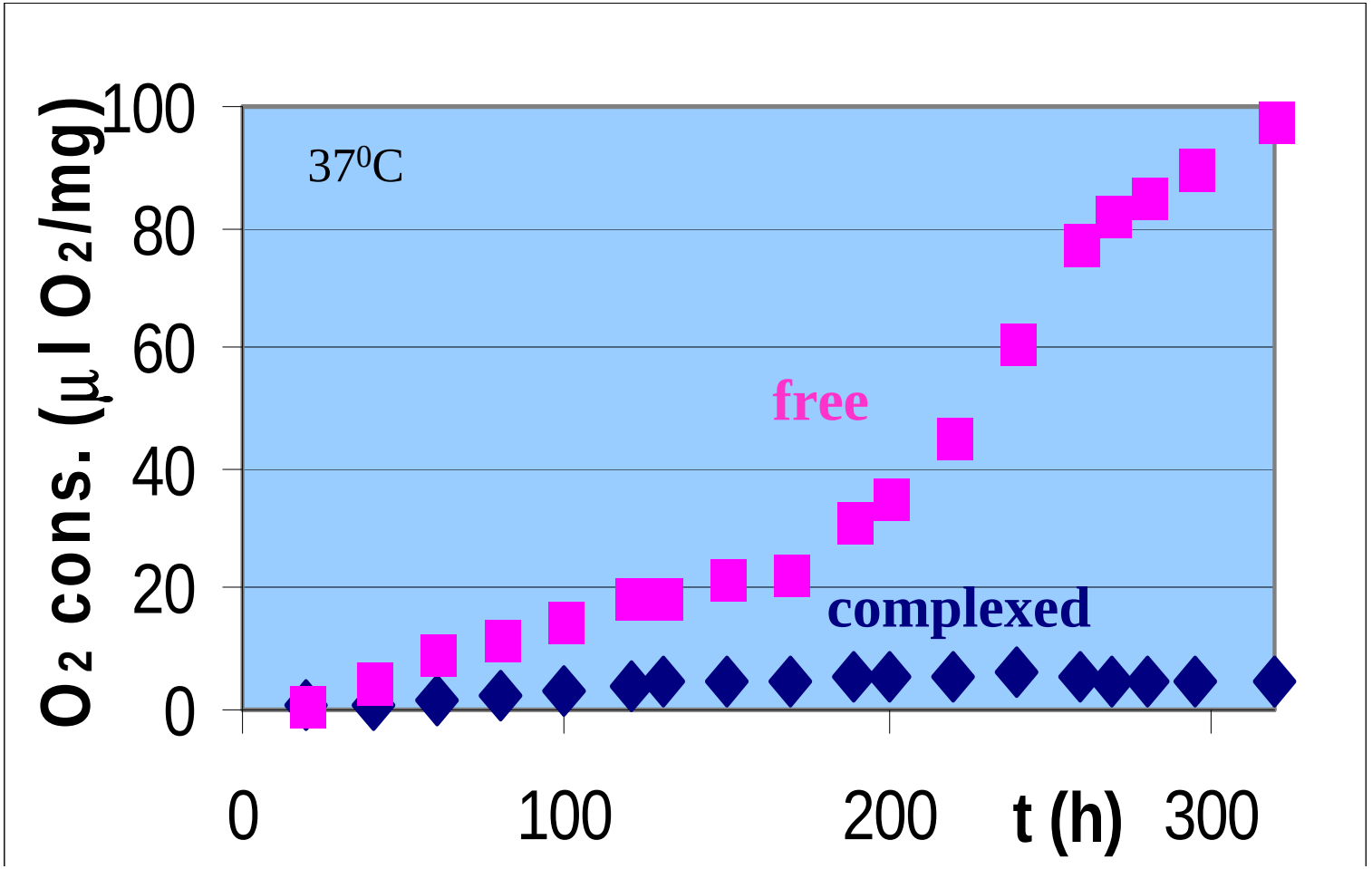


ASA + HPBCD = ASA/HPBCD

k1 → **SA**

k2 → **SA**

Oxygen consumption of free and βCD-complexed Chamomille Oil



Stability of Iodine in powders		
Formulation	**Iodine content (%), t=0**	**Iodine content (%) t=1h, 100°C**
Iodine/BCD powder	**1.05±0.02**	**1.01 (-3.8%)**
Iodine-talc powder	**0.54**	**0**

Stability of Iodine in vaginal suppositories			
Formulation	**Weight (n=10)**	**Iodine content (mg/dosage) t=0**	**Iodine content (mg/dosage) t=40h, 65°C**
Iodine/BCD vaginal supp.	**2.69 ±0.08**	**20.1 ±0.62**	**19.89 (-1.03%)**
Reference prep. (Iodine/PVP)	**2.94 ±0.12**	**20.0 ±0.90**	**19.96 (-0.35%)**

Stability and biological activity of selected proteins in HPBCD solutions

Protein	time (until no loss of activity)	time (until no aggregation)	time (until no dimerization)
IL-2	28 days (37^0C)	-	84 days ($+4^0$C)
TNF	28 days (37^0C)	-	28 days (37^0C)
OGH	-	7 days (25^0C)	-
HGH	-	4 days ($+4^0$C)	49 days ($+4^0$C)
Bovine Insuline	-	56days (25^0C)	56 days (25^0C)
Human insuline	-	4 days ($+4^0$C)	4 days ($+4^0$C)