LIMITS OF CYCLODEXTRIN APPLICATION IN ORAL DRUG PREPARATIONS

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ABSTRACT. Cyclodextrins are applied to facilitate formulation problems, to improve stability and bioavailability. Following factors are determining whether or not cyclodextrins can be applied in oral pharmaceutical preparations:

- properties of the selected CD: solubility, price, specific catalytic properties,
- the drug to be complexed: molecular weight, polarity, solubility,
- drug dose
- solubility properties of the complex and the "super solubility" /temporary over-saturation/
- complex stability and possibility to shift the dissociation equilibrium toward the appropriate direction
- legislative procedures

1. INTRODUCTION

The number of scientific papers, and published patent applications or patents dealing with drug complexation displays an explosionlike increase during the last years. Overwhelming majority of these papers report promising results, which seem to be realizable on industrial scale, too. (1,2,3,4). Notwithstanding this amazing number of publications may be misleading, alluring to efforts that yield only unfruitful experiments.

This paper scrutinizes the limits of cyclodextrin application in orally administered drug preparations. This field is very broad because a vast number of drugs can be complexed. Nevertheless also this field has its definite limits, over which only a negligible rate of succes on account of technical, or economical reasons can be expected. The knowledge accumulated so far on this field allows us to delineate the sensible limits of cyclodextrin applications in drug complexation. Taking these

Journal of Inclusion Phenomena 2, 487–501. 0167-7861/84.15.

limits into account, valuable time and work can be spared not chasing unattainable goals.

2. PURPOSE OF CD-APPLICATION

CDs can be applied in oral preparations either for complexation of the drug or as auxiliary additives, carriers, diluents, or tablet ingredients . (3,4,5,6).
Inclusion complex formation of a drug results in the modification of its physical and chemical properties. These modifications are very often advantageous,

a./ in formulation of drugs:

- liquid compounds can be transformed into crystalline form which is suitable for tablet-manufacturing;
- bad smell and sometimes taste can be covered by complex formation;
- incompatible compounds can be mixed when reacting components or one of them are complexed;

b./ improvement of physical and chemical stability:

- volatile compounds can be protected from evaporation;
- cyclodextrin inclusion complex protects oxidizable compounds from oxidation by air;
- rate of decomposition, disproportionation, polymerization, autocatalytic reactions etc. is considerably decreased;
- sensitivity to light, gastric acid, etc. is reduced;

c./ bioavailability of poorly soluble drugs can be enhanced;

- solubility in water as well as the rate of dissolution of poorly soluble substances can be increased;
- after the oral administration of poorly water soluble drugs higher blood levels can be achieved if they are complexed with cyclodextrin (= possibility for reduction of doses);
- undesired side effects can be reduced.

d./ as excipient (carrier, diluent): in tablet formulation of very low drug content (e.g. contraceptive steroides);

e./ tablet disintegrant: highly swelling CD-polymers have been prepared, which are not absorbable, not digestible. Applying them in small amounts rapid disintegration of tablets is achieved on contacting with water.(7,8).

3. PROPERTIES OF CDs AS LIMITING FACTORS

The CDs are very different in their properties. For the above mentioned purposes the following properties are to be considered.

- The selected CD has to form an inclusion complex

of appropriate stability and solubility with the drug to be complexed. A drug forms complexes of very different stability with the various CDs (Table I.).

Table I.

Some characteristic properties of cyclodextrins

Characteristics	α	β	γ	DIMEB
number of glucopyranosidic units in a molecule	6	7	8	7
molecular mass, dalton	972	1135	1297	1331
solubility at 20 °C in water g/100 ml	14,5	1,8	23,2	30
cavity diameter, Å	5,7	7,8	9,5	7,8
hydrolysis by Aspergillus oryzea α-amylase	negligible	slow	rapid	not hydrolyzed
V_{max} value (min^{-1})	5,8	166	2300	0
Complex stability (M^{-1}) with				
Hydrocortisone	110	1300	2400	2300
Methyltestosterone	60	770	-	4800
Prednisolone	-	3000	1400	7800

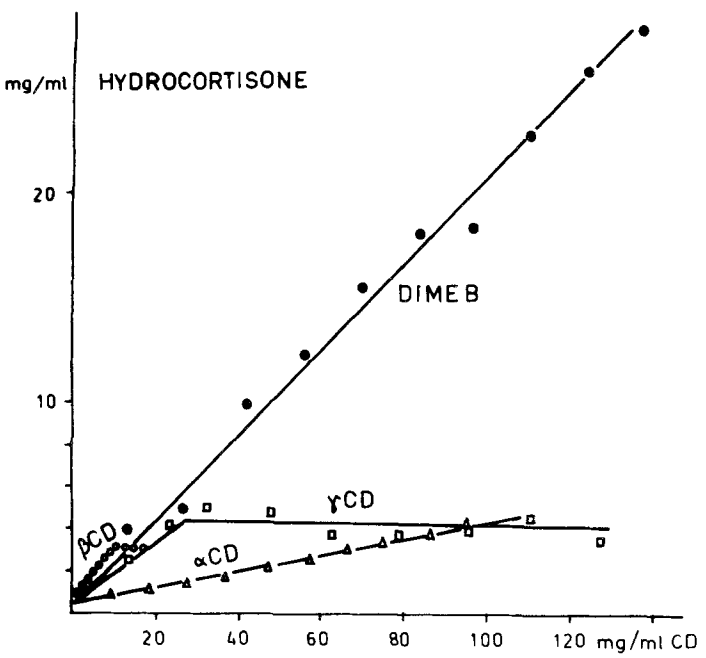

Fig.1. Solubility of hydrocortisone in various CD-solutions at 25 °C.

The stability constant has direct influence on the absorption, and blood level of the complexed drug. (See later).

- The solubility of the formed complexes can be very different. Fig.1. illustrates the solubility of a steroide as a function of the CD concentration. The dimethyl-βCD results in an unmatched solubility enhancement however γCD is also excellent in this respect.

- Toxicity, resorption and metabolism: detailed toxicity studies have been made until now only on βCD, (9,10, 11), flavour- βCD complexes are already marketed in Hungary. Metabolic studies proved that α- and βCD are metabolised similarly to starch and glucose in rats. (12,13). According to subchronic oral toxicity studies γCD is not toxic (14); considering its rapid amylolytic degradation (15) γCD is expected to be the more tolerable of the 3 CDs in parenteral application. DIMEB is apparently not absorbed from the intestinal tract. (16).

- Price: for the coming years βCD is the only economically feasible CD for all-purpose utilization. For several high-priced drugs the use of γCD can be considered too, however its price must drop strongly before a widespread utilization can be considered.

- Specific properties: Unexpected phenomena sometimes prevent the application of a particular CD. E.*g.* solubility and bioavailability enhancement of spironolactone has been aimed by various authors by forming its βCD complex. (17-20). Scrutinizing the source of the apparent loss of a fraction of the substance, based on UV absorption spectra a catalytic phenomena was recognized: βCD catalyzes the splitting of the thioacetal group, and the active metabolite forms a stable βCD complex. (21). Intact spironolactone however can be complexed with γCD. (22).

4. PROPERTIES OF DRUGS AS LIMITING FACTORS

Not all the drugs are suitable for CD-complexation. Many compounds can not be complexed, or complexation results in no essential advantages. In other cases the ratio of drug in the complex is too low; one or two tablets of acceptable weight would not contain the required dose. Inorganic compounds generally are not suitable for CD-complexation. Exceptions are (3); non-dissociated acids (HCl, HBr, HJ. H_3PO_4, etc), halogens, gases (CO_2, C_2H_4, Kr, Xe, etc). Metal ions (Cu, Ag) form hydroxy-complexes. Outer-sphere complexes of anions can be detected in aqueous solutions. Inorganic salts- KCl, Fe- salts, etc. can not be complexed.

Organic compounds of apolar character yielding solid complexes suitable for oral drug formulations are complexed under the following preconditions:

- more than 5 atoms (C, P, S, N) form the skeleton

- solubility in water is less than 10 mg/ml
- consist of less than 5 condensed rings
- molecular weight should be between 100 and 400;

with smaller molecules the drug content of the complex is too low, large molecules do not fit the CD-cavity. Strongly hydrophilic, too small or too large molecules e.g. peptides, proteins, sugars, polysaccharides, polyalcohols, etc. can not be complexed. Ionized species are generally better hydrated, better soluble than their non ionized forms therefore they are weaker complex forming partners.

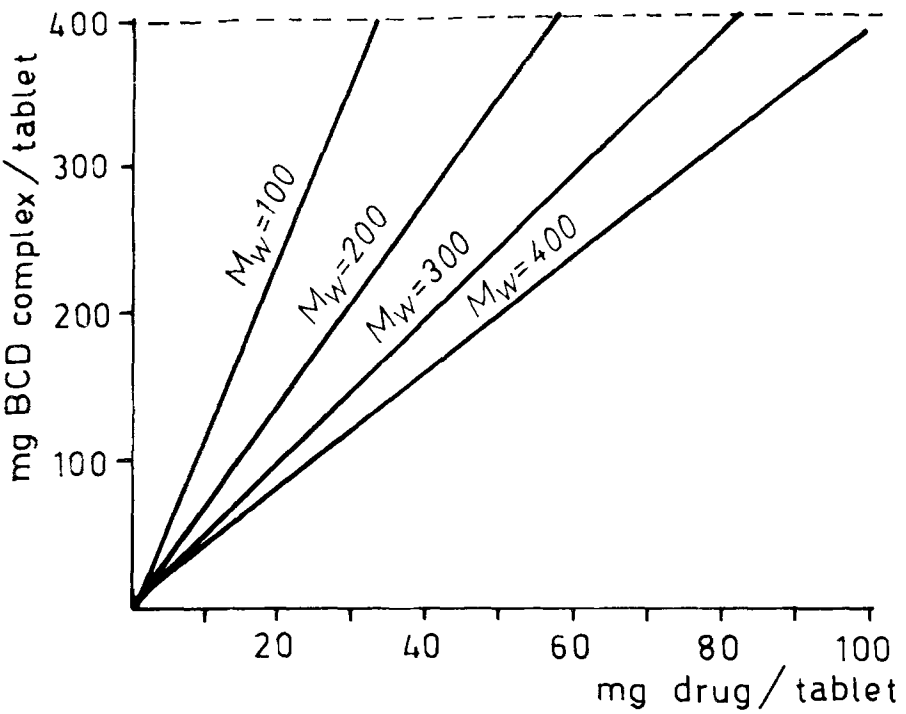

Fig.2. Correlation between dose of drug to be administered, amount of drug-complex to be tablet ed and molecular weight of drug; BCD = 1:1 complexes

5. DRUG DOSE AS LIMITING FACTOR

An unsurmountable limiting factor in selecting the drug for complexation is the dose of the complex that has to be administered orally. Fundamental requirement that the mass of a tablet should not exceed 500 mg.
Since the drugs to be complexed have molecular weights between 100-400, and cyclodextrins have rather large molecular weight (972, 1132, and 1297 for α-, β- and γ-cyclodextrins) 100 mg complex contains only about 5-25 mg active ingredient. (23).

Relatively small guest molecules sometimes show surprisingly unfavourable stoichiometry. E.g. vitamin K_3 (menadione, 2-methyl-naphtoquinone) needs 3 βCD molecules to form a stable, crystalline complex (24).
Menadione content of this complex is only 4,2-4,5 %, thus its practical utilization is not economic; γ-cyclodextrin however forms 1:1 crystalline complex with menadione (25).
If the single dose of a drug is not more than 25 mg then even a complex of 5 % active substance content can carry the necessary dose in a single tablet of 500 mg weight.
Thus, in the case of complex forming drugs, the relationship of the required dose and the molecular weight determines the feasibility of oral administration in cyclodextrin complexed form.
The dose imposed limits of drug complexation are illustrated in Fig.2. for 1:1 complexes.
Cyclodextrin drug complexes usually have 1:1, 2:1, or 3:2 stoichiometry but 1:2, 2:3, 3:1, 4:1 and 5:2 ratios have also been reported (26).

A 3000 I.U. D_3-vitamin tablet contains only 0,075 mg cholecalciferol, a Prostarmon-E tablet contains only 0,5 mg PGE_2; the active ingredient content of a nitroglycerin tablet is 0,5-4 mg, these and similar drugs are ideal for cyclodextrin complexation.

6. DISSOLUTION AND "SUPER SOLUBILITY"

The usual conventions of the pharmaceutical industry are apparently limiting the application of CDs in oral preparations to well defined crystalline complexes. The dissolution rate and the temporary formation of metastable supersaturated solutions however help to surpass these limits in certain cases.

The hydrophobic drugs being molecularly dispersed and enwrapped into capsules of molecular size (= CD) in a hydrophylic matrix, are rapidly dissolved in water. The rate of dissolution - expressed by a first order rate constant calculated from the time necessary to reach the half of the maximum attainable solubility - are by one order of magnitude higher than the rate of dissolution of

the non-complexed drug under identical conditions (similar grain size, temperature, agitation, etc.). This is important for the enhancement of bioavailability. There is however another very important, not yet duly appreciated consequence of this strongly accelerated dissolution; the concentration of the dissolved drug generally considerably exceeds its equilibrium solubility, a metastable supersaturated solution is formed. Therefore dissolution tests with complexed drugs results in uncommon dissolution profiles: an anomally high peak is observed in the first minutes on the dissolved substance vs. time curve, which later on decreases (Fig.3.). Generally the equilibrium solubility is higher for the complexed drug than for the non-complexed one, nevertheless the temporary "super solubility" of the drug is an important factor in the rapid absorption of the drug. Intravenous-like blood level curves were observed after oral administration of CD-complexes of poorly soluble drugs. (Fig.4.)

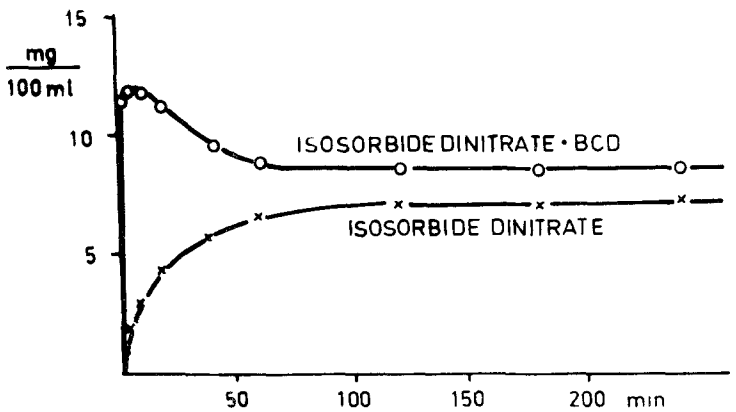

Fig.3. Dissolution of isosorbide dinitrate and its βCD-complex at 25 °C, 50 mg isosorbide dinitrate/ 50 ml, grain size less than 200 μm.

Enhanced dissolution rate and bioavailability were observed with drugs that could not have been converted into well-defined CD-complexes; a simple coprecipitate of a drug with CD (made e.g. by cooling their common solution) results in improved solubility properties. The mechanical mixture of drug and CD for the coprecipitate can not be substituted. In aqueous solution interaction can almost always be demonstrated between CD and the drug, with not-complexable drugs too! Appropriate fragments of molecules which are too large to be included into the CD-cavity- e.g. peptides (containing aromatic aminoacids), antibiotics, etc. - interact with CD; therefore rapidly cooling their common solution a coprecipitate is separated that

contains the drug in a very finely dispersed "micronized" state. On contacting again with water (gastric juice) the apolar-apolar interaction helps the rapid re-dissolution, and the accelerated absorption. Therefore for bioavailability enhancement the preparation of a real CD-complex is not always necessary, in special cases a "solid solution"-like coprecipitate is adequate to reach the desired effect.

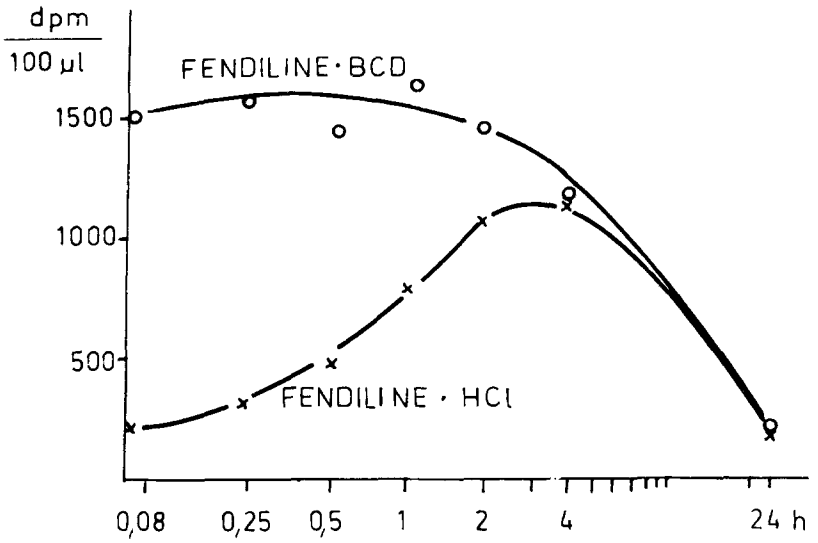

Fig.4. Blood radioactivity in rats after oral administration of identical dose of ^{14}C-labelled Fendiline-hidrochloride or Fendiline-βCD complex. (Fendiline = N-/phenylethyl/-3,3-diphenylpropylamine).

7. COMPLEX STABILITY AS LIMITING FACTOR

The differences in blood level curves obtained after the administration of free or complexed drug can be attributed to the different free drug concentrations in the gastrointestinal fluid controlled by the dissolution rate, the solubility and complex dissociation equilibrium.
Fig.5. is a simplified scheme that illustrates the significance of the dissociation equilibrium in determining the concentration of the free, dissolved drug.
The value of $F_{dissolved}$ determines the value of $F_{absorbed}$ i.e. the attainable blood level.

To find a correlation between complex stability constant and blood level the following considerations have been applied: (27).

a./ Only dissolved free drug molecules can be absorbed from the gastrointestinal tract and enter the circula-

tion.

b./ Cyclodextrin can not be absorbed either in free or in complex form.

c./ The mechanism of absorption and the rate constant of its first order kinetics is not modified by the presence of cyclodextrin.

d./ Since cyclodextrin can not enter the circulation it does not effect the elimination processes of the drug from the blood.

The amount of the free dissolved drug $F_{dissolved}$ depends on the stability constant determined at body temperature only by the CD, and the drug and the volume of the liquid phase. The correlation between ratio of dissolved to non-dissolved drug, volume and K_d at fixed parameters is illustrated by Fig.6. In computer simulation of blood-level curves keeping the pharmacokinetic and physicochemical parameters of the drug constant, varying only the stability constant of the complex, different blood level curves could be obtained. (Figure 7.). The height and the time necessary to attain the blood level peaks are listed in Table II.
As a consequence of the higher dissolution rates of the complexes the blood level curves reach their maxima in a shorter time after administration of the complex compared to the free drug.

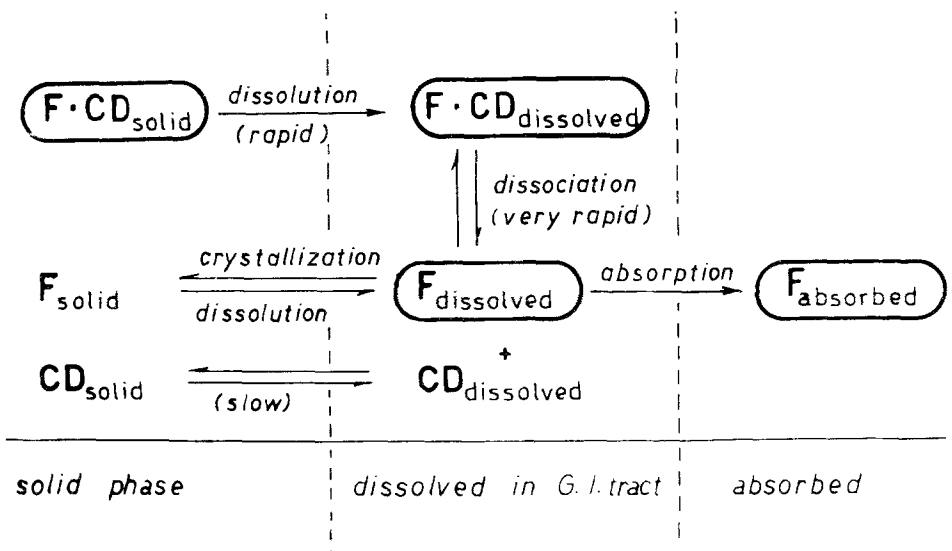

Fig.5. Schematic representation of the dissolution-dissociation- absorption pathway of an orally administered CD-complexed drug.

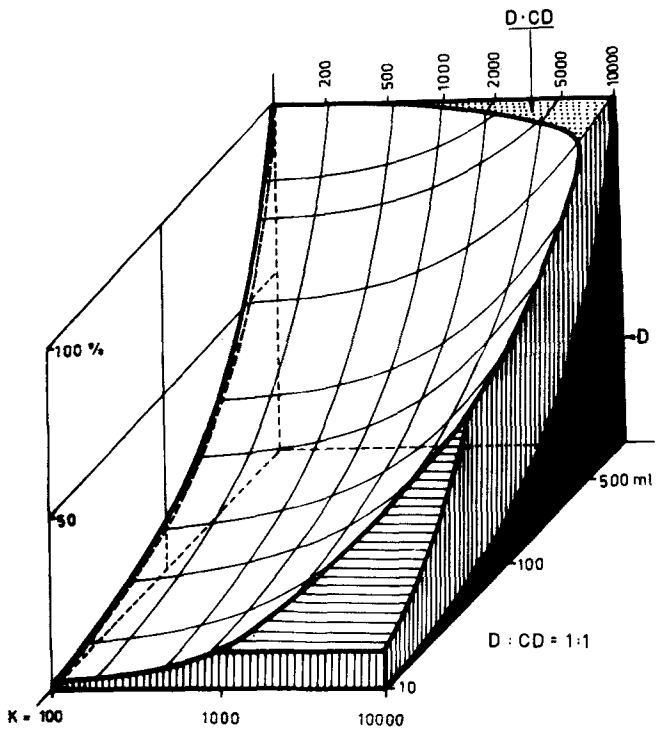

Fig.6. Correlation between complex dissociation constant, (100-10000) dissolution volume (10-1000 ml), and dissolved drug in % (free + complexed). Hypothetic solubility of the complex: 10^{-3} mol/l. Black area: free dissolved drug, vertically hatched area: dissolved complexed drug.

At low stability constants the degree of dissociation is high enough to ensure a high free drug concentration in the gastrointestinal fluid which results in a rapid increase in the blood level and high value of the peak. With increasing stability constant the degree of dissociation decreases, a lower free drug concentration can be reached in the gastrointestinal fluid. The blood level peak will be shifted towards higher values on the time scale and a significant decrease in the peak height is observed, in all cases however enhanced biological response compared to the free drug can be expected.
Administering excess cyclodextrin together with the cyclodextrin complex of the drug the dissociation equilibria can be shifted towards a higher molar ratio of complexed drug in the gastrointestinal fluid. These changes have great influence on the shape and peak-height of the blood level curves, as can be seen on Figure 8. The molar ratio values in Table III. represent the total initial

drug: cyclodextrin ratio in the gastrointestinal. With lower stability constants the amount of excess cyclodextrin enhances the concentration of the free dissolved drug, thus a higher blood level will be attained in a shorter time. At higher stability constants, however, the dissociation is supressed remarkably on addition of cyclodextrin in excess, and a decrease in the height of the blood level peak as well as an elongation of the time, necessary to reach the peak can be observed. In extreme cases a real retardation can be achieved (27).

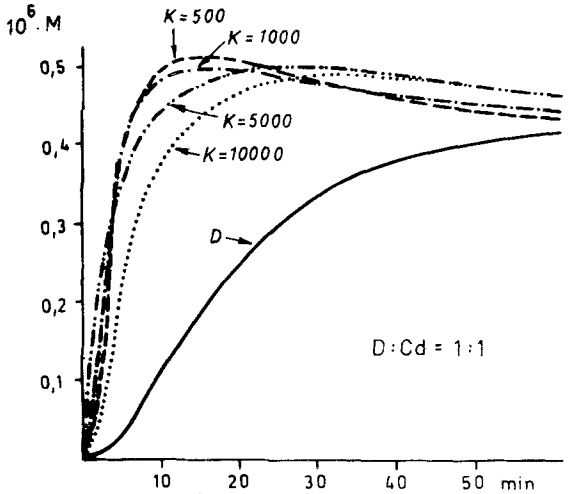

Fig.7. Theoretical blood level curves obtained after oral administration of free drug or its cyclodextrin complexes with different stability constants.

Table II. Correlation between the complex stability constant K_d and the peak of the computer simulated blood level curves (27).

K_d litre mole^{-1}	Blood level peak height M	time min
Free drug	$0,412\ 10^{-6}$	94
500	$0,509\ 10^{-6}$	14
1000	$0,497\ 10^{-6}$	16
5000	$0,490\ 10^{-6}$	22
10000	$0,483\ 10^{-6}$	30

8. CD DERIVATIVES AND POLYMERS

Derivatization or polymerization of CDs open new fields, widening considerably the application possibilities limited by the factors mentioned in the previous points.

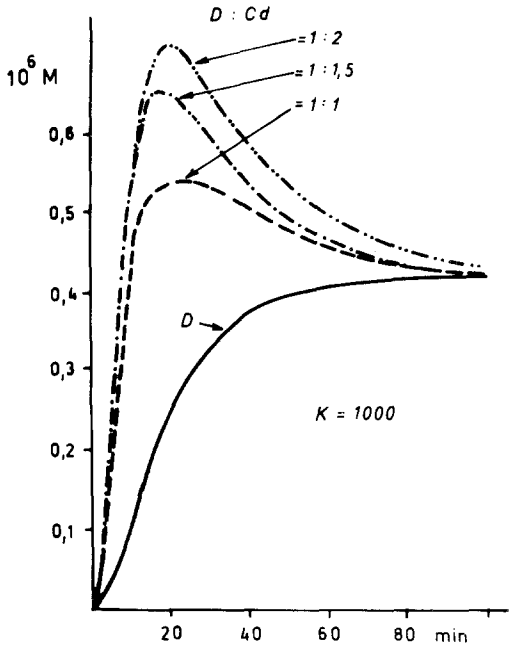

Fig.8. Theoretical blood level curves after administering free drug or its cyclodextrin complex with solid cyclodextrin in excess (stability constant of the complex is 1000 litre mole ad^{-1}).

Table III. Effect of cyclodextrin excess on the peak of the computer simulated blood level curves. (27).

K_d litre $mole^{-1}$	Drug: βCD molar ratio	Blood level height M	peak time min
free drug	1:0	$0,412\ 10^{-6}$	94
1000	1:1	$0,538\ 10^{-6}$	23
	1:1,5	$0,652\ 10^{-6}$	18
	1:2	$0,708\ 10^{-6}$	18
5000	1:1	$0,500\ 10^{-6}$	22
	1:2	$0,492\ 10^{-6}$	35
10000	1:1	$0,483\ 10^{-6}$	30
	1:2	$0,384\ 10^{-6}$	42

Promising results have been reported on three groups of these substances recently

- Methylated CDs (mainly heptakis-2,6-di- and heptakis-2,3,6-tri-O-methyl- βCD, viz DIMEB and TRIMEB resp.) and

- soluble CD polymers (mainly crosslinked βCD, with a molecular weight less than 10000), all of them characterized by a solubilizing effect much higher than that of the parent CDs, moreover (28,29)

- insoluble, rapidly swelling crosslinked βCD-polymer which acts as a tablet disintegrating agent (7,8). A few percent of this substance incorporated into the tablets reduces drastically the time of tablet-disintegration on contacting with water.

These substances have not been studied yet thoroughly and produced on industrial scale, no competent toxicological studies have yet been published, however, application of one or more of them in oral drug preparation is expected in the future.

9. LEGISLATION

Application of a new substance in drugs formerly not consumed by humans is subject to long-lasting legislation procedure. The alleged high toxicity of orally administered βCD published in 1957 (30) had been refuted by detailed six months toxicity studies on rats and dogs (10,11). Based on competent toxicological documentation βCD-flavour complexes (31) are already legislated and marketed in Hungary. Permission has been given to carry out preliminary human experiments with βCD, and particularly with βCD-indometacine (32) in Hungary, having performed six months animal toxicity studies with this latter product, too. Probably, the first drug complexes will be considered as new compounds by the Health Authorities, therefore long lasting toxicity studies will be required.

CDs modify the bioavailability of drugs only. Recognizing that orally administered CD-complexes dissociate in the gastro-intestinal tract before absorption, and it is the drug only that is absorbed, it is hoped that after favourable experiences with the first fully documented drugs, only the pharmakokinetic and clinical trials will be required by the Health Authorities without the complete pre-clinical studies.
Prerequisition is of course the usual documentation of toxicological and metabolic studies on the corresponding CD.

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