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Potential Impact of Cyclodextrin-Containing Formulations in Toxicity Evaluation of Novel Compounds in Early Drug Discovery

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Abstract

Cyclodextrins (CDs) are widely used as enabling excipients to improve in vivo drug delivery. The ability of CDs to form inclusion complexes with drugs and thereby improving solubility and stability of drugs is well established, and has been successfully used for several drugs on the market. Combined with well established preclinical and clinical safety profiles for selected CDs, they are of interest as excipients in preclinical and clinical stages of drug development. Another feature of CDs is their demonstrated ability to mitigate local toxicities of drugs. While this feature makes them attractive from a clinical drug delivery perspective, it may not be ideal from a preclinical toxicology evaluation perspective when the new chemical entities have intrinsic irritant or cytotoxic characteristics, which may be shielded by CDs. Herein, we review use of CDs in pharmaceuticals, focusing on their potential to mitigate toxicities of compounds, and suggest that this very potential may undermine toxicity evaluation, especially by oral route, of novel compounds during early drug discovery.

Abbreviations

CD: Cyclodextrins; HP-β-CD: Hydroxypropyl-β-cyclodextrin; SBE-β-CD: Sulfobutylether-β-cyclodextrin

Introduction

Cyclodextrins are cyclic oligosaccharides composed of glucopyranoside units. They are derived from starch by the enzyme glucosyltransferase, and are named based on the number of glucose units, and chemical modification. The parent CDs are α-, β-, and γ-cyclodextrins, with six, seven and eight glucose residues, respectively. Parent and chemically modified CDs, e.g., hydroxypropyl-β-cyclodextrin (HP-β-CD) and sulfobutylether-β-cyclodextrin (SBE-β-CD) are important excipients used worldwide in products from the pharmaceutical, food and cosmetic industries [1-6]. Specifically, the ability of CDs to allow formulation of novel compounds at high concentration has made them important excipients in nonclinical toxicology studies.

UTILITY of CDs

CDs have a cup-like structure with a hydrophilic exterior and a hydrophobic interior, giving them the ability to encapsulate or form inclusion complexes with hydrophobic guest molecules in an aqueous environment (Figure 1). This very mechanistic feature provides the ability for CDs to 1) improve solubility and dissolution and thereby, oral bioavailability of compounds, e.g., haloperidol and HP-β-CD [7]; 2) improve chemical and physical stability and thereby, shelf life of compounds, e.g., sulfamethoxazole/trimethoprim and HP-β-CD [8]; and 3) mask odors and tastes, e.g., dextromethorphan HBr and β-CD [1]. For these very reasons, CDs are widely used in pharmaceutical, food and cosmetic industries. Specifically, in pharmaceuticals, CDs are used to improve in vivo drug delivery. A comprehensive list of marketed drugs (worldwide) formulated with CDs includes branded, generic, and over-the-counter products are provided in Table 1. The CD-containing formulations deliver drugs via various routes. Further, the ability of CDs to complex with molecules may allow treatment of specific conditions: α-CD and potential to decrease serum cholesterol [9]; Sugammadex (a modified γ-CD) and reversal of neuromuscular blockade [10]; and HP-β-CD and Niemann-Pick disease Type C [11].

Figure 1: Formation of HP-β-CD-drug inclusion complex.

Safety of CDs

Parent CDs are found in >200 food products and are considered as natural products (Japan), novel food/food additive (EU) and, generally regarded as safe (GRAS) for use as additives/carriers/flavor protectants in food products (US) [6]. Some of the CDs (γ-CD, HP-β-CD and SBE-β-CD) are also listed as inactive ingredients in approved drug products (USFDA) [14]. When given orally, CDs are generally not well absorbed intact in the gastrointestinal tract, although renal effects subsequent to systemic absorption are reported [12,15]. In the gastrointestinal tract, CDs are hydrolyzed to varied extents depending on the type. The parent CDs, α- and β-, but not γ-CD are practically resistant to salivary and pancreatic amylases, and all are degraded by colon microflora [5,6,12]. Chemically modified CDs are more

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resistant to degradation, and are generally excreted intact in feces [5]. The most common findings with orally administered CDs (α-, β-, γ-, HP-β- and SBE-β-CD) are loose and soft feces in rodents and non-rodents [15,16]. Orally administered HP-β-CD is also reported to be associated with hepatotoxicity as evidenced from increases in serum transaminases in rodents [15,17]. Although CDs are hemolytic in vitro, the toxicological implication of this in vivo is negligible [16], likely due to low concentrations administered parenterally. Parenterally administered CDs are excreted intact in the urine and are associated with renal toxicity. Complexation of CDs with cholesterol or its esters and accumulation of insoluble cholesterol complexes in renal tubule cells likely leads to renal injury and dysfunction [18]. For further details on the safety of CDs, please refer to reviews from Gould and Scott [15], Stella and He [16] and monographs on α-, β-, γ- CDs from International Programme on Chemical Safety [19-21]. The LD50s or NOEL/NOAELs for selected CDs are listed in Table 2.

Table 1: List of drugs with selected cyclodextrins marketed world-wide.

Drug	Cyclodextrin	Route	Trade name (Reference)
Aceclofenac	β-CD*	Oral	Acerap (A), Flexidol (A)
Alprostadil	α-CD	Intracavernous	Edex (B), Caverject Impulse (B)
Amiodarone	SBE-β-CD	Intravenous	Nexterone (B)
Aripiprazole	SBE-β-CD	Intramuscular	Abilify (B)
Benexate	β-CD	Oral	Lonmiel (C), Ulgut (C)
Carfilzomib	SBE-β-CD	Intravenous	Kyprolis (B)
Cetirizine hydrochloride	β-CD	Oral	Zyrtec chewable (B), Generic Cetirizine HCl chewable (D)
Cholecalciferol	β-CD	Oral	Natures Aid Vitamin D3 (E)
Chlorphenaramine maleate + acetaminophen	β-CD	Oral	Cold Remedy Soothing (B)
Desloratadine	β-CD	Oral	Generic Desloratadine (B)
Dextromethorphan hydrobromide/ Guaifenesin	β-CD	Oral	Stona Cough syrup (B)
Ethinylestradiol/ Drospirenone	β-CD	Oral	Yaz (B), Safyral (B), Beyaz (B)
Fenofibrate	β-CD	Oral	Generic Fenofibrate (B)
Flunarizine	β-CD	Oral	Fluner (A)
Itraconazole	HP-β-CD	Intravenous	Sporanox (B)
Levothyroxine sodium	HP-β-CD	Oral	Leventa (B)
Maropitant	SBE-β-CD	Subcutaneous	Cerenia (B)
Metronidazole	β-CD	Topical	Metrogel (B)
Naphazoline hydrochloride	β-CD	Ophthalmic	Clear Eyes Cooling Itchy Eye relief & Redness relief (B)
Nicotine	β-CD	Oral	Nicorette (C)
Nimesulide	β-CD	Oral	Abinim-B (A), Nizer (A)
Octinoxate/ Avobenzone	HP-β-CD	Topical	Bleve Bvibrant (B)
Piroxicam	β-CD	Oral	Cycladol (A), Feldex (A), Pyrodex (A)
Pramipexole dihydrochloride	β-CD	Oral	Generic Pramipexole (B)
Risperidone	HP-β-CD	Oral	Generic Risperidone (B)
Telavancin	HP-β-CD	Intravenous	Vibativ (B)
Voriconazole	SBE-β-CD	Intravenous	Vfend (B)
Ziprasidone mesylate	SBE-β-CD	Intramuscular	Geodon (B)

Compiled from the following sources: (A) http://www.medlineindia.com, (B) http://dailymed.nlm.nih.gov, (C) Loftsson et al. [12], Davis and Brewster [13], (D) http://www.drugs.com and (E) Natures aid. For additional CDs and drugs [12,13]. * β-CD = betadex.

Improvement of Toxicity Profiles of Drugs Formulated with CDs

CDs are shown to improve tolerance and/or reduce local toxicity of several compounds (Table 3). Specifically, CDs 1) reduce gastroduodenal injury of several orally administered NSAIDs, e.g, HP-β-CD and flurbiprofen in rats [22]; 2) protect from compound-induced hemolysis in vitro, e.g, β-CD and flufenamic acid in human RBCs [23]; and 3) reduce tissue irritation/injury at the injection/application site of parenterally/topically administered compounds, e.g, β-CD and chlorpromazine in rats [24] and retinoic acid in humans [25]. This protection from local toxicities of compounds likely improves overall tolerability. Piroxicam-β-CD is reported to be better tolerated (relative to uncomplexed piroxicam) in clinical studies [26-28]. Similarly, pegylated liposomal irinotecan complexed with SBE-β-CD was better tolerated in mice than free irinotecan [29]. CDs could also affect the target organ toxicity profile of compounds, e.g, toxicity shifted from proximal to distal intestine when tiaprofenic acid was formulated with diethyl-β-CD based on absorption site changing from proximal to distal intestine [30].

Mechanisms leading to toxicity could range from simple precipitation causing irritation to intrinsic cytotoxicity, which are not always easy to discern for novel compounds. However, it will be helpful to understand the mechanisms to provide context around the toxicity finding and justify the use of CDs in toxicity evaluation. Although a simple cytotoxicity evaluation of test articles in vitro could indicate their potential to cause toxicity, especially, gastrointestinal toxicity in vivo, it is not foolproof as not all the compounds with gastrointestinal toxicity in vivo are highly cytotoxic in vitro. For example, NSAIDs such as indomethacin, rofecoxib and flurbiprofen are not highly cytotoxic in vitro (CC_{50} values of > 0.2 mM); yet they cause gastrointestinal toxicity in vivo. While it is well established that NSAID-induced decrease in prostaglandin synthesis is the leading mechanism of gastrointestinal toxicity [55], NSAIDs are also known to be direct irritants to gastrointestinal mucosa. This is supported by the fact that the gastrointestinal toxicity is significantly reduced when NSAIDs such as indomethacin, rofecoxib and flurbiprofen are administered as inclusion complexes with CDs. We have demonstrated mitigation of cytototoxicity in vitro of indomethacin, rofecoxib and flubiprofen by approximately 2-fold despite reduced precipitation in the presence of HP-β-CD, suggesting that CDs reduce local toxicities and/or improve tolerance of compounds primarily by forming inclusion complexes which effectively reduce direct contact/exposure of compounds to local tissue. Similarly, the examples cited in Table 3, suggest the ability of CDs to reduce local toxicities and/or improve tolerance of compounds by the encapsulation phenomenon. Therefore, from a preclinical toxicity evaluation perspective, use of a complexing formulation such as CDs could mitigate potential

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Table 2: LD50s or NOEL/NOAELs of selected CDs.

Cyclodextrin	Safety		Reference
α-CD	LD50	Rat, IV: 1,000 mg/kg	[19]
β-CD	LD50	Rat, oral: >5,000 mg/kg Rat, IV: 788 mg/kg Dog, oral: >5,000 mg/kg	[20]
γ-CD	LD50	Rat, IV: >3,750 mg/kg Rat, oral: >8,000 mg/kg	[21]
HP-β-CD	NOEL/ NOAEL	1-yr Rat, oral: 500 mg/kg/d 1-mo Dog, oral: 2250 mg/kg/d	[15]
SBE-β-CD	NOEL/ NOAEL	52-wk Dog, oral: 500 mg/kg/d 90-d Rat, oral: 3,600 mg/kg/d	[12]

Table 3: Improved tolerability and/or reduced toxicity of drugs as inclusion complexes with CDs*.

Drug	Cyclo-dextrin	Tolerability/Toxicity finding		References
		Route	Finding (Test system)**	
4-biphenylacetic acid	β-CD, HP-β-CD, DM-β-CD	Oral	Decreased incidence of gastric lesions (R)	[31]
5-fluorouracil (with folinic acid)	β-CD	Intravenous	Reduced phlebitis (Ra, H); improved tolerability as seen by weight loss and hematological parameters (R)	[32,33]
Amphotericin B	HP-β-CD, SBE-β-CD	In vitro	Reduced hemolysis (I, M)	[34]
Chlorpromazine	β-CD, SBE-β-CD	In vitro, intramuscular	Protection from hemolysis (I, H); Decreased tissue damage (Ra)	[23,24]
Diclofenac	HP-β-CD	In vitro	Reduced hemolysis (H)	[35]
DY-9760e	SBE-β-CD	In vitro, intravenous	Inhibited cytotoxicity (I); Inhibited hemolysis (I, Ra), Decreased local vascular irritation (Ra)	[36,37]
Etodolac	β-CD, HP-β-CD, γ-CD	Oral	Reduced gastric injury (R)	[38]
Flufenamic acid	β-CD	In vitro	Protection from hemolysis (I, H)	[23]
Flurbiprofen	HP-β-CD	Oral	Reduced gastric injury (R)	[22]
Indomethacin	β-CD, HP-β-CD	Oral	Reduced gastric lesions (R)	[39,40]
Irinotecan	SBE-β-CD	Intravenous	Decreased body weight loss (M)	[29]
Ketorolac	HP-β-CD	Oral	Reduced ulceration (R)	[41]
Meloxicam	β-CD	Oral	Reduced gastric injury (R)	[42]
Naproxen	β-CD	Oral	Reduced gastric mucosal damage/ulceration (R)	[43]
Nimodipine	HP-β-CD	Intramuscular	Reduced muscle damage (Ra)	[44]
Pilocarpine prodrug (O, O'-dipropionyl (1,4-xylylene) bis(pilocarpate)	SBE-β-CD	Ocular	Reduced irritation (Ra)	[45]
Phenylbutazone	β-CD	Oral	Reduced gastric injury (R)	[46]
Phenytoin	HP-β-CD	Intradermal	Reduced tissue injury (M)	[47]
Piroxicam	β-CD	Oral	Reduced gastroduodenal injury and/or blood loss (H)	[26-28]
Prednisolone	SBE-β-CD	Intramuscular	Reduced tissue damage (Ra)	[48]
Prochlorperazine	β-CD, γ-CD	In vitro, topical	Reduced hemolysis (I, H), Reduced irritation (G)	[49]
Ricobendazole	HP-β-CD	Subcutaneous	Reduced local irritation (S)	[50]
Retinoic acid	β-CD	Topical	Reduced irritation (H)	[25,51]
Rofecoxib	HP-β-CD	Oral	Reduced stomach injury (R)	[52]
Salicylic acid	β-CD	Oral	Reduced stomach injury (R)	[53]
Tiamulin	γ-CD	In vitro, Intramuscular	Prevent hemolysis (I); Reduced irritation (Ra)	[54]
Tiaprofenic acid	DE-β-CD	Oral	Shift of toxicity from proximal to distal intestine (R)	[30]

*Relative to respective drugs without CDs
** G = guinea pig, H = human, I = in vitro, M = mouse, R = rat, Ra = rabbit, S = sheep

tolerability and/or toxicity of novel compounds.

Impact of Using CD-Containing Formulations for Initial Toxicology Evaluation of Drug Candidates

In the natural course of drug development, it is not uncommon to steer towards novel formulations for preclinical toxicity evaluation. This is quite true in case of novel chemotypes for high molecular-weight compounds with less desirable physicochemical properties that make in vivo drug delivery difficult at high dosages necessary for toxicity studies. With CDs, formulation and delivery of high dosages may be practical with a potential for driving higher systemic exposures required for meaningful evaluation of systemic toxicity of such novel compounds. While this is a reasonable early formulation strategy to evaluate novel compounds with poor physicochemical properties, it has to be borne in mind the potential of CDs in mitigating local toxicity, as seen with the examples provided in the previous section and in Table 3. It is evident from these examples that CDs can encapsulate/form inclusion complexes with drugs, reduce direct contact/exposure to local tissue and thereby shield or mask the irritation or intrinsic toxicity potential of compounds that are otherwise potential irritants. Therefore, by analogy, if a novel compound with potential irritant properties were to be evaluated for tolerability and potential toxicities using CD formulation during early drug discovery, the compound may appear better tolerated and with higher safety margins. This is more likely true for gastrointestinal toxicity, if present, of orally administered compounds. This could be misleading and potentially problematic when the formulation is switched to a non-CD formulation later in drug development to accommodate later stage development/ longer term dosing. A non-CD (non-encapsulating or inclusion-forming) formulation would uncover the potential irritant properties of the compound with lower tolerability and eroding safety margins for toxicity which could impact or even terminate compound progression.

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Concluding Remarks

As the search for newer chemical scaffolds continues, the complexities of newer chemical entities grow posing problems for satisfactory in vivo drug delivery. Therefore, it is not uncommon to use excipients such as CDs to improve solubilization and in cases of orally administered drugs, oral bioavailability, thereby driving systemic exposures. While this is essential to adequately evaluate potential systemic toxicities of novel compounds, there is a likelihood of missing potential tolerability and/or toxicity of novel compounds as a result of complexation with CDs. The examples cited in this article while demonstrating the protective feature of CDs which are desirable from a clinical drug delivery/development perspective, also do suggest a limitation of CD formulations from a preclinical toxicity perspective, if they were to be evaluated for potential toxicities using CD formulations. While this potential does not alone preclude utility of CD formulations in toxicity evaluation of novel compounds, one has to be cognizant of potential role of CDs in mitigating toxicity especially for orally administered compounds undermining oral toxicity evaluation of novel compounds during early drug discovery.

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