Safety of 2-Hydroxypropyl-β-cyclodextrin (HP-β-CD)

Chemistry of cyclodextrins

Cyclodextrins (CDs) are a class of naturally-occurring compounds whose chemical structure is composed of several connected glucose molecules that create a hydrophilic (water-loving) exterior and a hydrophobic (oily, water-hating) interior cavity. This structure allows hydrophobic drugs and other therapeutic agents to be loaded into the interior cavity of the CD, which allows the loaded drugs to be dissolved in water. CDs can also be used to enhance the bioavailability and stability of drugs and also reduce adverse side effects such as irritation and bad odors or tastes.[1] Their structure can be changed by adding different functional groups, but this can drastically alter their properties, including their solubility, bioavailability, and toxicity. For example, methyl-β-cyclodextrin has been used to kill cancer cells, but its use is limited due to potential toxicity, including nephrotoxicity.[2] In contrast, other CDs have shown no toxicity and are suitable for use as drug excipients. Examples include sulfobutylether-β-CD, which is non-nephrotoxic and is used in at least 13 FDA-approved medications.[3] This clearly shows that CDs have different properties, including different toxicities, making it important to evaluate the safety of any new CD derivative.

2-Hydroxypropyl-β-cyclodextrin and its applications

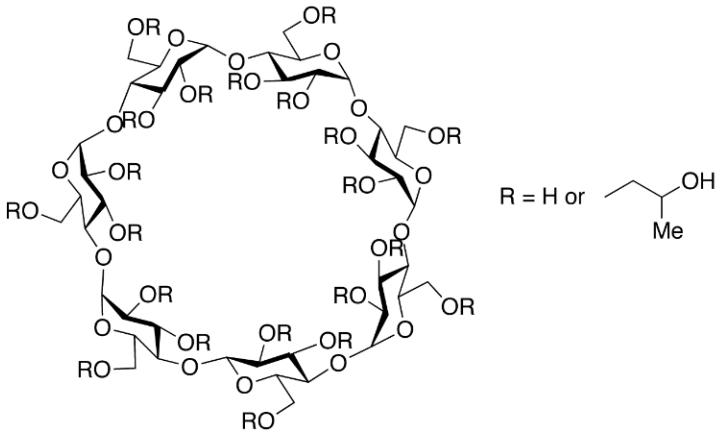

Figure 1 Chemical structure of 2-hydroxypropyl-β-cyclodextrin (HP-β-CD). The structure of β-CD may contain anywhere from 1 to 21 HP groups, as represented by R in the figure above.

2-Hydroxypropyl-β-cyclodextrin (HP-β-CD) is a derivative of β-cyclodextrin, to which hydroxypropyl groups have been added to increase the water solubility of the original β-CD molecule (Figure 1).[4] In 2016, the U.S. FDA recognized that HP-β-CD was suitable for oral and intravenous administration.[5] Over the years, the number of citations mentioning this compound in PubMed steadily increased (Figure 2), indicating extreme interest in this target. Both academic and commercial research has used this CD derivative to form complexes with a variety of drugs to improve their solubility and pharmacokinetics.

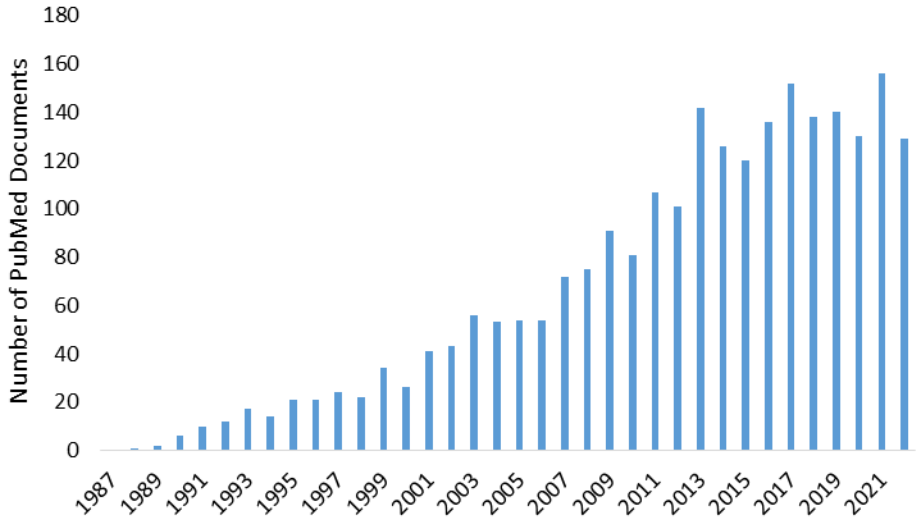

Figure 2 The number of citations mentioning 2-hydroxypropyl-β-cyclodextrin in PubMed.

In some of the earliest research on HP-β-CD, it was used to complex drugs and investigated for its ability to remove cholesterol.[4,6] Research continued, and it was eventually used to complex the broad-spectrum triazole antifungal agent, itraconazole, which was approved for intravenous administration by the FDA in 1999.[1,7] More recent studies have investigated this complex's oral administration.[8] HP-β-CD has also been used to complex the NSAID naproxen[9] and to increase the pharmacokinetics of an HIV-preventing drug.[10] HP-β-CD has been used as a potential therapeutic agent to treat various cancers,[2] including breast cancer.[11] Mouse models are often used as a proxy for humans when performing initial studies of new pharmaceutical compounds. In a study using a mouse model, researchers showed that it inhibited the growth of leukemia cells when administered without showing significant adverse effects.[2] When HP-β-CD was used to treat stroke symptoms in mice, the results confirmed that it could be safely applied multiple times per week for seven weeks total.[12] In a similar fashion to drug complexation, HP-β-CD can complex cholesterol in its internal cavity, which allows it to deplete intracellular cholesterol.[13] When used alone, scientific studies have shown that HP-β-CD can help reduce cholesterol without harmful side effects in human skin cells with high cholesterol by chelating (i.e., binding with) cholesterol and then removing it.[14]

HP-β-CD safety

Several governing agencies are responsible for assessing the safety of new compounds, including the Food and Drug Administration (FDA) in the United States and the Therapeutic Goods Administration (TGA) in Australia. The FDA has listed HP-β-CD as an approved inactive ingredient in several pharmaceuticals,[15] and a TGA assessment concluded that "There are no nonclinical objections to registration of generic voriconazole (Vorcon) containing HP-β-CD excipient in adults."[16] In fact, HP-β-CD is so safe that it has been included in the J&J/Janssen COVID-19 Vaccine (under the name hydroxypropylbetadex),[17] which has received provisional

approval for administration by the TGA.[18] It has also been investigated as an adjuvant for a flu vaccine in Japan.[19,20] As shown above, decades of research have clearly demonstrated the numerous pharmaceutical applications of HP-β-CD. However, as with any pharmaceutical compound, it is important to examine its potential toxicity, i.e., conduct pharmacological screening. A variety of factors affect the efficacy and safety profile of a drug, including intrinsic factors such as its chemical structure, administration route, and dose.

Structure

HP-β-CD was shown to be less cytotoxic than unmodified β-CD and methylated CDs.[21] For HP-β-CD, even the number of HP groups (Figure 1) must be considered. Studies have shown that HP-β-CD is generally non-cytotoxic, regardless of the number of HP groups, but a slight toxicity was noted for 10 HP groups, which decreased the Caco-2 cell viability to 80%.[22] A different study showed that HP-β-CD with a moderate number (~6) of HP groups showed slightly greater nephrotoxicity than higher or lower degrees of substitution. However, the reason for this was unclear and may be species-dependent, so the authors suggested that a similar study be conducted in humans.[23] Most studies have used an average number of 5 HP groups, which is generally considered safe.

Administration Route

HP-β-CD may be administered in a variety of routes, including orally, rectally, and intravenously. When discussing a compound's safety and toxicity, it is important to consider the administration route because of the chemical changes it may undergo as it circulates through the body. The administration route is also important because a drug may cause local irritation, and it also determines how quickly the drug will take effect. For example, first-pass metabolism occurs during oral administration but not when injected.[24] This can potentially alter the toxicity or efficacy of substances and lead to a lower drug concentration at the site of action. In contrast, during intravenous administration, a drug bypasses first-pass metabolism and absorption barriers and begins circulating to provide an immediate effect.

Oral

Studies have shown that various CDs are non-toxic when administered orally because they are not absorbed in the gastrointestinal tract. HP-β-CD was tolerated when administered orally with itraconazole at doses with an equivalent daily dose of HP-β-CD of 400 mg/kg.[25,26] One study also used it to enhance the bioavailability of itraconazole in 30 subjects, and only two subjects showed adverse effects, including a mild rash and a mild headache, which resolved within one day and did not recur.[27]

Injection

In 2007, 13 children were injected with 0.1 g/kg of HP-β-CD and showed no adverse effects.[28] More recently, HP-β-CD was injected into a child and halted the progression of early Niemann–Pick disease type C without signs of toxicity.[29] When injected into the tail vein of mice, HP-β-CD showed no pathological signs.[30] In another study, HP-β-CD was used to solubilize diclofenac to treat postsurgical pain and was intravenously administered to patients for ≤ 5 days postoperatively. The treatment did not show any worse cardiovascular adverse effects compared with the placebo group and showed only a 1.3% risk of these events during a follow-up period.[31] In a similar study, the same groups of authors investigated the safety of the injectable HP-β-CD-diclofenac complex and showed that when used to treat acute post-operative pain, it did not show renal safety risks greater than those of the placebo group.[32] Another study investigated the use of HP-β-CD-diclofenac in older patients (≥65 years), once again showing similar treatment-emergent adverse events as the placebo group and indicating that HP-β-CD did not produce significant adverse effects.[33] The most frequent adverse effects associated with HP-β-CD-diclofenac were generally constipation, infusion-site pain, and dizziness when injected as an intravenous bolus formulation.[34] HP-β-CD-diclofenac is safe for intramuscular injection[35] and has also been shown to reduce the need for opioids after surgery.[36] When used to complex progesterone in a 25 mg solution, HP-β-CD was just as safe as other commercially-available formulations.[37] It was also intravenously injected into healthy women in a formulation with letermovir and was tolerated when used daily.[38] HP-β-CD-diclofenac was also injected before third molar surgery to reduce pain, and 14% of patients showed minor adverse effects, and 2 of these patients showed flap necrosis, which resolved on its own.[39]

Dermal/Topical

Some studies have shown that HP-β-CD is safe when used in perfumes. It was also investigated as a means to treat recurrent herpes labialis, in which a 6-month double-blind study was conducted on 40 patients. The results showed that although HP-β-CD was not effective at treating this condition, it was nonetheless safe, and subjects in the treatment group given HP-β-CD did not show significantly different adverse effects compared with the placebo group.[40]

Rectal

There are limited studies on the rectal administration of HP-β-CD, but they have indicated that suppositories with up to 12% of HP-β-CD do not irritate the rectal mucosa.[41] It has also been used to complex 5-fluorouracil to treat colorectal cancer without any irritation or damage to rectal sites.[42]

Ocular

2-HP-β-CD/PLGA nanoparticle complexes were formed and used as eye droplets. They showed no worse irritation than saline droplets in rabbit models.[43] HP-β-CD is also used in commercially available aqueous eye drop products because it does not irritate the corneal epithelium.[44]

Spinal

Although some studies have implicated HP-β-CD in hearing loss in humans,[45] it was directly injected into cerebrospinal fluid intracerebroventricularly, i.e., directly into the spine, so that it could reach the brain. This administration route was chosen because HP-β-CD was being investigated as a treatment for Niemann-Pick type C1 disease, a fatal disorder that leads to the accumulation of cholesterol in various parts of the body, including the brain. Because of its ability to form a complex with cholesterol and eliminate it from the body, the authors investigated whether HP-β-CD could also remove cholesterol from the brain. Unfortunately, hearing loss was observed in patients when HP-β-CD was injected via the spine.[46,47] In another study, when it was administered via the spine in two humans, it showed no adverse side effects during treatment, but one patient showed transient cloudiness of the lungs with a fever after two years. In 2020, researchers developed a potential method to reduce the ototoxicity of HP-β-CD by polymerizing it and then using this polymeric form *in vitro* to dissolve cholesterol and induce its efflux from macrophages. The polymerized form could be used at a high dose of 8 g/kg without inducing significant ototoxicity.[48] However, since HP-β-CD does not cross the blood-brain barrier,[49] current studies suggest that it does not pose such severe safety concerns when administered via any other route, which makes the polymeric form unnecessary for these routes.[50]

Dose

The dose of any drug is a determinant of its toxicity, which often manifests at doses above those needed to achieve a therapeutic effect; however, both toxic and therapeutic effects can occur simultaneously.[51] This is such an important issue that the TGA requires that when an already-approved drug is proposed for a new administration route or a higher daily dose, additional data must be provided that shows the effects of these new doses or routes.[16]

HP-β-CD is generally a relatively safe drug, but there are some adverse effects worth mentioning that have been observed *in vitro* and also in animal and human studies. A high dose of HP-β-CD (3.5 mM CD for 15 d) was shown to modestly inhibit the growth of HepG2 cells, potentially by disrupting their cholesterol homeostasis.[52] It has been shown to increase the risk of soft stool and diarrhea when administered orally at a dose of 16 grams or more per day, but this was a reversible side-effect, i.e., it disappeared when after the administration of HP-β-CD ceased. HP-β-CD solutions with a concentration of less than 10% did not induce tissue damage in rats when administered nasally. For rectal administration, solutions with a concentration of less than 12% HP-β-CD showed no rectal mucosa irritation in rabbits. A recent study from

Nature Scientific Reports suggested that HP-β-CD should only be used to treat high cholesterol because its proposed mechanism of action involves an up-regulation of cholesterol biosynthesis in normal human cells.[14] The FDA states that the maximum dose of 0.4% when HP-β-CD is administered intravenously. When used as an excipient for parenteral administration, HP-β-CD should not exceed 250 mg/kg per day over 21 days in humans more than 2 years of age. When used as an inactive ingredient, the FDA has specified the maximum daily exposures (MDE) of HP-β-CD depending on the administration route. For intramuscular and intravenous injection, the MDE is 1,333 mg, while for oral administration, the MDE ranges from 22 mg to 8,000 mg.[15] When up to 24 g of HP-β-CD was administered daily for 15 days, no side effects were observed.[16] The TGA has stated that the no-observed-adverse-effect level (NOAEL) of HP-β-CD is 320 mg/kg per day.[16] As noted above, a polymerized form of HP-β-CD could be used at a high dose of 8 g/kg without inducing significant ototoxicity.[48]

In renal-impaired patients, the dose is a particularly important factor because the liver may not be able to metabolize the drug as efficiently as a healthy liver. One study has shown that HP-β-CD-diclofenac could be safely administered to patients with mild to moderate renal insufficiency without needing to lower the dose of HP-β-CD.[53] Similarly, there are some concerns that children younger than 2 years old may experience osmotic nephrosis because they have a lower renal function than adults, which may lead to the accumulation of HP-β-CD.[16] However, in one study, infants from 7 months to 5 years old were treated with products that contained HP-β-CD, and no harmful effects were observed when they were given a daily dose of HP-β-CD of 100 mg/kg.[54] However, it is suggested that more data is needed to examine the association between HP-β-CD and nephrosis in children younger than 2 years old.[16]

Conclusions

More than 35 years of research from numerous peer-reviewed studies and federal agencies around the world has indicated that HP-β-CD is not only safe but has potential therapeutic effects when used in both mouse models and humans, including an ability to reduce cholesterol throughout the body. Multiple academic studies, as well as the US FDA and the Australian TGA, have confirmed that HP-β-CD is safe for administration via several routes, provided the administered dose does not exceed route-specific thresholds. Even when using HP-β-CD above the recommended concentration, evidence has shown that the side effects are relatively minor and generally reversible, with many typically resolving on their own. The only major documented issues associated with HP-β-CD have been associated with spinal administration in humans, which allowed HP-β-CD to directly enter the brain. Since HP-β-CD does not cross the blood-brain barrier, this is not a concern when it is administered via other more common routes, such as orally, rectally, or intravenously. Thus, it remains a safe, effective ingredient for solubilizing various drugs and also as a treatment for lowering cholesterol when used alone.

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