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SUPRAMOLECULAR SYSTEMS IN BIOPHARMACEUTICS AND PHARMACEUTICAL TECHNOLOGY

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ABSTRACT

The formation of well defined supramolecular structures is quite common in pharmaceutical technology and biopharmaceutics. The aim of the formation of such structures between drug and additives is the improvement of drug properties such as drug release from the formulation, drug pharmacokinetics or drug stability. Molecular recognition, reactivity/catalysis and transport processes are basic aspects of supramolecular chemistry. All these three functions can be exerted by cyclodextrins as host molecules for the formation of pharmaceutically interesting supermolecules.

KEY WORDS

supramolecular systems, pharmaceutical technology, biopharmaceutics, cyclodextrin inclusion compounds

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INTRODUCTION

Supramolecular chemistry is chemistry beyond the molecule, the designed chemistry of the intermolecular bond. In contrast, molecular chemistry is the chemistry of the covalent bond.

Surprisingly, the word supramolecular chemistry is not as yet common in pharmacy although such processes as molecular recognition, supramolecular reactivity/catalysis and transport are basic aspects of supramolecular chemistry.

Supramolecular chemistry can be subdivided into

- the formation of stoichiometric supermolecules
- the formation of molecular aggregates.

Figure 1 shows the relation between molecular and supramolecular chemistry /1/. A drug molecule is normally synthesized by formation of covalent bonds. This is molecular chemistry. This drug molecule can combine with other molecules by noncovalent bonds, e.g. with a receptor or an excipient molecule, to a supermolecule. A prerequisite for such a combination is the molecular recognition. Catalytic reactions or transformations are additional reactions which can possibly be exerted by the supermolecule.

Sometimes, two or more supramolecular units can be transformed to higher functional units with well defined microscopic polymolecular structures such as thin layers, membranes, vesicles or liquid crystals.

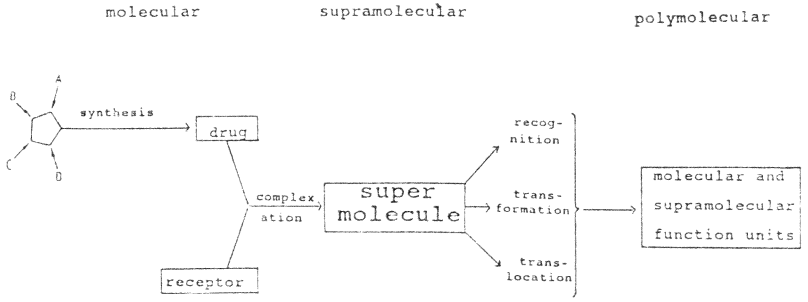


Fig. 1: Relation between molecular and supramolecular chemistry.

SUPRAMOLECULAR STRUCTURES IN PHARMACEUTICAL TECHNOLOGY AND BIOPHARMACEUTICS - AN OVERVIEW

The formation of supramolecular structures is quite common in pharmaceutical technology and biopharmaceutics. The aim of the formation of a supramolecular unit by interactions between drug and additives is the improvement of drug properties concerning drug release from the formulation, drug pharmacokinetics or drug stability. The self-aggregation of a poorly water-soluble drug and a suitable additive can form a better soluble supramolecular unit which can result in a faster therapeutic effect. Complexation between an easily soluble drug and an additive with a limited solubility in water results in a supermolecule with sustained release effects. The formation of a supermolecule between a chemically unstable drug and a suitable additive serves to improve drug stability. Higher organized supramolecular structures such as liposomes or niosomes can be involved

into the transport of drugs to a targeted organ.

Different types of supermolecules or supramolecular aggregates can be formed by noncovalent binding, in most cases by self-organization.

Molecular complexes

Caffeine is known to form soluble complexes with different compounds, like sodium salicylate, sodium benzoate or benzocaine /2/. Supermolecules of iodine with certain types of surfactants or water soluble polymers, so called iodophores, have been developed in order to overcome the disadvantages of iodine as a topical disinfectant /3/.

Inclusion compounds

Among the well known host molecules for inclusion formation - urea, thiourea, deoxycholeic acid, cyclodextrins only the latter one obtained a greater pharmaceutical significance. The physical chemical and biopharmaceutical properties of the included drug are influenced very much by the property of the surrounding host molecule /4/.

Micellar structures

Quite different supramolecular structures can be formed by micellization of surfactants /5, 6/. The characteristic orientation of small amounts of amphiphilic molecules occurs at the air-water interface. Beyond the critical micelle concentration the formation of small spherical or

cylindrical aggregates or micelles in the bulk of the solution begins. These supramolecular units can be used as solubilizer or as a transport form for drugs. Further increase of the surfactant concentration results in supramolecular aggregates where water molecules are lacking to fill the spaces between the still isolated micelles. Higher ordered hexagonal or lamellar structures are formed. Such liquid-crystalline or semiliquid-crystalline systems are involved in the fundamental structure of some semisolid formulations used in pharmacy such as microemulsions, ointment vehicles or the interface of emulsions.

Vesicles, liposomes

To date many efforts have been directed towards delivering drugs to specific sites within the body. The drug is combined with site-specific soluble or particulate carriers to supramolecular units which are mainly formed by self-organization. Examples of such colloidal particulate carriers are stabilized micellar systems, lipid vesicles, nanoparticles, polymer complexes etc. /7/.

Ion-pair transport

Another supramolecular transport system is ion-pairs. Highly ionized compounds or opposite charges form electrochemically neutral, more lipophilic complexes which can permeate membranes /8/.

Incompatibilities

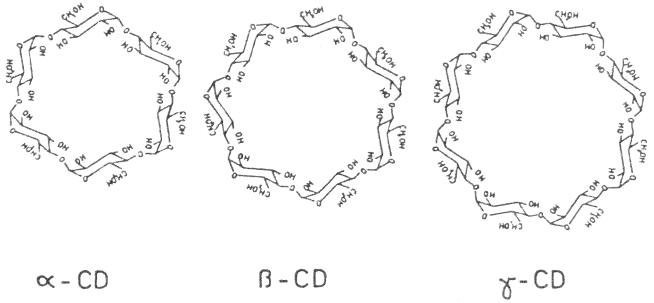
But the formation of supermolecules or supramolecular units can lead to undesirable visible or hidden incompatibilities which can decrease the chemical or physical stability of the product. Drug-drug or drug-additive interactions can influence absorption, distribution, metabolism or excretion.

CYCLODEXTRIN INCLUSION COMPOUNDS: A CLASS OF TYPICAL SUPERMOLECULES

Properties of cyclodextrins

The possibility to obtain supermolecules with different properties by minor changes of the basic structure of native cyclodextrin (CD) are of great interest for supramolecular chemistry /9/. CDs can exert the three fundamental functions of supermolecues, molecular recognition, catalytic effects and transportation. It can be distinguished between the native α-, ß- and γ-CD with different diameters in the cavity and a limited solubility, and the easily water soluble alkylated or hydroxyalkylated CDs /10/ (Figure 2).

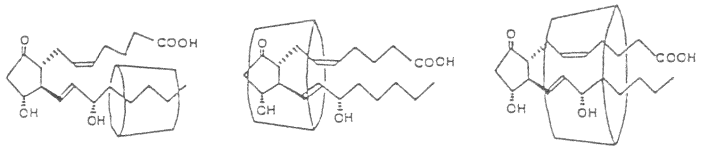
An important property of CDs is their ability to include guest molecules in the hydrophobic cavity. A single host molecule surrounds a single guest molecule. The guest molecule can be surrounded either completely or partially by the host molecule.



α-CD ß-CD γ-CD

Fig. 2: Cyclodextrins.

In solution, there exist primarily supermolecules in the molar ratio of 1:1. The importance of the size of the cavity for the formation of supermolecules can be demonstrated e.g. for the inclusion of prostaglandin E2 with α-, ß- and γ-CD, respectively /11/ (Figure 3). α-CD having a small cavity size preferably includes the aliphatic ω-side chain of prostaglandin molecule, while ß-CD accomodates the five-membered ring. On the other hand, the larger γ-CD cavity interacts with the prostaglandin in such a way that the whole of the guest penetrates the cavity.



α-CD ß-CD γ-CD

Fig. 3: Assumed structures of prostaglandin E2/cyclodextrin complexes.

When the molecular size of the guest is too bulky to be included in one CD cavity more than one CD molecule are available for inclusion. This is frequently the building structure in solid inclusion compounds. Some of the molecular structures are stacked on top of each other within the crystal, like coins in a roll, so that a channel-type structure is formed.

Very important for the different effects of the CD supermolecules are the solubilities of CDs and their derivatives. The limited solubilities of α-CD (14.5 g), ß-CD (1.85 g) and γ-CD (23.2 g $100 \cdot ml^{-1}$, room temperature) are sufficient to solubilize many poorly soluble drugs for a transport along the gastrointestinal tract, but insufficient for an intravenous transport.For many highly hydrophobic drugs to be transported the partly methylated, easily soluble (2,6-di-O-methyl)-ß-CD (DIMEB) proved to be the most effective solubilizer, remaining unexcelled until today. Regrettably this derivative is highly surface active and has a high affinity for cholesterol. In contrast, 2-hydroxypropyl-ß-CD (2-HPßCD) is absolutely nontoxic and has an acceptable solubilizing effect for poorly soluble drugs so that these can be transported within the blood. When ethyl groups are introduced into the hydroxyls of ß-CD, the CD solubility decreases with increasing degree of substitution.

The chirality of the CD molecule is important for the recognition of other molecules.

Supramolecular reactivity and catalysis

The channel structure of most solid inclusion compounds favours the stabilization of an included unstable drug /10/. This must be not the case with inclusion compounds dissolved in water. In solution, CDs can decelerate or accelerate oxidation, hydrolysis, decarboxylation, nitrosation isomerization etc. of included drugs. The reaction depends on the CD used and the kind and stability of the inclusion compound formed. CD-catalyzed reactions can be classified in the following two categories /10/.

- Covalent catalysis, in which CDs catalyze reactions between the catalytic sites of the CDs and the reactive sites of the guest molecule (Figure 4). The first step for an ester cleavage by CDs is complex formation between CD and substrate. The second step is the nucleophilic attack by one of the hydroxyl groups of the CDs on the substrate, resulting in a covalent intermediate. This intermediate then hydrolyses to the final product.
- Noncovalent catalysis, in which CDs provide their cavities as apolar or sterically restricted reaction fields without the formation of any covalent intermediates.

Different CDs can exert different catalytic effects against the same drug. ß-, γ-CD and DIMEB significantly catalyze the in vitro nitrosation of the slowly nitrosatable ephedrine; α-CD has no influence (Figure 5). Minor structural changes of a guest molecule can have opposite effects on the activity of the same CD. The alkaline hydrolysis of

p-aminobenzoic acid esters is decelerated both by α- and ß-CD, because the guest can be fully accomodated into both CDs /10/. However, in the case of o- and m-isomers

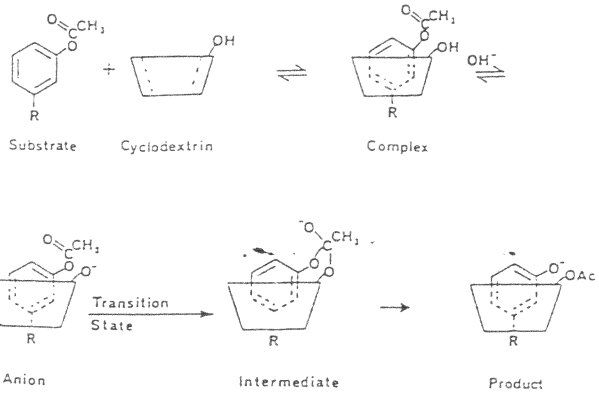


Fig. 4: Cyclodextrin catalyzed reaction: acetyl transfer by covalent catalysis.

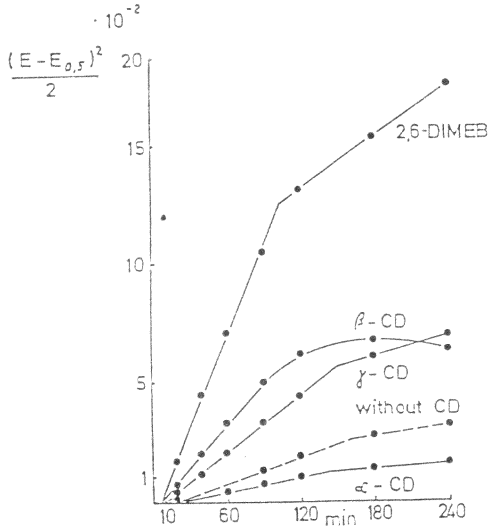


Fig. 5: In vitro nitrosation of ephedrine in presence of cyclodextrins.
pH 3.2

of the guest, only ß-CD shows stabilizing effects, while the α-CD accelerates the hydrolysis. The o- and m-substituents cannot enter into the narrow α-CD cavity, the partial penetration of the phenyl moiety brings them sterically near to the CD-rim hydroxyls. In this case the CD behaves as an enzyme while, when the penetration is deeper, it behaves as a stabilizer. This is also one principle of molecular recognition which can be performed by CDs.

Molecular recognition

CDs detect not only the length and thickness of a guest but also distinguish between enantiomer guest molecules owing to their chirality. Therefore, CDs receive more and more significance in analytical chemistry.

The administration of ´empty´ CD molecules to the blood provides the opportunity for the formation of a complex with constituents of the blood serum. Intravenous administration of 2-HPßCD to rats leads to a transient decrease in plasma cholesterol levels. The complex can be transported rapidly from the intravascular to the extravascular compartment. The increased transport rate explains the decrease in plasma cholesterol levels after CD injection /13/. In a potentially life saving indication, 2-HPßCD was employed to accelerate the elimination of vitamin A in a child suffering from familial vitaminosis A. The treatment was effective in improving the normal elimination of the vitamin and did not cause noticeable toxicity even at a total injected dose of 30 g /14/. This principle of

molecular recognition is paired with the transportation of the recognized substance by the CD as a carrier.

Transportation

The transport of guest molecules can be performed by means of mobile CDs. Only the formation of a soluble supermolecule between an easily soluble CD derivative and a poorly soluble drug enables the administration of some drugs to patients. Table 1 compares the solubility enhancement of a number of drugs afforded by ß-CD and 2-HPßCD /11/. Especially extreme is the solubility enhancement of the steroid anaesthetic alfaxalone in water (solubility in water 3.6 $\mu g \cdot ml^{-1}$) by 20% solutions of γ-CD (944 times), DIMEB (7500 times) and 2-HPßCD (8056 times) /10/.

In conclusion, the properties of a drug molecule as a constituent of a supermolecule or a supramolecular system can be changed fundamentally. This survey can only give a limited insight into some important systems related to pharmaceutical technology and biopharmaceutics. Supramolecular systems play also an important role beyond the formulation of the drug and beyond the drug release in the body. Supramolecular chemistry is a fundamental part of biochemical recognition and transportation of substances across membranes and of distribution. The drug-protein complex is a supramolecular unit. Metabolism is a result of the catalytic effects produced by the enzyme-substrate

Table 1

Solubility enhancement of drugs in water by ß-CD and 2-hydroxypropyl-ß-CD

	Water solubility ($mg\ ml^{-1}$)	Enhancement factor	
		ß-CD	2-HPßCD
Diazepam	55.2	3.6	2.8
Digitoxin	15.5	27	150
Digoxin	66.5	90	57
Flurbiprofen	44.0	2.4	28
Indomethacin	22.9	2.5	1.7
Phenytoin	28.0	10	14
Prednisolone	145.0	14	9
Progesterone	13.2	3.1	88
Testosterone	31.4	2.7	50

ß-CD: saturated solution
2-HPßCD: 20 per cent solution

supermolecule. A better understanding of the principles of these processes will also be helpful for the further drug development.

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