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Review
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CYCLODEXTRIN-BASED PHARMACEUTICALS

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Summary

Cyclodextrins, cyclic oligosacharides, are useful pharmaceutical excipients, which have attracted widespread attention. The ground for their popularity from a pharmaceutical point of view is in their ability to change undesirable characteristics of the drugs, such as unpleasant taste, low aqueous solubility, chemical instability and improving the drug bioavailability by inclusion complex formation. Due to their biocompatibility, cyclodextrins may be used in formulations indented for different routes of drug application including oral, ocular, nasal and even parenteral route. This article outlines the importance and functionality of cyclodextrin in different dosage forms and indicates the possible directions of future development.

Keywords: cyclodextrin; inclusion complex; drug delivery; aqueous solubility; chemical stability; bioavailability

INTRODUCTION

The main goal of pharmaceutical research is the development of new and improved drugs with fewer side effects. Over the years drug discovery has evolved to the point that rational drug design and high-throughput screening techniques have become routine. Through this processes it is possible to rapidly identify active compounds. But many of new drug molecules have failed *in vivo*. Retrospective studies have shown that more than 40 % of new drug failures in development can be connected with poor biopharmaceutical properties of the drug molecule, such as low solubility and/or poor drug permeability across the biomembranes in the body. For a drug molecule to be successfully delivered to the site of action *in vivo*, the drug must possess sufficient aqueous solubility. This allows efficient drug dissolution and delivery of dissolved drug molecule

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to the mucosal surface of the body. At the same time, the drug must possess sufficient lipophilicity to be able to pass through lipophilic mucosal membrane of the body. Various formulation techniques have been developed in an effort to overcome these and other obstacles in sufficient drug delivery. One of approaches may be in the use of drug-cyclodextrin inclusion complexes [1, 2]. Because of their multifunctional characteristics and bioadaptability, cyclodextrins are capable of alleviating the undesirable properties of drug molecules in various routes of administration through the formation of inclusion complexes. Thus, cyclodextrins have important role in development of new drugs, as swell as in optimisation of pharmaco-therapeutic properties of already known drugs.

The aim of this article is to give an insight into physicochemical properties of cyclodextrins and their inclusion complexes with emphasis on their current pharmaceutical applications. In addition, other possible application and future trends in development of cyclodextrin-based drug formulations will be discussed.

CHEMICAL STRUCTURE OF CYCLODEXTRINS

Cyclodextrins are a group of structurally related cyclic oligosacharides produced by bacterial starch degradation [3]. Naturally occurring cyclodextrins (a-, b- and g-cyclodextrin, respectively) are consisting of 6, 7 or 8 a-[1,4] linked D-glucopiranose units. Cyclodextrins with less than 6 glucopiranose units cannot be formed due to sterical reasons, while cyclodextrins with more than 8 glucopiranose units (so called large cyclodextrins) are described in the literature, but their pharmaceutical importance is still under investigation [4]. Because of the chair conformation of the glucopiranose units, the cyclodextrins are shaped like a truncated cone (Figure 1). The hydroxyl groups are orientated to the exterior surface of the molecule providing hydrophilic properties.

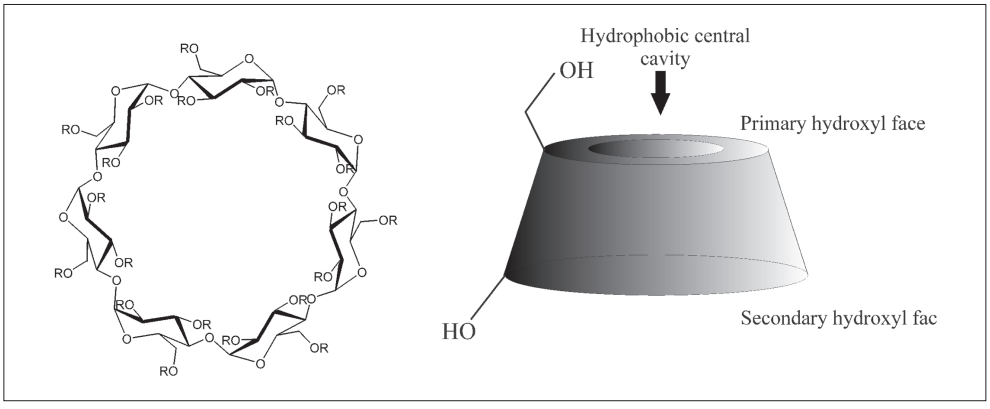

Figure 1. The chemical structure of b-cyclodextrin (R=H).

Table 1. The physiochemical properties of some pharmaceutically important cyclodextrin derivates.

CYCLODEXTRIN	N[(a)]	R	Substitution[(b)]	MW[(c)]	Solubility in water (mg mL^{-1})[(d)]
α-cyclodextrin	6	–H	–	972	145
β-cyclodextrin	7	–H	–	1135	18.5
2-hydrohypropyl-β-cyclodextrin	7	$–CH_2CHOHCH_3$	0.65	1400	> 600
sulfobutylether-β-cyclodextrin sodium salt	7	$–(CH_2)_4SO_3^-Na^+$	1.8	1312	> 500
randomly methylated-β-cyclodextrin	7	$–CH_3$	0.9	2163	> 500
γ-cyclodextrin	8	–H	–	1297	80

(a) Number of glucopiranose units
(b) Average number of substituents per glucopiranose unit
(c) Molecular weight (MW) in Daltons
(d) Solubility in pure water at 25°C

Due to lack of the rotation around a-[1,4] bonds, the primary hydroxyl groups are orientated to the narrow edge of the cone, while the secondary groups are at wider edge of the molecule. The central cavity of the molecule is lined with skeletal carbon and etheral oxygen atoms of the glucopiranose units, which gives it a lipophilic character.

Due to strong bonding of the cyclodextrin molecules in the crystal state, the water solubility of natural cyclodextrins is much lower compared to the corresponding linear dextrins. Also, the formation of intermolecular hydrogen bonds between 2- and 3-hydroxyl group of the adjacent glucopiranose units diminish the ability of cyclodextrins to form hydrogen bonds with the surrounding water molecules. This is especially pronounced in case of b-cyclodextrin, where the belt consisted of 7 hydrogen bonds was formed, limiting its solubility (Table 1). In case of a-cyclodextrin only 5 of possible 6 hydrogen bonds are formed due to sterical reasons, while g-cyclodextrin hydrogen has noncoplanar and more flexible structure. Therefore, the water solubility of a- and g-cyclodextrin are 7.8 and 11.2 times higher than that of b-cyclodextrin. The substitution of any hydroxyl group involved in hydrogen bond formation, even with lipophilic moiety such as methyl group, results in disruption of intermolecular hydrogen bonds that dramatically increase the cyclodextrin solubility in water. The number of possible isomers generated by random substitution of b-cyclodextrin is large, since it has 7 primary and 14 secondary hydroxyl groups in the structure. This contributes to the transition of the crystalline β-cyclodextrin to amorphous compound in case of its derivates, additionally contributing to the water solubility. Till now, more then 1500 different cyclodextrin derivates have been synthesized and described in the literature [2, 3, 5]. Some hydrophilic

cyclodextrin derivates of pharmaceutical importance are listed in Table 1. Other derivates include lipophilic derivates (alkylated and acetylated cyclodextrins), cyclodextrins with pH dependent solubility (carboxymethyl-b-cyclodextrin) and different cyclodextrin based polymers [3].

TOXICOLOGICAL AND REGULATORY CONSIDERATIONS

Safety is a primary concern when considering new excipients intended for use in pharmaceutical formulations. Therefore, toxicological issues and biological fates of cyclodextrins have been thoroughly investigated. Cyclodextrins are resistant to the degradation by human salivary and pancreatic amylases. Due to high molecular weight and hydrophilic nature (log $P_{o/w}$ between –3 and 0), natural cyclodextrins permeate the lipophilic biological membranes with considerable difficulties. Therefore, only 1-3% of applied cyclodextrin dose is absorbed in gastrointestinal tract, while dermal, ocular and nasal bioavailability is even lower. The absorbed cyclodextrins are excreted intact via the kidney. The bulk of orally administered cyclodextrins is metabolised in colon, by the colon micro-flora to primary metabolites, such as acyclic maltodextrins, maltose and glucose. After absorption to the systemic circulation, primary metabolites are further metabolised and finally excreted as CO_2 and H_2O [3, 6, 7].

The toxicological studies have demonstrated that orally administered cyclodextrins are practically non-toxic, due to lack of absorption from the gastrointestinal tract. Furthermore, a number of safety evaluations have shown that γ-cyclodextrin, hydroxypropyl-β-cyclodextrin and sulphobutylether-b-cyclodextrin appear to be safe even when administered parenterally. β-cyclodextrins form complexes with cholesterol that accumulate in the kidney and produce renal tubule damage, while α-cyclodextrin and methylated-β-cyclodextrins produce dose dependent haemolysis. Therefore, they are not suitable for parenteral administration [1,6].

Cyclodextrins are relatively new form a regulatory point of view and policies on their use are still not standardised. The regulatory status of cyclodextrins is continuously evolving and current state in presented in Table 2. Consensus seems to be building among regulators that cyclodextrins are excipients and not a part of the drug substance, which is logical based on their physiochemical properties as drug solubilizers and stabilizers [7].

INCLUSION COMPLEX FORMATION

In aqueous solution, cyclodextrins are able to form inclusion complexes with many drugs by incorporating the drug molecule, or more often a lipophilic moiety of the drug molecule into central cavity (Figure 2.). This process may be explained as drug

Table 2. The regulatory status of some pharmaceutically important cyclodextrins.

Cyclodextrin	Pharmacopoeia		
	PH. EUR.[a]	USP/NF[b]	JPC[c]
α-cyclodextrin	Yes	No	Yes
β-cyclodextrin	Yes	Yes	Yes
2-hydrohypropyl-β-cyclodextrin	Yes	Yes	No
sulfobutylether-β-cyclodextrin sodium salt	No	No	No
randomly methylated-β-cyclodextrin	No	No	No
γ-cyclodextrin	In progress	Yes	Yes

(a) European Pharmacopoeia 5th Edition (2005)
(b) United States Pharmacopoeia 28th Edition/National Formulary 23rd Edition (2005)
(c) Japanese Pharmaceutical Codex (1997)

encapsulation at the molecular level. The main driving force leading to the inclusion complex formation is in the release of enthalpy rich water molecules from the central cavity of the cyclodextrin molecule. No covalent bonds are formed or broken during the inclusion complex formation. Electrostatic, van der Waals or hydrophobic interactions and hydrogen bonding between included drug moiety and cyclodextrin molecule are leading to the conformational strain release of cyclodextrin molecule, additionally contributing to the inclusion complex formation. Since the drug/cyclodextrin interactions are relatively weak, drug molecules included in the cyclodextrin cavity are in rapid equilibrium with the free drug molecules in the solution [3, 5].

Cyclodextrins will form the inclusion complexes with drug molecules that have compatible geometry and are less polar than water. Most drug molecules will form 1:1 complexes with cyclodextrins, but the 1:2 and higher order complex formation have

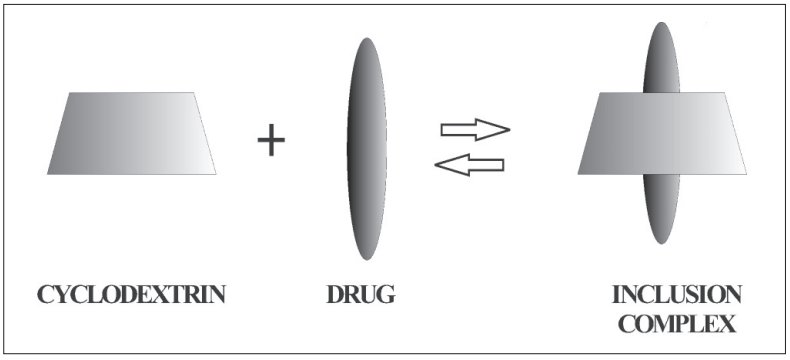

Figure 2. Schematic illustration of the inclusion complex formation.

been reported. Inclusion complex formation will change the physiochemical properties of the drug, such as its solubility and chemical stability. The cyclodextrin molecule forms a hydrophilic shield around encapsulated lipophilic moiety of the drug, increasing the apparent solubility of the drug. Also, inclusion complex formation may protect chemically labile drug molecules from the surrounding environment, thereby reducing or even preventing drug hydrolysis, oxidation, racemization and enzymatic decomposition. Therefore, cyclodextrins are very useful pharmaceutical excipients suitable for the development of different drug formulations. The list of some available drug formulations containing cyclodextrins is presented in Table 3 [3, 5, 8].

CYCLODEXTRINS IN DRUG FORMULATIONS

Stability issues may limit the feasibility of a pharmaceutical formulation. This is especially pronounced in case of aqueous drug formulation, due to potential hydrolysis or oxidation of an active compound. Many studies have shown that stability of chemically labile drugs can be improved through complexation with cyclodextrins. Very illustrative example is in the stabilising effect of cyclodextrins on different prostaglandins that allowed the development of suitable formulations [3]. One of these compounds, PGE_2 posses potent oxytocin-like effect and was of interest as a possible agent for the labour induction in childbirth. The high instability of this agent complicated the development of a suitable formulation. Inclusion complex formation using β-cyclodextrin resulted in a significantly increase of the PGE_2 stability in solid state. Cyclodextrin based PGE_2 sublingual formulation (Prostarmon E; Ono) was approved for Japanese market in 1976. Prostamon E is highly effective and represents a significant medical advance, especially for the labour induction in oxytocin-insensitive individuals, but also for its tendency to produce less bleeding after delivery. Another prostaglandin, PGE_1 relaxes smooth muscles and increases the blood flow. This compound might be used in treatment of peripheral circulatory disorders, but the clinical utility of PGE_1 was limited by its metabolic degradation. The stabilising effect of a-cyclodextrin on PGE_1 allowed the development of parenteral formulation (Prostavastin) that showed activity against chronic arterial occlusion and arteriosclerosis. Also, PGE_1/α-cyclodextrin formulation was effective in treatment of male erectile dysfunction [9]. Intracavernous application of the complex was found to be effective in subjects who were not responsive to sildenafil citrate (Viagra®, Pfizer).

Another goal that might be obtained by inclusion complex formation is the reduction of unpleasant drug's taste or smell [8,10]. The adstringent and irritating effect of nicotine excluded its direct consumption in the form of sublingual tablets or chewing gums. This problem was successfully solved by inclusion complex formation using β-cyclodextrin. The molecular encapsulation prevented the direct contact of nicotine with the

taste buds in the oral cavity, allowing the formulation of sublingual tablets for smoking cessation (Nicorette Microtab®). Another similar example is cetizirine hydrocloride, an antyhystaminic drug used for allergic symptoms relief. Inclusion complex formation with β-cyclodextrin reduced very bitter taste of this drug, allowing the formulation of a chewing tablet. This kind of formulation provided easy consumption of the drug and relief of allergic symptoms in situation when water is not available (e. g. during driving).

The most common pharmaceutical application of cyclodextrin is their use as solubilizers [5]. In ophthalmology, the local drug administration in form of aqueous solutions drops is preferred. The development of suitable formulation may be considerably hampered by drug solubility, since the drug dose must be dissolved in 0.03-0.05 mL of aqueous solution [12]. The solubilizing effect of cyclodextrin would allow the incorporation of the drug dose into volume suitable for ocular application. Cyclodextrins are proved to be useful excipients in eye drop formulations of various drugs including different corticosteroids, carbonic anhydrase inhibitors, pilocarpine, cyclosporins, diclophenac, etc. It is likely that the use of cyclodextrins in topical delivery to the eye will expand the selection of drugs available for the use in ophthalmology [13]. Isotonic drug solutions may be prepared by using up to 20% (w/v) concentration of hydroxypropyl- or sulphobutylether-β-cyclodextrin at physiological pH-values. Addition of water-soluble polymers to the aqueous cyclodextrin solution would further increase the drug solubility due to ternary drug-cyclodextrin-polymer complex formation [5, 14]. Also, the cyclodextrins have been used to reduce the ophthalmic drug irritation and to increase the drug stability in the ophthalmic formulations. The drawback of the cyclodextrin use in ophthalmic formulation is in the fact that they may interact with the preservatives in the formulation, reducing their efficiency [12]. The solution of this problem might be in the use of a novel cyclodextrin derivate containing quaternary amino groups. This cyclodextrin derivate has been shown to be a multifunctional agent having the effect on the drug solubility and acting as antibacterial agent [5].

The cyclodextrin drug solubilization was successfully applied in development of formulations aimed for systemic drug delivery via the nasal mucosa (15). The large absorptive surface and high vascularity of the nasal mucosa ensure a rapid absorption of compounds under circumvention of the hepatic first pass elimination. The pharmacokinetic drug profile after nasal application is often similar to that of parenteral application. The easy accessibility of the nasal route facilitates self-medication, thus improving patient compliance when compared to parenteral route [16]. Randomly methylated-b-cyclodextrin was successfully applied in development of nasal formulation aimed for pulsed oestrogen therapy in treatment of climacteric symptoms (Aerodiol). The nasal absorption of oestrogen from cyclodextrin-based formulation was rapid and peak plasma concentrations were achieved within 10-30 minutes after application. The oestrogen

plasma levels returned to baseline within 2 hours. This pattern is more akin to physiological oestrogen secretion that that associated with oral or transdermal application. Also, oral application of oestrogen generated high oestrone/oestradiol ratio, while nasal delivery gived rise to more physiological ratio of those hormones [17,18]. Randomly methylated-β-cyclodextrin was also used in development of dihydroergotamine nasal formulation aimed for migraine treatment. The benefit of nasal drug application in this case is in fact that migraine attacks are usually accompanied by vomiting therefore oral drug application is inadequate [19]. Numerous studies have demonstrated that cyclodextrins are efficient nasal permeation enhancers for different drugs, including hormones and peptides [15]. The cell-culture based studies indicated that randomly methylated-b-cyclodextrin might open the tight junctions in the nasal mucosa triggering paracellular drug absorption. The possibility of using the cyclodextrins as nasal absorption enhancer is currently under investigation. Histological and cell-culture based studies [20] showed that cyclodextrins did not induce mucosal damage and had no significant influence on the nasal ciliary movement [21]. Further, clinical data [15] showed no significant adverse effect, indicating that cyclodextrins are effective and safe excipients in nasal drug delivery.

In solid state, cyclodextrins convert the drug of interest, which is usually crystalline, into a dispersion of the amorphous drug in the cyclodextrin carrier. Importantly, the dispersion is a result of a molecular encapsulation by cyclodextrins [3]. Improved complex solubility and amorphous drug state will increase the drug dissolution rate and generally will enhance the oral bioavailability of the drugs with low water solubility. After dissolution of the inclusion complex in gastrointestinal tract, cyclodextrins are acting as true carriers by keeping the hydrophobic drug molecules in solution and delivering them to the surface of the biological membrane, where drug permeation across the membrane occurred. The relatively lipophilic gastrointestinal membrane has low affinity for the hydrophobic cyclodextrin molecule and they remain in the aqueous membrane exterior. Numerous studies have confirmed the increased oral bioavailability and faster onset of action for many drugs upon cyclodextrin complex formation, including carbamazepine, digoxin, furosemide, glibenclamide, itraconasole, ketoprofen, nifedipine, spironolactone, etc. In the same time, cyclodextrins may reduce some side effects of orally administered drugs [2,8,22].

Nonsteroidal anti-inflamatory drugs (NSAIDs) are widely used for the treatment of painful and inflammatory conditions, but they chronic application may result in upper gastrointestinal tract irritation and even bleeding. The very illustrative example is piroxicam, the drug useful in the treatment of osteoarthritis and rheumatoid arthritis, as well as gout, acute musculoskeletal disorders and dysmenorrhoea. The relatively long pharmacokinetic half-life of the drug allows the possibility of once a day dosing in contrast to many other NSAIDs, but poor water solubility leads to the slow onset of

action. The inclusion complex formation using β-cyclodextrin increased the drug solubility more than fivefold. The enhanced drug solubility leads to the increased drug dissolution rate and faster absorption rate. This resulted in higher piroxicam plasma levels at early time after application to humans and consecutive faster onset of drug action. Several endoscopic studies as well as a research using adhesive radio-substrates have revealed significant reduction of gastroduodenal damage after administration of piroxicam-β-cyclodextrin complex to humans [1,23]. Therefore, several branded piroxicam-β-cyclodextrin based formulations are available worldwide (Table 3).

The limitation in the use of cyclodextrins in oral drug administration is in the effect of cyclodextrins on the formulation bulk. Incorporation of cyclodextrins into solid dosage forms will increase the formulation bulk at least 4-fold. Therefore, the cyclodextrins can be used only in solid dosage formulation of relatively potent drugs with the single dose up to 100 mg. In other cases, the formulation size would be too large, and swallowing the tablet would not be possible [22].

Taking into consideration the numerous advantages of the cyclodextrin complexation of the drugs, it is not evident why the number of approved and marketed cyclodextrin based formulation of long known (generic) drug is relatively low. The price and approval status of the cyclodextrins is no more a restricting factor for their use. The crucial problem is in fact that for approval of any new formulation of already known (generic) drug, a bioequivalence test has to be performed. A cyclodextrin-based formulation is practically never bioequivalent with the reference product (the earlier approved formulation), but significantly superior in terms of improved solubility, faster and more complete absorption that leads to enhanced biological activity of the drug. Therefore, cyclodextrin based drug formulation will not be a simple generic, but a supergeneric drug. In this case, the authorities are requesting the repetition of the largest part of long lasting and very costly clinical studies. Therefore, the costs of development will be nearly as high as in case of an original drug. In the same time, the market for cyclodextrin-based formulation will be considerably narrower. Taking into account that the absorption of the drug in reduced dose from cyclodextrin-based formulation is faster than from its original formulation, then a simple Clinical I phase should be satisfying from regulatory point of view. All deviation between the pharmacological effect of the original formulation and cyclodextrin-based formulation is the consequence of quicker and more complete absorption of the last one. No further change in pharma-codynamic or therapeutic effect of the drug might arise in consequence of the cyclodextrin complexation [8]. Taking into account the superior therapeutic effect of cyclodextrin based formulation, such as reduced drug dose that may decrease the number and intensity of the side effects as well as faster onset of drug action, it might be expected that in the near future the number of cyclodextrin based formulations on the market will grow.

Table 3. Some of marketed drug formulations containing cyclodextrin.

Drug	Trade name	Indication	Formulation	Company (country)
a-cyclodextrin				
Alprostadil (PGE_1)	Prostavastin Caverject	Chronic arterial occlusive disease	Intravenous solution	Ono (Japan) Pfizer (Europe)
Cefotiam hexetil HCl	Pansporin T	Antibiotic	Oral tablet	Takeda (Japan)
Limaprost	Opalmon, Prorenal	Buerger's disease	Oral tablet	Ono Japan)
PGE_1	Edex	Erectile disfunction	Intracavern injection	Schwartz Pharma (Germany)
b-cyclodextrin				
Benexate	Ulgut Lonmiel	Antiulcerant	Oral capsule	Teikoku (Japan) Shionogi (Japan)
Dexamethasone	Glymesason	Analgesic, antiinflamatory	Dermal ointment	Fujinaga (Japan)
Dinoprostone (PGE_2)	Prostarmon E	Induction of labour	Sublingual tablet	Ono (Japan)
Diphenhydramine/Chlorteophilin	Stada-Travel	Travel sicknes	Chewing tablet	Stada (Europe)
Nicotine	Nicorette Microtab Nicogum	Smoking cessation	Sublingual tablet, chewing gum	Pharmacia (Sweden) Pierre Fabre (France)
Nimesulide	Nimedex Mesulid Fast	NSAID	Oral tablet, oral sachet	Novartis (Europe)
Nitroglycerin	Nitropen	Coronary dilatator	Sublingual tablet	Nippon Kayaju (Japan)
Omeprazole	Omebeta	Proton pump inhibitor	Gastro resistant capsule	Betapharm (Germany)
Piroxicam	Brexin Cicladol Flogene	Analgesic, antiinflamatory	Oral tablet, suppository	Bipharm i Hermes (Germany) Pharmafontana (Hungary) Ache (Brasil)
Tiaprofenic acid	Surgamyl	Analgesic	Oral tablet	Roussel-Maestrelli (Italy)
hydroxypropyl-b-cyclodextrin				
Cisapride	Propulsid	Gastrointestinal mobility stimulant	Supository	Janssen (Belgium)
Hydrocortisone	Dexocort	Mouth wash against aphta, gingivitis, etc.	Solution	Actavis (Iceland)
Indomethacin	Indocid	Antiinflamatory agens	Eye drop	Chauvin (France)
Itraconazole	Sporanox	Esophageal candidiosis	Oral solution	Janssen (Belgium)
Mitomycin	Mitozytrex MitoExtra	Chemoterapeutic agent	Intravenous solution	SuperGen (USA) Novartis (Switzerland)
randomly methylated-b-cyclodextrin				
17-β-Oestradiol	Aerodiol	Postmenopausal hormone replacement therapy	Nasal spray	Servier (France)
Cloramphenicol	Clorocil	Antibiotic agent	Eye drops	Oftalder (Portugal)
sulphobutylether-b-cyclodextrin				
Voriconazole	Vfend	Antimycotic	Intravenous solution	Pfizer (USA)
Ziprasodine maleate	Geodon, Zeldox	Antishizophrenic	Intranuscular injection	Pfizer (USA)

CYCLODEXTRINS IN CONTROLLED DRUG DELIVERY SYSTEMS

From the viewpoint of the optimised pharmacotherapy, drug release should be controlled in accordance with the therapeutic purpose and the pharmacological properties of active substance. There has been growing interest in developing rate or time controlled oral preparations with the aim to achieve the zero-order or pH-independent drug release. This may provide a constant blood concentration of the drug for a prolonged period of time. Controlled release formulations offer the advantages such as reducing the dosing frequency, prolonging the drug efficiency and avoiding the toxicity associated with the administration of a plain tablet. To design such advanced dosage form, a suitable carrier materials are used to overcome the undesirable properties of drug molecules. Cyclodextrins are potential candidates for such role [24].

Hydrophobic cyclodextrins, such as alkilated and acylated derivates of are useful as slow release carriers for water-soluble drugs. Diethyl- and triethyl-β-cyclodextrin were the first slow release carriers used in conjunction with diltiazem and isosoribide dinitrate to obtain prolonged drug release in dogs. The peracylated cyclodextrins with medium alkil chain lengths (C_4-C_6) are particularly useful as novel hydrophobic carriers, because of their multifunctional characteristics, such as bioadhesive properties and ability to form films. Therefore, they can be used in oral and transdermal formulation of the drugs with short biological half-life [25].

Polymeric drug delivery systems, such as tablets, microparticles and hydrogels are often used to obtain the controlled drug release. The drug release from those formulations may be controlled by the swelling of the polymer matrix or by its erosion. The incorporation of hydrophilic cyclodextrins into polymeric drug delivery systems can modify the drug release pattern by increasing the drug solubility or diffusivity across the swollen polymer layer. Since hydrophilic cyclodextrins are readily soluble in water, they may act as channelling or wicking agents, improving hydration of the polymer matrix or promoting its erosion. This would allow the complete release of the drugs with low water solubility. Controlled release formulations of many drugs, such as carbamazepine, nicardipine, piroxicam, etc were successfully formulated using different polymers and hydroxypropyl-b- or sulphobutyether-β-cyclodextrin [26-29].

Osmotic pumps are the oral drug delivery systems in which the drug release is controlled by osmotic pressure. They are consisted of the drug reservoir, which can be either a solution or a solid formulation mixed with an osmotic agent enclosed with a semipermeable membrane. After oral application, the gastrointestinal fluid penetrates through the semipermeable membrane and dissolves the drug in the reservoir, as well as the osmotic agent. Under the created osmotic pressure, the drug is released continuously at a controlled rate through a vent pre-drilled by a laser beam. This kind of formulation may provide the zero-order drug release through a period of time up to 12 hours.

Sulphobutylether-b-cyclodextrin may be useful in formulation of the oral pumps, since it is a multifunctional agent. This cyclodextrin derivate posses osmotic activity and it is excellent drug solubilizer, providing the controlled and complete release of the drugs with low water solubility. The use of sulphobutylether-β-cyclodextrin in formulation of osmotic pump tablet for chloropromasine gained prolonged and pH-independent drug release *in vivo*, without compromising the oral bioavailability of the drug [24,30].

Cyclodextrins may be used to obtain colon-specific drug delivery. Colon drug delivery systems are designed to permit targeted drug release in the terminal ileum and proximal colon. The objective of delivering drugs to these parts of the gastrointestinal tract is in providing of local delivery for treatment of colonic diseases, such as ulcerative colitis, colon cancer or constipation. Also, the drug absorbed via the colon will bypass the hepatic first pass metabolism. Further advantage of the drug delivery to colon may be obvious from the viewpoint of circadian biorhythm. The drug passage to the colon will occur approximately 8 hours after oral application. Therefore, colon delivery can provide a nocturnal release of drugs for diseases that are characterised by nighttime or early morning onset, such as asthma, hypertensia, cardiac arrhythmias, etc. The drug/cyclodextrin inclusion complexes are not suitable for colon delivery due to their high solubility. The formation of drug/cyclodextrin conjugate, in which the drug in linked by ester bond to one of hydroxyl group of the cyclodextrin molecule via a suitable spacer, would allow colon specific drug delivery. The cyclodextrin molecule produces sterical hindrance to hydrolysis of the ester bond in upper part of the gastrointestinal tract thus prohibiting the drug absorption. The drug-cyclodextrin conjugates are firs subjected to the cyclodextrin ring opening by bacterial enzymes in colon, followed by ester linkage hydrolysis and subsequent drug absorption in colon [25]. The formation of biphenylylacetic acid conjugates with α- and γ-cyclodextrin provided colon specific drug delivery in rats, with 4 to 5 time higher oral drug bioavailability compared to the drug alone (31). Ketoprofene/α-cyclodextrin conjugate was demonstrated to be delayed-release type prodrug for colon-specific delivery. The combination of cyclodextrin conjugate with a ketoprofene/hydroxypropyl-β-cyclodextrin inclusion complex as a fast-release fraction yielded the repeated-release preparation. The oral application of this preparation shoved strong anti-inflammatory effect on carageenan-induced acute oedema in rat paw model during 12 hours after application. In the same time, the onset of drug action upon administration of this formulation was very fast [32].

OTHER POSSIBLE APPLICATIONS OF CYCLODEXTRINS IN PHARMACY

Advances in biotechnology have allowed the large-scale production of therapeutically important peptides offering the possibility of treating some until now untreatable diseases. But the therapeutical use of these compounds was hampered due to chemical

and enzymatical instability of the peptides, poor absorption through biological membranes, rapid plasma clearance, peculiar dose-response curves and immunogenicity. Different approaches have been used to solve this problem and cyclodextrin complexation seems to be an attractive solution.

The interaction between cyclodextrins and peptides or proteins is restricted since their molecules are too hydrophobic and bulky to be wholly included in the cyclodextrin cavity. Also, the topological constrains of the peptide backbone may reduce the inclusion complex formation. The interaction between polypeptides and proteins could be only local, including the inclusion complex formation between accessible hydrophobic residues of amino acids such as L-tryptophan, L-tyrosine and tercbutyl-D-serine. Therefore, cyclodextrins have be used to solubilize and stabilize various biomedically important peptides and proteins including growth hormone, interleukine-2, tumor necrosis factor, albumine, γ-globuline, etc. [33,34].

The property of insulin to form reversible and irreversible aggregates in solution leads to complication in the development of long-term insulin therapeutic systems. This limits the rate of insulin subcutaneous absorption, leading to the inadequate regulation of the blood glucose level after a meal. These problems are further complicated by the tendency of insulin to adsorb to the surface of a container. Some hydrophilic cyclodextrins, including maltosyl- and hydroxypropyl-β-cyclodextrin, significantly inhibit the absorption of insulin to hydrophobic surfaces of containers and its aggregation in neutral solution. Probably, cyclodextrins caused the perturbation of the intermolecular hydrophobic contacts between aromatic side chains across the monomer-monomer interfaces, leading to the inhibition of peptide self-association [35].

The cyclodextrins may have significant role in production of pharmaceutically important proteins. The particular problem in production of proteins by genetically engineered cells stems from the fact that proteins are overproduced in the form of cytoplasmic aggregates or inclusion bodies, in which proteins are misfolded and therefore functionally inactive. Weak interactions of cyclodextrins with unfolded proteins may enhance the solubility of denaturised proteins by masking the exposed hydrophobic residues, thereby assisting the re-folding of the proteins. In this way cyclodextrins may act as artificial chaperones in the protein folding process [36].

As it was mentioned earlier, some hydrophilic cyclodextrin derivates such as a- and randomly methylated-b-cyclodextrin are demonstrated to be potential permeation enhancers of the polypeptides across the biomembranes allowing systemic delivery of peptide and protein drugs via various mucosal routes (nasal, rectal, etc.). When compared with other permeation enhancers, they have rather mild and reversible effect on the mucosa. The effectively of cyclodextrins as permeation enhancers may be further upgraded by simultaneous application of other permeation enhancers or polymers such as chitosan [37].

The high external hydrophilicity of natural cyclodextrin, as well as their hydrophilic derivates, reduces the possibility of intimate contact with biological membranes. For this reasons, several amphiphilic cyclodextrin derivates has been synthesized. Amphiphilic cyclodextrins were obtained by grafting aliphatic chains of different length (C2-C18) by an ester bond on the primary hydroxyl ("medusa like cyclodextrins") or secondary hydroxyl groups of cyclodextrin molecule ("skirt shaped cyclodextrins"). Due to ester bond, this cyclodextrin derivates are susceptible to being biodegradable. One of the interesting characteristics of amphiphilic cyclodextrins is their ability to spontaneously form nanospheres and nanocapsules without the presence of a surfactant (38). The nanoparticles based on amphiphilic cyclodextrin can be prepared directly from pre-formed drug/amphiphilic cyclodextrin inclusion complex using nanoprecipitation technique. The obtained nanoparticles have high drug loading capacity and reduced burst effect during the drug release [39]. This may be explained in terms of particular nanoparticles architecture made of organised cyclodextrin molecules that offers the opportunity to associate drug molecules at different levels within the nanostructure, i.e. surface adsorption, matrix entrapment or interaction with the cyclodextrin cavity. The size range of cyclodextrin-based nanoparticles (90-250 nm) is compatible with an intravenous administration and they can be sterilised by gamma irradiation [38, 40]. This sterilisation technique has insignificant influence on particle size, drug loading and drug release properties. According to the studies on human blood samples and L929 mouse fibroblast cells, amphiphilic cyclodextrins were reported to be non-hemolytic and non-cyctotoxic [41, 42]. Recent *in vivo* studies have confirmed those results, since no particular signs of toxicity were observed after intravenous administration of amphiphilic cyclodextrins to rats [43]. This all indicates that cyclodextrin based nanoparticles may become important drug delivery system for drug targeting.

Another interesting field where cyclodextrins may be applied is in the gene delivery. The lack of safe and efficient gene-delivery methods is a limiting obstacle to human gene therapy. In recent years, a variety of effective polymers have been designed especially for non-viral gene delivery [44]. Among them, numerous cyclodextrin-containing polymers gained notable interest [45]. A common property of all cyclodextrin-containing polymers for nucleic-acid delivery is that they are polycations. One of important feature that is observed with cyclodextrin-contained polycations is their low *in vitro* and *in vivo* toxicity compared to other polycations without cyclodextrin molecule in their structure, such as poly-L-lysine and polyethylendimine [1,45]. Cationic polymers are able to deliver nucleic acid into cells by self-assembling with the anionic DNA via electrostatic interactions to subsequently form positive charged particles with size up to 500 nm, that are taken up by cells.

The important feature unique to the cyclodextrin-containing cationic polymers is that they can be modified by compounds capable of forming inclusion complexes. This may be archived using polyethylene glycols compounds terminated with adamantine, that form inclusion complexes with cyclodextrins on the particle surface. This method of surface modification does not involve the portions of polycations that bind to the DNA, therefore the disruption of particle is avoided. Obtained surface modification of cyclodextrin-containing cationic particles provided sterical stabilisation and reduction of the elimination rate from the blood stream by phagocytes. This approach has been extended to cyclodextrin-grafted polyethilenedimines and shown to produce delivery vehicles that can target tumour and liver tissue in mice with either plasmids or oligonucleotides [46,47]. It is likely that gene delivery systems based on cyclodextrin-containing polycations might become an important tool for human gene therapy.

CONCLUSION

Cyclodextrins are known more than 100 years. This period of time was necessary for the evolution of cyclodextrins from interesting chemical odities to enabling pharmaceutical excipeient. Due to their biocompatibility and multifunctionality, cyclodextrins may be used to alleviate undesirable characteristics of the drugs. In the same time, cyclodextrin based technology is continuously developing, therefore cyclodextrins still may be regarded as novel excipients of unexplored potential.

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Sažetak

Ciklodekstrini u ljekovitim oblicima

Ciklodekstrini, ciklički oligosaharidi, predstavljaju skupinu farmaceutskih pomoćnih tvari koja je svojom multifunkcionalnošću privukla značajan interes. Temeljni razlog njihove popularnosti je u svojstvu ciklodekstrina da stvaranjem inkluzijskih kompleksa mijenjaju nepovoljne karakteristike lijekova, kao što je neugodan okus, niska topljivost u vodi i kemijska nestabilnost. Također, ciklodekstrini mogu povećati bioraspoloživost lijeka neovisno o putu primjene. Zahvaljujući biokompatibilnosti i netoksičnosti, ciklodekstrini se mogu koristiti u ljekovitim oblicima namijenjenim za različite putove primjene, uključujući oralni, okularni, nazalni te parenteralni put. Cilj ovog članka je istaknuti važnost i funkcionalnost ciklodekstrina u različitim ljekovitim pripravcima te naznačiti smjerove daljnjeg razvoja.

Ključne riječi: ciklodekstrin; inkluzijski kompleks; primjena lijeka; topljivost u vodi; kemijska stabilnost; bioraspoloživost.