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Review Article

Cyclodextrin Complexed Generic Drugs are Generally not Bio-equivalent with the Reference Products: Therefore the Increase in Number of Marketed Drug/ Cyclodextrin Formulations is so Slow

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Abstract

Taking into consideration the numerous advantages of the cyclodextrin (CD) complexation of drugs, it is not evident why are not approved and marketed many more long known (generic) drugs in CD-complexed form. The price and approval status of the CDs is not any more a serious restricting factor for their use. The crucial problem is, that for approval of any new formulation of a known (generic) drug a bioequivalence test has to be performed. A CD-formulated drug is practically never bioequivalent with the reference product (the old, earlier approved formulation), but significantly better, results in improved solubility, faster and more complete absorption, in enhanced biological activity, etc. The average increase of AUC values of 35 orally (or sublingually) administered drug/CD complexes (as compared with the plain drug, or its classical formulation, of course at identical drug doses) in different species (human, rat, rabbit, dog, pig) is 1.81 ± 0.53 fold, the average increase in c_{max} of 26 drugs is 1.71 ± 0.47 fold, attained in an 0.55-fold shorter time after oral administration. The CD-formulated drug will not be a simple generic but a 'super generic' drug[1]. In this case the authorities are requesting the repetition of the largest part of the long lasting and very costly clinical studies. This is why the costs of development will be nearly as high as in case of an original drug, nevertheless its market generally will be considerably narrower. If it is acceptable that, the absorption of a drug (in reduced dose!) from its CD-complex is faster than from its original formulation (lower T_{max}) then a simple Clinical I. phase should have to be satisfying for the regulatory authorities. All deviation between the pharmacological effect of the original formulation and the CD-formulated drug is resulted by the quicker and more complete absorption of the last one. No any further significant change in pharmacodynamics or therapeutic effect of the drug might arise in consequence of the CD complexation.

Introduction

Difficult to find a drug which has not yet been studied for complexability with cyclodextrins (CDs), and almost in all cases some significant advantage has been reported.

Altogether more than 5000 papers and patents described the improvement of practically all known problematic drugs by CD complexation. From 1995 to middle of 2003 the monthly newsletter Cyclodextrin News [1] published the abstracts of 1741 drug/CD related papers and of 715 patents/applications for 515 drug actives. Generally CD complexation of a poorly soluble drug (the absolute majority of orally administered drugs) results in improved (accelerated, enhanced) dissolution rate, solubility and bioavailability (Figure 1).

The concerns about eventual toxic effects of CDs are largely eliminated, the industrially produced and available CDs are involved into the Pharmacopoeias [6].

The bioavailability of a drug even in the same person might be very different, depending on conditions of the absorption, for example in case of widely differing gastric pH values. Ketoconazole at a gastric pH of 6.5 (for example after swallowing an antacid, or a proton pump inhibitor, like omeprazole) will not be practically absorbed. From its βCD/tartaric acid ter-

† Deceased.

[1] When the patents and other exclusivities for an original drug are expired (both for the chemical entity as well as for its approved formulation), a clone of this drug (generally produced and marketed by other companies) is called a ''generic drug'' (or commodity generic). It must be a perfect copy of the original, must contain the same active ingredient (amount, dose unit), formulation (tablet or injectable or liquid, etc.), containing the same vehicles, must perform identical dissolution, stability, biological absorption and effectivity.

If the formulation (other ingredients) or the route of delivery (e.g. injection instead of tablet) are different, then this drug is not a simple (generic) but is called a 'specialty generic' or 'super generic'.

If a drug (a well known, long used one) in form of a CD-complex is incorporated into a new formulation, it is not a generic. It seems to be evident to consider a CD-complex containing drug formulation as a 'super generic' – except of course those cases when the drug substance is itself an original drug.

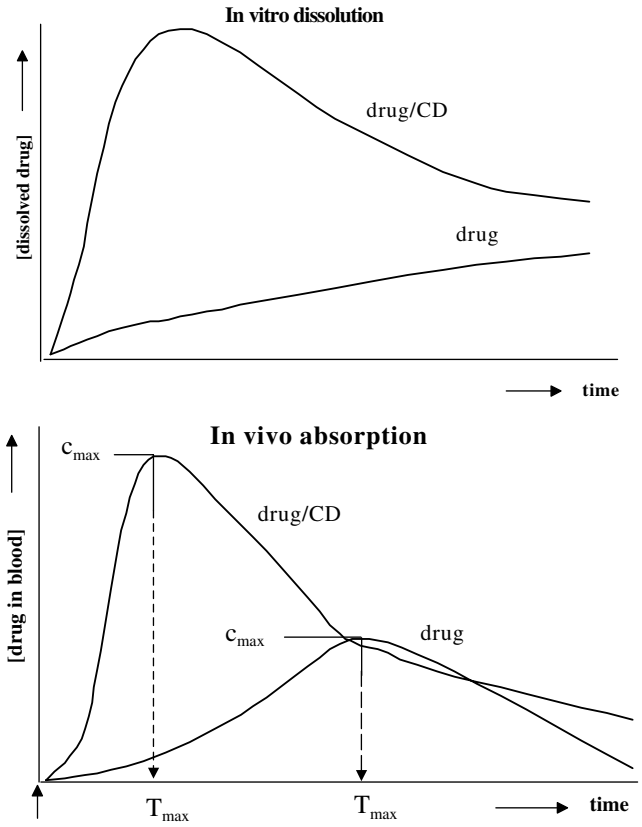

Figure 1. The bioavailability of a poorly soluble drug will be improved by CD complexation, because it, (1) will be dissolved faster; (2) will attain a higher solubility; (3) will be absorbed faster: the time between administration and onset of biological effect (e.g. pain-reduction) will be shorter (shorter T_{max}); (4) will result in a more complete absorption (higher AUC).

nary complex even at this extreme gastric pH a quite acceptable absorption will be attained. Ketoconazole AUC values in rabbits at a gastric pH of 6.5 (after an omeprazole treatment) for identical doses of plain ketoconazole, ketoconazole/βCD binary and ketoconazole/βCD/tartaric acid ternary complexes were 0.053, 0.651 and 3.858 μg h/ml, respectively. The binary complexation resulted in a 12-fold, the ternary complexation in a 73-fold enhancement of bioavailability.

Advantageous effect of CDs, or when is it worth to formulate a drug with CDs? [2–4]

At formulating drug substances to pharmaceutical products frequently arise difficulties, like:

- the drug is poorly soluble its dissolution from the oral formulation is slow, limited, pH dependent etc.
  – poor bioavailability
- the drug is soluble only in such organic solvents, which can not be injected
  – no injectable or ophthalmic (eye drop) aqueous solution can be prepared
- the drug is irritating to mucous membranes, tissues or skin
  – its utility is restricted
- the drug is sensitive to destructing factors, like oxygen, light, water, etc.
  – limited shelf-life (or can not be launched at the market at all)
- the drug is a liquid, volatile and/or sublimable, bad smelling or a very hygroscopic solid
  – no stable solid preparation can be produced
- the drug is very bitter, adstringent tasting
  – no pediatric formulations (solution or suspension), or chewable tablet can be produced
- the drug is difficultly formulable: extremely low doses, sticky, lipid like consistence, non-soluble in water, or incompatible with other components of the formulation
  – problematic dosing and content uniformity
- etc.

The molecular encapsulation of the drug, i.e. its inclusion complexation with appropriately selected cyclodextrin in many cases bring the solution to such problems.

The primary consequences of the cyclodextrin complexation of drugs – and relevant, typical examples are as follows:

- the *rate of dissolution* and the *solubility limit* increases (frequently by a factor of 10^1–10^3), resulting in an accelerated and significantly improved bioavailability. It means a reduction of T_{max}, an increase of c_{max} and AUC. (Figure 1.) For example these parameters for granulated nimesulide and granulated nimesulide/β-cyclodextrin complex (marketed as MESULIDE FAST) are: the T_{max} 2.17 *versus* 1.00 h, the c_{max} 4.69 *versus* 4.95 $\mu g \times ml^{-1}$, and the AUC (0–24 h) 17.32 *versus* 38.42 μg h/ml.
- the solubility of Itraconazol is so poor that to prepare aqueous *injectable* solution is hopeless. Formulating it with hydroxypropyl β-cyclodextrin both a liquid oral formulation as well as an injectable solutions are produced, marketed as SPORANOX.
- the *adstringent*, *irritating effect* of Nicotine excludes its direct consumption, e.g. in the form of a sublingual tablet or a chewing gum, but in the form of Nicotine/β-cyclodextrin complex the mucous membrane (the taste buds in the oral cavity) can not get into direct contact with the Nicotine, because it is enwrapped molecularly into the cyclodextrin capsules. This is the essence of the sublingual tablet for smoking cessation: NICORETTE MICROTAB contains the Nicotine in form of β-cyclodextrin complex.
- many compounds, like benzaldehyde, cinnamaldehyde, lipid soluble vitamins, aroma substances are prone to rapid *loss*, mainly from solid formulations, *through oxidation volatilization, polymerization.*

Powder aroma formulation, which contain cyclodextrin complexed flavor components are produced, marketed, e.g. lemon peel oil is fully destroyed by atmospheric oxygen within 2 days when mixed with any excipient powder, but remains fully stable without any extra protection for years, when complexed with β-cyclodextrin. The flavor will be released from the complex only when dissolved in water or saliva etc. Such cyclodextrin based powder aromas are produced, and marketed in countries like France, Japan, Hungary, etc.

- such ingredients as garlic oil – the active component of a popular paramedical product in several countries- are *very bad smelling*, and lost their active ingredient content rapidly through disproportionation of the allylsulfides to allylpolysulfides, decomposition of the ajoen to inactive compounds, and by volatilization. Cyclodextrin complexation is the perfect solution of the problem. The very first cyclodextrin-containing drug that got the approval form the German Health Authorities was a garlic oil/β-cyclodextrin complex containing tablet, marketed under the names XUND and TEGRA.
- the dextrometorphan bromide is *utterly bitter* – a typically pediatric drug, i.e. administrable only as a 'spoon medicine', as solution or suspension. Its very bitter taste can be reduced to a level, which then can be covered by the usual taste-masking sweetening-flavoring compositions. Cetirizine is a bitter anti-allergic drug. When formulated with β-cyclodextrin the masking of the bitter taste is so successful, that a chewable tablet can be produced from it. Ibuprofen – also a bitter drug- in cyclodextrin complexed form is appropriate for production of a sparkling tablet (or powder in sachet) formulation which is devoid of the bitter taste.
- a typically difficulty formulable drug is for example the *very oxygen sensitive, poorly soluble* unsaturated cyclic hydroxy fatty acid derivative Prostaglandin E_1. Its dose is only 20 μg/vial, after dissolving it is injected or further diluted for infusion. One freeze-dried vial of the marketed product (PROSTAVASIN, EDEX, VIRIDAL) contains besides the 20 μg PGE_1 also 646 μg α-cyclodextrin, which stabilizes, and solubilizes the Prostaglandin. The sublingual PROSTARMON tablet contains 0.5 mg Prostaglandin E_2, complexed with β-cyclodextrin.

The Table 1. illustrates the steadily increasing use of cyclodextrins in the drug formulation.

Taking into the consideration all the mentioned advantageous effects of CDs on drugs, as well as the very large number of promising published results, it is not obvious why are not produced and marketed much more drug/CD formulations?

To get an unanimous answer three groups of factors

– which restrict the use of CDs in drug formulations – have to be scrutinized:
  – the technical limits of drug/CD complexation
  – the legal aspects: authority approvals
  – the economical feasibility of the development of a drug/CD complex.

The technical limits of the drug/CD complexation [4, 5]

Speaking only of the numerous advantages of drug/CD complexation can be widely misleading, because there are just as many limiting factors, which restrict the applicability of CDs to certain types of drugs. Not all drugs are suitable for CD-complexation. Many compounds cannot be complexed, or complexation results in no essential advantages. Inorganic compounds generally are not suitable for CD-complexation. Exceptions are non-dissociated acids (HCl, HI, H_3PO_4, etc.) halogens, gases; (CO_2, C_2H_4, Kr, Xe, etc.). Inorganic salts such as KCl, Fe-salts, etc. cannot be inclusion complexed.

General preconditions – (not without exceptions!) – to form a medicinally useful CD-complex of a drug molecule include characteristics such as

– more than 5 atoms (C, P, S, N) form the skeleton of the drug molecule;
– a solubility in water is less than 10 mg/ml;
– a melting point temperature of the substance is below 250 °C, (otherwise the cohesive forces between its molecules are too strong);
– the guest molecule consists of less than 5 condensed rings; and
– a molecular weight between 100 and 400, (with smaller molecules the drug content of the complex is too low, large molecules do not fit the CD-cavity of one CD unit).

Strongly hydrophilic, too small or too large molecules such as peptides, proteins, enzymes, sugars, polysaccharides, etc. generally cannot be complexed. Nevertheless, when large water soluble molecules contain appropriate complex forming side-chains – e.g. an aromatic amino-acid in a polypeptide - they will react with CDs in aqueous solutions, resulting in modified solubility and stability (e.g. the stability of an aqueous solution of insulin, or many other peptides, proteins, hormones, enzymes is significantly improved in presence of an appropriate CD).

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

Table 1. Approved and Marketed Drug/CD Formulations (2003)

Drug/cyclodextrin	Trade name	Indication	Formulation	Company/country
PGE_2/βCD	Prostarmon E	Induction of labour	Sublingual tablet	Ono, Japan
PGE_1/αCD	Prostavasin	Chronic arterial occlusive disease erectile disfuction	Intraarterial inj. Intracavern inj.	Ono, Japan Schwarz, Germany
PGE_1/αCD 500 μg/amp.	Prostandin 500	Controlled hypotension during surgery	Infusion	Ono, Japan
OP-1206/γCD	Opalmon	Buerger's disease	Tablet	Ono, Japan
Piroxicam/βCD	Cicladol, Brexin	Antiinflammatory, analgesic	Tablet, sachet and suppository	Masterpharma, Chiesi, Italy
Garlic oil/βCD	Xund, Tegra, Allidex, Garlessence	Antiartherosclerotic	Dragees	Bipharm, Hermes, Germany Pharmafontana, H, CTD, USA
Benexate/βCD	Ulgut, Lonmiel	Antiulcerant	Capsules	Teikoku, Japan, Shionogi, Japan
Iodine/βCD	Mena-Gargle	Throat disinfectant	Gargling	Kyushin, Japan
Dexamethasone, Glyteer/βCD	Glymesason	Analgesic, antiinflammatory	Ointment	Fujinaga, Japan
Nitroglycerin/βCD	Nitropen	Coronary dilator	Sublingual tablet	Nippon Kayaku, Japan.
Cefotiam-hexetil/αCD	Pansporin T	Antibiotics	Tablet	Takeda, Japan
Cephalosporin (ME 1207)/βCD	Meiact	Antibiotics	Tablet	Meiji Seika, Japan.
Tiaprofenic acid/βCD	Surgamyl	Analgesic	Tablet	Roussel-Maestrelli, Italy
Diphenhydramine.HCl chlortheophylline + βCD	Stada-Travel	Travel sickness	Chewing tablet	Stada, Germany
Chlordiazepoxide/βCD	Transillium	Tranquilizer	Tablet	Gador, Argentina
Piroxicam/βCD	Flogene	Antiinflammatory, analgesic for pediatric use	Liquid	Aché, Brasil
Hydrocortisone/HPβCD	Dexacort	Mouth wash against aphta, gingivitis, etc.	Liquid	Island
Itraconazole/HPβCD	Sporanox	Esophageal candidiosis	Liquid	Janssen, Belgium
Cloramphenicol/methyl βCD	Clorocil	Eye drop, antibiotic agent	Liquid	Oftalder, Portugal
Cisapride/βCD	Coordinax Prepulsid	Gastrointestinal mobility stimulant	Rectal suppository	Janssen, Belgium
Nimesulide/βCD	Mesulid Fast Nimedex	Non-steroid antiinflammatory	Oral sachet	Novartis (LPB), Italy
Ziprasidone mesylate/sulphobutyl βCD	Zeldox, Geodon	Antischizophenic	i.m. inj.	Pfizer, USA
Nicotine/βCD	Nicorette Nicogum		Subligual tablet chewing gum	Pharmacia Upjohn, Sveden, Pierre Fabre, France
Dextromethorphan/βCD	Rynathisol	Antitussive		Synthelabo, Italy
Cetirizine/βCD	Cetirizin	Antiallergic	Chewing tablet	Losan Pharma, Germany
Voriconazole/sulfobutyl-βCD	VFEND®	Antimycotic	i.v. inj.	Pfizer, USA
Mitomycin/HPβCD	MitoExtra Mitozytrex	Antiinflammatory	Infusion	Novartis, Switzerland
Diclofenac Na/HPγCD	Voltaren ophtha	Non-steroid antiinflammatory	Eye drop	Novartis, Switzerland
Omeprazole/βCD	Omebeta	Proton pump inhibitor	Tablet	Betapharm, Germany
Tc-99 Teboroxime/HPγCD	Cardiotec	Radioactive imaging agent	i.v. inj.	Bracco, USA
17-β-Estradiol/MeβCD	Aerodiol	Nasal pray	Liquid	Servier, France

a single tablet of 500 mg weight, otherwise the possibility of a powder sachet or sparkling-tablet formulation has to be taken into consideration. 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 CD complexed form.

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 CD complexation, but even the 20 mg piroxicam containing BREXIN tablet is a widely marketed successful product.

If the K_a stability constant of a complex is low ($< 10^2\,mol^{-1}$) the existence of the complex can be demonstrated in solution, but on removing the water the obtained product is often only a mixture (e.g. a coprecipitate) which contains the host and guest in a very fine microcrystalline dispersion (shown by its X-ray diffraction pattern). By removing the water an important component of the driving force for complexation is eliminated: the repulsive forces between water and the hydrophobic drug. Upon contacting with water the complex formation is an instantaneous process, i.e. in solution the guest is really included in the CD-cavity, and the dissociation-association equilibrium (depending on concentration of host and guest and the temperature) is reached within seconds.

In such cases the guest is not protected against external destructive factors, like oxygen or humidity, but if the guest is stable enough, and only its low solubility is problematic, such intimate mixtures can be utilized for preparation, e.g. solid formulations of improved bioavailability. If, however, the guest is unstable then only full complexation, even in the anhydrous state can be of use.

The 'approval barrier' for consumption of CDs

The first publication (52) on toxicity of CDs was simply deterrent. D. French – otherwise one of the most outstanding personalities of the CD research – published in 1957 the first observation – without ever publishing the experimental details...

> *In unpublished attempts to investigate the ability of animals to utilize Schardinger dextrins, B.H. Thomas and D. French fed rats a diet in which a part of the carbohydrate was supplied by highly purified β-dextrin. The animals refused to eat the test diet except in very small quantities and within a week all animals on the ration were dead. Post-mortem examination did not reveal the cause of death.*

Nothing has been published about the analysis of the cyclodextrin, which was fed to the rats: organic solvent content? other impurities? percentage of cyclodextrin in the diet? Such fundamental data as the number of treated rats, the existence of a control group or information on dosing have never been available. It is well known that rats have an extremely sensitive sense of smell. They detect toxic substances by smell, and refuse to eat such substances. Since then, thousands of rats have been fed cyclodextrins in rather large doses. Refusal of a CD-containing diet has never been observed [6]. This fact allows one to conclude that there was a rather high level of toxic organic solvent impurity in French's cyclodextrin.

During the following 25 years, until encouraging results of adequate toxicological studies became available, these few lines, cited above, deterred many scientists from developing CD-containing products for human use.

αCD (Alfadex)

Pharmeuropa Vol. 10. No. 2, pp. 237–239 (1998) published the draft for the αCD monograph (CD News 12/11,1998). The final monograph is published in the supplement 2001 of European Pharmacopoeia (CD News 15/2, 2001).

The FAO/WHO status of αCD is disclosed by the 57th report of the Joint FAO/WHO Expert Committee on Food Additives (WHO Techn. Rep. series No. 909, pp. 40–42, CD-News 17/1, 2003).

The report summarized the submitted toxicological data and based on the expected consumption data classified the αCD as food additive.

The predicted mean intake of α-cyclodextrin by consumers, based on individual dietary records for 1994–1998 in the USA the proposed maximum levels of use in a variety of foods, would be 1.7 g/day (28 mg/kg of body weight per day) for the whole population and 1.6 g/day (87 mg/kg of body weight per day) for children aged 2–6 years.

The Committee concluded that there was enought information to allocate αCD an ADI 'not specified'[2].

βCD (Betadex)

In Japan the cyclodextrins were declared in 1978 to be enzymatically modified starch ad therefore their use in food products has been permitted. Both α and βCD are included in the Japanese Pharmaceutical Excipients Compendium since 1994.

In Hungary the Ministry of Health approved the use of βCD for stabilization of flavors (flavors/βCD complexes) in 1983. The French authorities granted in 1986 a limited approval for the use of CD as flavor carrier (support d'arôme). In the Netherlands, the Ministry of Health officially declared βCD to be an enzymatically modified starch (1986) and, as such, applicable in all those food products in which, according to the already existing vertical regulations (positive lists of ingredients) the use of enzymatically modified starch is permitted.

[2]ADI "not specified" is used to refer to a food substance of very low toxicity which, on the basis of the available data (chemical, biochemical, toxicological and other) and the total dietary intake of the substance arising from its use at the levels necessary to achieve the desired effect and from its acceptable background levels in food, does not, in the opinion of the Committee, represent a hazard to health.

The corresponding authorities of the two Benelux countries (Ministerie van Volksgezondheid en van het Gezin in Belgium and Laboratorie National de Santé in Luxemburg) followed this act (in 1986) with identical decisions. In March 1987 the Spanish authorities also approved the utilization of βCD in foods. In Denmark, βCD is approved in chewing gum. The German Bundesgesundheitsamt considers βCD to be a nontoxic auxiliary substance in drug formulations. However, in every drug the role and effect of CD has to be documented, and approved as a new drug. In Italy the piroxicam-βCD complex was approved in 1988. βCD is described in the Handbook of Pharmaceutical excipients since 1994.

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) allowed an 0–5 mg/bw kg ADI value for βCD in 1995. The USP National Formulary XVII (7th Supplement pp. 3174–3175) published the draft of an official monograph for βCD, and the USP-NF XVIII pp. 2220–2221 (1995) published the final monograph (see also UPS XXV, pp. 2515).

In Nov. 1997 the US Federal Register announced that βCD is GRAS (Generally Recognised as Safe). (CD-News, 16/2, 2002)

In 2002 the Environmental Protection Agency has received a pesticide petition from Wacker Biochem. Corp. to establish an exemption from the requirement of tolerance for αCD, βCD and γCD in or on raw agricultural commodities resulting from the use of α-, β-, and γCD as ingredients in formulations.

A new monograph for βCD has been published in the First Supplement to the Fourth Edition of the Food Chemicals Codex. βCD is published in Annex V of the Official Journal of the European Community-Food Additives as a carrier only for food additives up to 1 g/kg food.

The US Federal Register Vol. 61, No. 161, (Sept. 20, 1996) as well as the European Pharmacopoeia (3rd Edition, 1997) (CD-News 12/6, 1998) contains the monograph on βCD.

γCD

Detailed and reassuring toxicity data on γCD have been published by the Regulatory Tox. & Pharmacol. Vol. 27, 1998 on oral toxicity studies in dogs and rats, embriotoxicity/teratogenicity studies in rats and rabbits, and on absorption, disposition, metabolism and excretion of ^{14}C labeled γCD.

The γCD was well tolerated up to 20% of the diet (corresponding to 11–12 g/bw kg), no any sign of toxicity has been observed. Its metabolism resembles closely to that of starch and linear dextrins (CD-News, 13/2,1999).

Earlier acute oral toxicity examinations of γCD showed no mortality or toxic effects at the highest dose tested, 16 g/kg bw/day in mice, and 8 g/kg bw/day in rats. Intravenously or subcutaneously administered γCD also was well tolerated. The iv. injected γCD had a LD_{50} of approx. 10 g/kg bw. in mice and > 3.75 g/kg bw in rats (CD-News, 15/4, 2001).

γCD is available in the USA as a Generally Recognised As Safe (GRAS) dietary ingredient (GRAS Notice No. GRN 000046). γCD is being considered for approval under EU Novel Food regulations. It is considered to be food in Japan and hence explicit approval is not required. There are no Codex standards in relation to γCD.

Based on JECFA's safety assessment of γCD for certain specified uses, γCD was considered to be a substance of low toxicity which did not represent a hazard to human health. Also the Food Standards Australia and New Zealand agrees with the JECFA allocation of an ADI 'not specified' and concluded that γCD is safe for human consumption at the proposed levels (CD-News, 17/10, 2003).

Hydroxypropyl βCD

HPβCD was the first CD derivative which has been developed directly as a parenteral drug carrier. The commercially available HPβCD is a mixture of a very large number of isomers and homologues. The common characterizing parameter is the average number of hydroxypropyl groups attached to one CD unit (degree of substitution = DS), but depending on the reaction conditions even at identical DS in HPβCD samples of different origin the actual product distribution might be quite different. The homogeneous, crystalline mono-2-hydroxypropyl-βCD is only poorly soluble – the practically infinite solubility of the commercial product is due to the extreme heterogeneity of the product.

The most important quality requirements for a HPβCD dedicated for use as parenteral drug carrier are the possible lowest content of non-substituted βCD and of the endotoxin content.

Safety, pharmacokinetic and pharmacodynamic studies both in animals and in humans have been performed [7].

The Pharmacopoeial Forum Vol. 28(4), (July–August 2002) published a preview on the monograph for hydroxypropyl βCD (= hydroxypropyl–betadex) (CD-News 16/10, 2002).

For long time the HPβCD has been considered as a fully innocuous substance, but chronic treatment of animals with rather high doses revealed, that HPβCD causes body weight to decrease, plasma chemistries to change and the spleen to become hyperplasic.

Sulfobutyl-βCD (SBE)

The sulfobutyl ethers of βCD are very well soluble in water, are good solubilizers for many poorly soluble drugs, and according to our present knowledge, the less

toxic among all CD derivatives when applied as parenteral drug carrier.

The most frequently used βCD sulfobutyl ether contains 7 sulfobutyl groups/βCD unit. The trade name of this product is CAPTISOL®. (CD-News 13/5, 1999)

The first Captisol-based product was approved in September 2000 in Sweden. The approved product is Pfizer's rapid-acting intramuscular antipsychotic ziprasidone, which is marketed in the USA as GEODON. Pfizer's intravenously delivered antifungal Voriconazole (VFEND) was approved in March 2002 Europe and July 2002 in the USA.

Captisol is being utilized in formulation development in over 170 pharma and biotech companies world wide. 25 companies are using Captisol products to move compounds through preclinical safety evaluations. Captisol has been developed for use in parenteral formulations. (CYCLOPEDIA, a quarterly information letter of CyDex, Inc. 4/1, 2001) For oral formulations the other CDs and CD derivatives also can be used, at much lower prices.

Methylated CDs

The methylated CDs are the presently known most effective solubilizers for poorly soluble substances. Methylated CDs have two main types: the so-called RAMEB (randomly-methylated βCD, available with DS = 1,8, i.e. 1.8 methyl group is attached in average to one CD ring unit). The RAMEB is an amorphous, infinitely soluble, hygroscopic substance.

The so called DIMEB is available in three different qualities, as DIMEB-50, DIMEB-80, and DIMEB-95. All three products are crystalline products, very well soluble in cold water, but crystallizes very rapidly at elevated temperature which depends on the homogeneity of the product. The DIMEB-50 contains at least 50% heptakis (2,6-di-O-methyl)βCD, the DIMEB-80 contains at least 80%, and the DIMEB-95 contains at least 95% of this isomer, i.e. < 5% (or even less), hardly detectable traces of isomers or homologues.

Because the methylated CDs have the highest affinity toward the most lipophylic components of the cell-membranes (cholesterol and phospholipids) they have the highest haemolysing capacity. The haemolysis is, however, a typically concentration dependent phenomena, at appropriately low concentration not any traces of haemolyis can be observed. At very low concentration the CDs generally exert stabilizing effect on the cell-membranes, only at higher concentration takes place the desorganization of the membranes by sequestering the mentioned lipid components. Therefore, if a very poorly soluble, highly active drug has to be administered in extremely low doses – for example a radioactive marker - its solubilization can be performed with DIMEB. The DIMEB is not accumulated in the body, is excreted rather rapidly through the kidneys.

The economical feasibility (or the bioequivalence paradox)

When an *original drug* (which previously never has been approved and consumed) is developed (and patented) in form of a CD complex, i.e. all preclinical and clinical studies are performed with the drug/CD complex (formulation), then no reference product exists for a comparative bioequivalence test. In this case all preclinical studies (stability, toxicology, pharmacology) and all clinical studies – i.e. the usual long lasting and very expensive procedure has to be done resulting in an original, patent protected drug. The originator company in 8–12 years spends hundreds of millions of USD on development and marketing but then – till expiry of the patent enjoys the exclusivity on the market for at least 8–12 years. (Figure 2). Being alone on the market a successful drug brings an extra profit which covers the costs of the development of a series of other new drugs.

The situation is quite different in case of a *generic drug* (Figure 2).Years before the expiry of the patent of an original drug a number of generic companies start to copy the original drug. Their goal: to develop a generic formulation of the original drug, which is bioequivalent with the original one, and to launch it on the market immediately, as soon as the patent expires. The costs of a bioequivalence study are relatively modest, the tests take not more than a few weeks. All development process takes no more than 3–4 years, therefore shortly after the expiry of the originator's patent the same drug under various names are marketed by a series (5–10 or more) generic companies, most of them is present on the market only in one country. The originally high price drops to about 1/3 of the original one. The originator can keep only about half of its earlier exclusive market the other half is divided between 5, 10 or even more generic companies. Consequently their profit will be only a few percent of that of the originator's one, because their market share will be only 5–10%, at the price reduced to about 1/3 of the original one. Nevertheless it is generally a rewarding business, because their development and marketing costs reaches only a small fragment of the total cost of the originator, mainly due to avoiding the most costly phase of the development – the clinical trials.

New drug formulation, superior in its performance when compared to other products which contain the same known active ingredient (drug) (which is not patent protected anymore, eventually never has been, being a long known substance) is called a *super generic*. Most drug/CD complexes – studied and the reported in the literature – belong to these super generic drugs.

Their active ingredient is generally known, (available, approved, may be used and marketed without any restriction in the known, accepted formulation) or the patent for the drug just expired (or near to expiry). The formulation, the chemical-analytical, preclinical works-including toxicological, stability and bioequivalence tests need just as much time and costs as the develop-

ment of a generic formulation. But in most cases the bioequivalence tests lead to Janus-faced results: the performance of the super generic (CD)-formulation is too good! – because blood level shows shorter T_{max}, higher c_{max}, larger AUC values (Table 2). Performing also pharmacodynamic studies, the drug shows higher

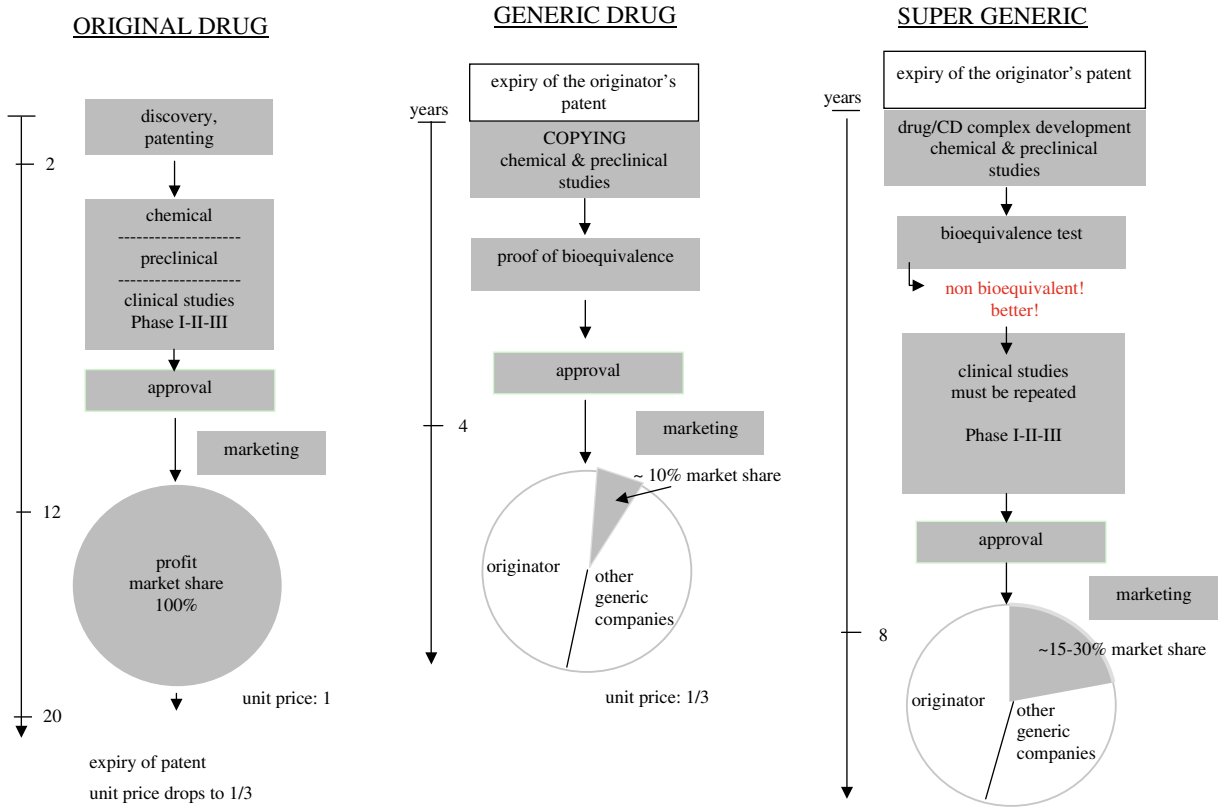

Figure 2. Schematic representation of the development and costs for an original drug, a generic drug, and a super generic drug.

Table 2. Examples for enhancement of bioavailability of drugs CDs (reference: the same drug. in non-complexed form or as commercial product)

Drug	CD	Adm. route	AUC** enhancement X fold	Cmax** enhancement X fold	Tmax** reduction X fold	Species	Refs.
Cephalosporin	α	Oral	1.6	–	–	Dog	[8]
Menaquinone	DIMEB	Oral	2.46	2.2	0.73	Dog	[9]
Cefotiam hexetil	α	Oral	1.02	1.22	0.75	Human	[10]
Ipriflavon	β	Oral	1.35	1.72	–	Rat	[11]
Digoxin	γ	Oral	2.10	1.21	0.85	Human	[12]
		sublingual	1.11	1.75	0.70	Human	[12]
Danazol	β	Oral	2.36	1.53	–	Dog	[13]
Dexamethasone	HPβ	i.v.	1.9 (0–1 h)*	–	–	Dog	[14]
	HPβ	i.v.	1.13 (0–1 h)*	–	–	Dog	[17]
RS 82856	β	Oral	2.5	2.5	–	Dog	[15]
Chlotazole	RAMEB	Oral	1.12	1.42	0.5	Rat	[16]
	β	Oral	1.09	1.18	0.66	Rat	[16]
Carbamazepine	HPβ	Oral	2.39	–	–	Rat	[22]
	HPβ	Oral	2.09	2.37	0.38	Rat	[23. 24]
Spironolactone	β	Oral	2.33	–	–	Human	[18]
	β	Oral	2.15	–	–	Human	[19]
	DIMEB	Oral	3.0	–	–	Rat	[20, 41]
	SBE–7β	Oral	3.0	–	–	Rat	[20, 41]
1–Hexylcarbamoyl-5-fluorouracil	*O*–carboxy methyl–*O*–ethyl–βCD	Oral	1.20	–	–	Dog	[21]

Table 2. Continued

Drug	CD	Adm. route	AUC** enhancement X fold	Cmax** enhancement X fold	Tmax** reduction X fold	Species	Refs.
Piroxicam	β	Oral	1.8	–	–	Rabbit	[27, 32]
			1.8			Human	[28]
	β	Oral	1.35	1.43	0.32	Human	[29]
Renin inhibitor	β	Oral	1.69	1.27	–	Rat	[30]
Rutin	HPβ	Oral	3.0	–	–	Dog	[31]
Diclofenac–Na	β	Oral	1.4	1.4	0.16	Rat	[32]
Danazol	HPβ	Oral	2.37	–	–	Rat	[33]
Deflazacort	β	Oral	1.52	1.70	0.57	Rabbit	[34]
	β + tartaric acid	Oral	1.37	1.69	0.56	Rabbit	[34]
Ketoconazole	β + tartaric acid	Oral	1.42	1.75	0.78	Rabbit	[35]
Tolbutamide	HPβ	Oral	1.6	1.87	0.47	Rabbit	[36, 37]
Ibuprofen	HPβ	Oral	1.15	1.19	0.33	Dog	[38]
Phenitoin	SBE–7β	Oral	2.0	1.6	–	Dog	[39]
Albendazole	HPβ	Oral	1.35	1.8	0.7	Sheep	[40]
Flurbiprofen	β	Dermal	3.0*	–	–	Rat	[42]
Clomipramine	HPβ	Sublingual	1.57	–	–	Rat	[43]
Fluoxetine	γ	Oral	2.50	–	–	Human	[44]
Artemisin	β	Oral	1.5–2.0	1.7–2.9	–	Human	[45]
	γ	Oral	1.3–1.7	1.4–2.4	–	Human	[45]
Furosemide	β	Oral	1.8	–	–	Human	[46]
Nimesulide	β	Oral	2.22	1.05	0.46	Human	[47]
Nitrendipine	HPβ	Oral	1.84	2.13	0.81	Rat	[48]
Amiodarone	α	Oral	1.68	–	–	Pig	[49]
	β	Oral	1.41			Pig	[49]
	DIMEB	Oral	1.61	–	–	Pig	[49]
Dehydroepiandrosterone	αCD + glycine	Oral	2.00	–	0.23	Human	[50]
Glibenclamide	βCD	Oral	5.4*	6*	0.53	Rabbit	[51]
Lonidamine	βCD	Oral	1.46	4.26	0.66	Rat	[25]
	HPβCD	Oral	1.85	1.12	0.66	Rat	[25]
Prednisolone	βCD	Oral	1.35	1.48	0.5	Human	[26]
Average			1.8 ± 0.53 (n = 44)	1.71 ± 0.47 (n = 26)	0.55 ± 0.20 (n = 19)		

*Not involved in the average.

**$= \frac{\mathrm{AUC_{CD\text{-}complex}}}{\mathrm{AUC_{ref.formulation}}}, \frac{^{C}\mathrm{max\ with\ CD\ complex}}{^{C}\mathrm{max\ with\ ref.formulation}}, \frac{^{T}\mathrm{max\ with\ CD\ complex}}{^{T}\mathrm{max\ with\ ref.formulation}}$.

(eventually too high) and quicker therapeutic effect. To reduce the drug dosis is an obvious idea, but this super generic formulation is not bioequivalent with any already approved formulation, consequently all the clinical trials have to be repeated. It means that the development of a super generic formulation is just as expensive, as the development of a new, original drug (Figure 2). Nevertheless, its market share hardly will approach more than the half of the original drug's (during its patent life). At any rate, the order of magnitude of the development costs is similar to that in case of the original drug, therefore it is beyond of the horizon for the majority of generic companies (Figure 3). Only a few examples are known, when a patent-expired drug has been developed to a successfully marketed product in a series of countries. Of course similar marketing and scientific promotion (large number of publications, and presentations at medical

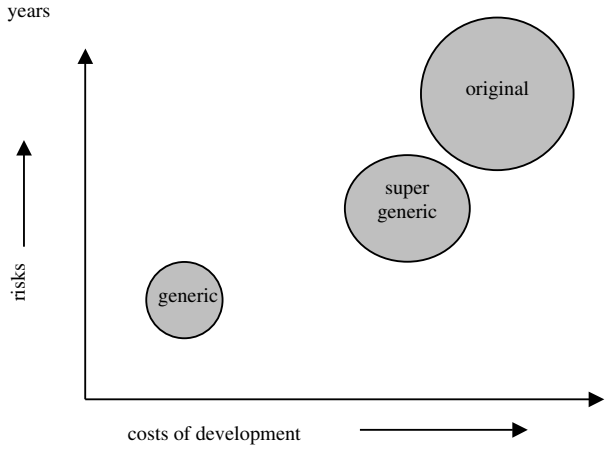

Figure 3. Correlation between the total profit, or risks and costs of development for an original drug, a generic and a super generic drug formulation.

Table 3. Which CD for what purpose?

	Drugs			Cosmetics	Foods	Biotechnology	Anal. chem.	Chemical industry
	Parenteral	Per os	Topical					
αCD	+	+ + +	+ + +	+ + +	+	+	+	+
βCD	–	+ + +	+	+	+ +	+ +		+ + +
γCD	+	+ + +	+ + +	+ + +	+ + +	–		+ + +
HPβ	+ +	+ +	+ + +	+ + +	–	+ +	+ +	+ +
SBE	+ + +	+	–	–	–	–	+ +	–
MeCD	+	+	+	–	–	+ + +	+ +	+ + +

– = not recommended, either on account of toxic side effects or too high prices.
+ = in limited number of cases.
+ + = can be recommended, but for the same purpose there is a better or cheaper candidate.
+ + + = most recommended because of existing approval (or GRAS-status), acceptable price and good technical performance.

conferences) are preconditions for a such a success. An illustrative example is the piroxicam βCD complex (BREXIN = BREXIDOL = CICLADOL) which is marketed by CHIESI FARMA (Parma, Italy) since 1987 in a steadily increasing number of countries.

During the last 20 years, since the first publication on the piroxicam/βCD complex in 1985, 145 publications have been dedicated to its preparation, structure, chemical–physical properties, toxicology, pharmacokinetics, clinical test, in 5 years intervals: between 1985 and 1989 = 14; 1990 and 1994 = 53; 1995 and 1999 = 44 and since 2000 = 34 publications.

Conclusion

Complexation of a drug with an appropriate CD (available at acceptable price, involved in Pharmacopoeia, see Table 3) upon oral administration generally results in a considerable increase of the blood level peak ($c_{max} = + 71 \pm 47\%$) in a shorter time ($T_{max} = \sim 55\%$) and a very significant increase in the AUC value, + 81 ± 50%, as compared with the plain drug, and in many cases with the old, long approved and marketed formulation.

Any most sophisticated (non-CD-based) formulation hardly can surpass the performance of the CDs regarding the above mentioned pharmacokinetic parameters.

It is assumed, that in many cases with a simple reduction of the drug dose the same AUC could be attained as with the reference product. The only significant deviation from the reference product in the bioequivalence study will be the shorter T_{max}, i.e. the time between the drug administration and the time at attaining the drug blood level peak. In absolute majority of the cases the shortening of the T_{max} to nearly half of its original value is a positive result.

The reduced total doses very probably leads to reduction of the side effects, too.

Probability of occurrence of any new unexpected, undesired effects is insignificant. Therefore demand for repetition of the same complete clinical II and III phases which were performed with the old approved reference product used in the bioequivalence test do not seems to be justified.

Taking into consideration the very voluminous literature with the unambiguous positive effects of CDs on the improvement of bioavailability a more flexible evaluation and judgment of the bioequivalence test results – after due reduction of the drug doses in the CD-containing formulation – would accelerate explosions like the number of approved and marketed drug/CD formulations.

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