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Cyclodextrins. new opportunities for their application in the production of medicines

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ABSTRACT

Cyclodextrins are among the most important and promising macrocyclic hosts, as they are inexpensive, water-soluble natural products, non-toxic, easily functionalizable and commercially available. The chemistry of cyclodextrin creates many research areas. This review is devoted to studies of cyclodextrins in polymer chemistry and their applications in drug delivery systems. Click reactions as the possibility of producing polymer chains with covalently linked cyclodextrins are described and examples of the use of such polymers in drug delivery are described.

Keywords: Cyclodextrin, pharmacy, chemistry, chemical structure

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INTRODUCTION

Cyclodextrins (CDs) are naturally occurring cyclic oligosaccharides that have recently become available as pharmaceutical adjuvants. In the pharmaceutical industry, cyclodextrins are mainly used as complexing agents to increase water solubility of poorly soluble drugs and increase their bioavailability and stability [1]. Cyclodextrins are able to act as the host of a host-guest complex. Due to their structure, cyclodextrins possess this property: their molecules have a hydrophilic external surface and a through hydrophobic cavity, comparable in size to the size of many organic and inorganic compounds [2]. The cyclodextrin ring is hydrophilic on the outside and relatively stable on the inside. In a liquid or solid state, cyclodextrin molecules are capable of forming compounds with other molecules. These compounds exhibit new physicochemical properties that are not characteristic of the substance separately.

According to the chemical structure, cyclodextrins are built of six, seven or eight (n = 6,7,8) d-glucopyranose units linked by a 1,4-glycosidic link and, accordingly, have the names α-, β- and γ-cyclodextrins (fig. 1).

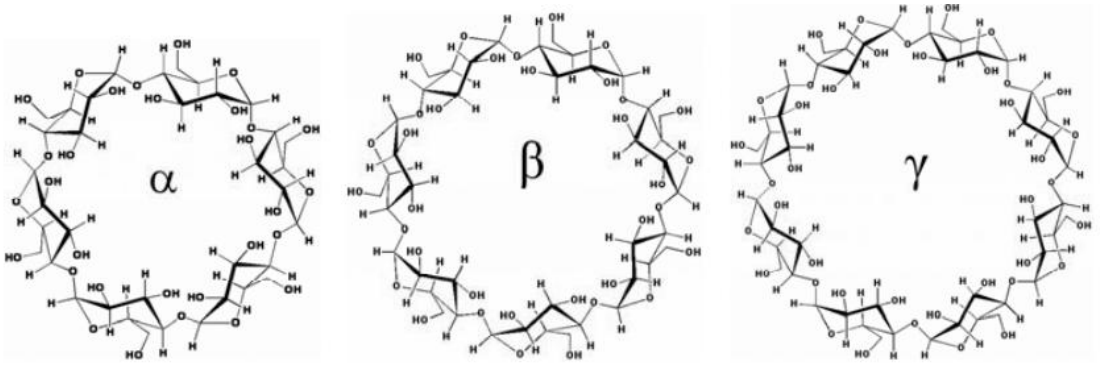

Fig. 1 Structural formulas of cyclodextrins

MATERIAL AND METHOD

In this article, we attempted to study the potential use of cyclodextrins in the synthesis of new drugs using the scientific literature from the database PubMed, Scopus and GoogleScholar

RESULTS

Of the natural cyclodextrins, β-cyclodextrin has acquired promising value, due to its viability, and α- and γ-cyclodextrins are currently expensive [3]. The European Pharmacopoeia (Ph.Eur.) Includes quality standards α-CD (Alphadex), β-CD (Betadex) and HP-β-CD (Hydroxypropyl-betadex), γ-CD - in the Japanese Pharmacopoeia.

In 2000-2004, α-CD, β-CD and γ-CD were listed by the FDA for use as a safe (GRAS) food supplement, and HP-β-CD is listed as inactive pharmaceutical ingredients, in addition to the European Commission also acquired α-CD, β-CD as food additives .. (E459).

The EMA (European Medicines Agency) EMA / CHMP / 495747/2013 provides guidelines for the use of cyclodextrins in dosage forms. Oral availability of cyclodextrins is very low, there are no adverse interactions with vitamins or other nutrients. In large doses (> 1000 mg / kg / day), cyclodextrins can cause reversible diarrhea and an increase in the cecum in animals [12]. There are some data on children under two years of age who received oral solutions of itraconazole up to 200 mg HP-β-CD / kg / day for 2 weeks, which were well tolerated and safe [13].

Studies of nasal administration of water-soluble cyclodextrin complexes of steroid hormones have shown that they provide a rapid increase in the level of drugs in the systemic circulation, avoiding intestinal and hepatic metabolism of the first pass of drugs, while cyclodextrins do not affect the epithelial membranes of the nose [14]. Cyclodextrins not only improve pulmonary drug delivery, but are also absorbed by themselves. Studies conducted with animals have shown that the bioavailability of cyclodextrins is of the order of 66%, 74% and 80%, respectively [14].

When using animal oil suppositories containing β-CD, RM-β-CD or HP-β-CD, it was found that a significant amount of intact HP-β-CD or RM-β-CD is excreted in the urine within 24 hours after administration . Moreover, when β-CD was administered in vivo together with ethyl 4-biphenylacetate (EBA, anti-inflammatory prodrug), relatively high doses of HP-β-CD (> 26% of the dose) and RM-β-CD (> 21% of the dose) compared with β-CD (> 5% of the dose) were

absorbed from the rectum of the animal [15]. Cyclodextrins can also act as amplifiers for rectal absorption of drugs, including themselves: the higher the dose of cyclodextrins, the higher the percentage of absorption. In rats, up to 5% β-CD and 26% HP-β-CD can be absorbed. Suppositories with up to 230 mg of β-CD and 12% HP-β-CD do not cause irritation of the rectal mucosa, but α-CD potentially causes damage to the layer of epithelial cells [14-15].

Cyclodextrins are poorly absorbed transdermally, so when applying an aqueous solution of HP-β-CD, the absorption was low - 0.02%. On the contrary, when cyclodextrins were used under occlusive dressings and / or with vehicles containing absorption-enhancing agents, penetration was significantly enhanced. When hydrophilic ointment containing EBA and β-CD c prodrug complexes in occlusal conditions is applied to the skin of animals in high doses, cyclodextrins are released from the carrier in the following order: -CD <RM-β-CD <HP-β-CD, sequence, which corresponds to the order of enhancing the release of EBA. The amount of remaining cyclodextrins in the carrier 24 hours after application was 88%, 57%, and 47% for β-CD, RM-β-CD, and HP-β-CD, respectively [16-17].

Cyclodextrins increase the solubility of the drug in water, thereby reducing local irritation and increasing stability. Cyclodextrins enhance drug penetration when used in ophthalmogolia, transferring lipophilic water-insoluble drug molecules through the aqueous layer of mucin, thereby increasing drug delivery to the surface of the cornea of the eye [18].

Also, α -CD can mediate the transport of drugs through the layers of the cornea, in addition, it can directly affect the membrane of the structure, especially with layers of lipoid epithelial cells that cause some destabilization of the barrier, resulting in increased permeability for itself and the drug molecule [19].

Intravenous cyclodextrins quickly disappear from the systemic circulation and are excreted by the kidneys intact. The time t½ varies from 20 to 100 minutes, with the exception of RM-β-CD, in which t½ is 7 hours.

Alpha-CD, β-CD and RM-β-CD showed renal toxicity at relatively low doses after parenteral administration. High doses of HP-β-CD and SBE-β-CD can cause tubular renal tubular vacuolation without loss of renal function in animals. This temporary increase in apical vacuole size is also seen as an adaptive response to the excretion of osmotic agents, such as glucose, mannitol and dextran, at high concentrations. Long-term treatment causes these mostly reversible effects at lower doses. HP-β-CD and SBE-β-CD are considered safe at relatively high doses and are most commonly used in parenteral preparations.

The route of administration of the drug	α- CD	β – CD	γ - CD	HP-β-CD	SBE-β-CD	RM-β-CD
Oral		+	+	+	+	
Nasal						+
Rectal		+		+		
Dermal		+	+	+		
Ocular		+		+		+
Parenteral	+			+	+	

From the presented table, it is seen that the most used among cyclodextrins is HP-β-CD.

The safety and toxicity of HP-β-CDs usually depends on the route of administration and the type of HP-β-CD used. When taken orally, HP-β-CD is slightly absorbed from the gastrointestinal tract and is thus practically nontoxic due to its hydrophilic nature.

HP-β-CD is considered safe for parenteral administration and is usually used with antitumor and immunomodulating drugs [4]. The Food and Drug Administration (FDA) approved liposomal pharmaceuticals such as doxorubicin (Doxil), daunorubicin (DaunoXome), cytarabine (DepoCyt) and amphotericin B (Abelcet), which were less toxic alternatives to conventional drugs forms [5].

The formation of an inclusion complex with non-toxic agents leads to an improvement in the physicochemical properties of the drug. Most anticancer drugs were included in the complex with cyclodextrin and their derivatives to improve / increase solubility and stability, increase bioavailability and dissolution, reduce toxicity and change physicochemical characteristics [6-7].

The complexation of doxorubicin with γ-CD and HP-γ-CD led to an increase in permeability through the blood-brain barrier due to membrane destruction [58]. Similarly, the conjugate of β-CD-

PEG with folic acid increased the solubility of chlorambucil. The complexation of 9-nitro-camptothecin with HP-β-CD led to a significant increase in antitumor activity with low toxicity [8].

There are studies in the literature on the toxicity of HP-β-CD [9]. The studies revealed that HP-β-CD is well tolerated in tested animal species (rats, mice, and dogs), especially when administered orally, and shows only limited toxicity. In studies with a shorter duration, small biochemical changes were noted, while studies with a longer duration, up to three months, led to additional minor hematological changes, but there were no histopathological changes. With intravenous administration, histopathological changes were observed in the lungs, liver, and kidneys, but all results were reversible and no effect was achieved.

Carcinogenicity studies showed non-carcinogenic changes noted in the urinary tract, but these changes were also reversible and did not impair renal function. There was no effect on the development of the embryo and fetus in either rats or rabbits. It has been shown that HP-β-CD is also well tolerated by humans, with the main side effect being diarrhea, and no side effects on kidney function have been reported to date. The authors of [10] conducted studies on the effect of HP-βC-D on Nimann-Peak type C disease (NPC), which is a fatal hereditary neurodegenerative disease characterized by massive accumulation of cholesterol in lysosomes and late endosomes due to a defect in intracellular cholesterol transport. Studies have shown that 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) eliminates the defect in cholesterol accumulation in an animal model. HP-β-CD is known to bind cholesterol; however, the mechanisms by which HP-β-CD mediates cholesterol release from LE / LY compartments are still unknown. In addition, another derivative of cyclodextrin (CD), 2-hydroxypropyl-γ-cyclodextrin (HP-γ-CD), has been shown to reduce intracellular cholesterol accumulation in NPC patient cells and in the NPC mouse model. The data showed that treatment with both CDs induces the expression of lysosome-associated membrane protein in cells obtained from patients with NPCs. As a result of the research, the range of application of cyclodextrins in medicine was expanded.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are very effective drugs, but their use is associated with a wide range of adverse reactions that make up a wide clinical spectrum, ranging from dyspepsia, heartburn and stomach discomfort to more serious events. One of the ways to develop NSAIDs with better gastrointestinal tolerance is by combining these molecules with cyclodextrins (CD), which leads to the formation of so-called “inclusion complexes” that may have physical, chemical and biological properties that differ from the properties of the drug or cyclodextrin.

CONCLUSION

The piroxicam-β-cyclodextrin complex has been used in Europe for 25 years. The preclinical and clinical pharmacology of piroxicam-β-cyclodextrin shows that the inclusion complex of β-cyclodextrinpiroxicam is better tolerated from the upper gastrointestinal tract than free piroxicam, while preserving all the analgesic and anti-inflammatory properties of the parent compound. In addition, the drug is endowed with a fast absorption rate, which leads to a more rapid manifestation of analgesic activity, an effect confirmed in several clinical studies. Analysis of available tests shows that piroxicam-β-cyclodextrin has a gastrointestinal tract safety profile that is better than that of uncomplexedpiroxicam [11].

Thus, numerous studies and experience of use have shown that HP-β-CD are well tolerated, non-toxic, when used in safe concentration ranges, are used to improve a variety of dosage forms - tablets, ointments, suppositories, eye drops, etc., have a high biocompatibility, easily decomposed and excreted by the body. On their basis, you can create unique modifications of many drugs, which is a huge breakthrough in pharmaceutical technology.

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