

Cyclodextrins as a Drug Delivery Carrier for Anti-Cancer Drugs

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REVIEW ARTICLE

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DOI [10.22270/hjhs.v5i4.86](https://doi.org/10.22270/hjhs.v5i4.86)

ABSTRACT

Cyclodextrin “molecules are large with a number of hydrogen donors. Cyclodextrins are widely used as “molecular cages” in the pharmaceutical, agrochemical, food and cosmetic industries. In the pharmaceutical industry they are used as complexing agents to increase the aqueous solubility of poorly soluble drugs and to increase their bioavailability and stability. Chemotherapeutic treatment for cancer has limitations such as poor drug solubility, non-specificity, poor bioavailability and poor survival rate. The lack of efficient treatment has created the need to develop and implement novel technology based on combination strategy of cyclodextrin complexation and nanotechnology with a view to make the therapy more useful and acceptable. The review deals with cyclodextrin and its applications in anti-cancer drug delivery for cancer treatment.

Keywords: Cyclodextrin, poor water solubility, drug delivery, cancer therapy, cyclodextrin, liposome

1. Introduction

Cyclodextrins are chemicals and physically stable macromolecules made by protein degradation of starch. They are water-soluble, biocompatible in nature with hydrophilic outer surface and lipophilic cavity. (1) They have the shape of truncated cone or torus rather than perfect cylinder because of the chair conformation of glucopyranose unit. (2) The CDs of biomedical and pharmaceutical interest are cyclic oligosaccharides made up of six to eight dextrose units (α -, β -, and γ -CDs, respectively) joined through one to four bonds. The most common natural cyclodextrins are α , β , and γ consisting of 6, 7, and 8 glucopyranose units. (3,4) The derivatives of β -cyclodextrin are listed in Table 1.

Cyclodextrin molecules are large with a number of hydrogen donors. Cyclodextrins are widely used as “molecular cages” in the pharmaceutical, agrochemical, food and cosmetic industries. (5) In the pharmaceutical industry they are used as complexing agents to increase the aqueous solubility of poorly soluble drugs and to increase their bioavailability and stability. (6) Cyclodextrin

consists of (α -1,4)-linked α -D-glucopyranose unit with a lipophilic central cavity and the structures of various CDs are as shown in Figure 1. The naturally occurring cyclodextrins have limited aqueous solubility due to the strong intermolecular hydrogen bonding in the crystal state. Substitution of the H-bond forming -OH group has improved their solubility. (7, 8)

Inclusion complexes are formed when the “guest” molecule usually a drug is partially or fully included inside the “host’s cavity” (9). The outer sphere of cyclodextrins is compatible with water, which allows hydrogen bonding cohesive interactions. (10-12) Due to this feature, CDs form inclusion complexes with a wide variety of hydrophobic compounds and change the physicochemical and biological properties of guest molecules. (13) The ability of a CD to form an inclusion complex is a function of steric as well as thermodynamic factors. The driving force for complexation involves the removal of water molecule from hydrophobic cavity and formation of Vander Waal forces, hydrophobic, and hydrogen bond interactions. (14-16) The approach used for complexation is phase solubility study as described by

Higuchi and Connors, which examines the effect of cyclodextrin (solubilizer/ligand) on the drug being solubilized (substrate) and

several examples of cyclodextrin enhanced solubility for various drugs are listed in Table 2.

Table1. Pharmaceutical derivatives of β -cyclodextrins

Cyclodextrin	R=H or
B-Cyclodextrin	-H
2-Hydroxypropyl- β -cyclodextrin	-CH ₂ CHOHCH ₃
Sulfobutylether- β -cyclodextrin sodium salt	-(CH ₂) ₄ SO ₃ ⁻ Na ⁺
2,6 dimethylated- β -cyclodextrin	-CH ₃
Branched β -cyclodextrin	Glucosyl or maltosyl group

2. Cyclodextrin Complexation with Anticancer Drugs

“Chemotherapy has limited therapeutic effect. Limited aqueous solubility (hydrophobicity), degradation in gastrointestinal fluids, insufficient in vitro stability (shelf life), low bioavailability, short in vivo stability (half-life), affinity for intestinal and liver cytochrome P450 (CYP3A4) and P-glycoprotein (P-gp) in the intestinal barrier, poor intestinal permeabilities, and strong dose dependent side effects of promising anticancer drug candidates have long been obstacles in treatment of cancer. (17,18) Lack of selectivity and short blood circulation time which cause various toxic side effects are also issues of major concern. (19) The narrow therapeutic index of some anticancer drugs and the fact that these cytotoxic drugs damage not only cancer cells but also normal and healthy tissue is a major challenge. Multidrug resistance, due to increased efflux pumps such as P-glycoprotein (Pgp) in the cell membrane, which transport most of anticancer drugs out of the cell, is also major problem. (20, 21) Thus, there is a need to develop such a delivery system, which combines safety, efficacy, and convenience. The lack of efficient treatment has created the need to develop and implement novel technology based on combination strategy of cyclodextrin complexation and nanotechnology with a view to make the therapy more useful and acceptable.

The formation of inclusion complex with nontoxic agents leads to improvement in physicochemical properties of drug. (22-27)

Complexation of doxorubicin with γ -CD and HP- γ -CD led to an increase in permeability across blood brain barrier, due to the disruption of the membrane. (28) Similarly, the β -CD-PEG folic acid conjugate increased the solubility of chlorambucil. Complexation of 9- nitro camptothecin with HP- β -CD led to significant enhancement in antitumor activity with low toxicity. (29)

3. Drug in Cyclodextrin in Liposome” as a drug delivery carrier

“Liposomes can encapsulate hydrophilic as well as hydrophobic drug in its aqueous core and lipid bilayer respectively. Additionally, their composition can be adapted to achieve predetermined release and circulation in biological environment. In comparison with ICs, liposomes can encapsulate and retain drug molecule with better stability profile, has long circulation time when PEGylated and are able to deliver drug pay load to the specific sites. But, it is observed that the amount of drug loaded in the bilayer is limited and is determined by the drug to lipid molar ratio which is generally low. Further, lipophilic drugs incorporated in higher amount in bilayer may destabilize the membrane thus impacting formation of stable bilayer thus releasing the content prematurely. (30, 31)

CD and liposomes have been extensively explored as carrier containers to deliver drugs efficiently. However, they differ in their structural properties, drug encapsulation and retention efficiencies and in vivo behavior.

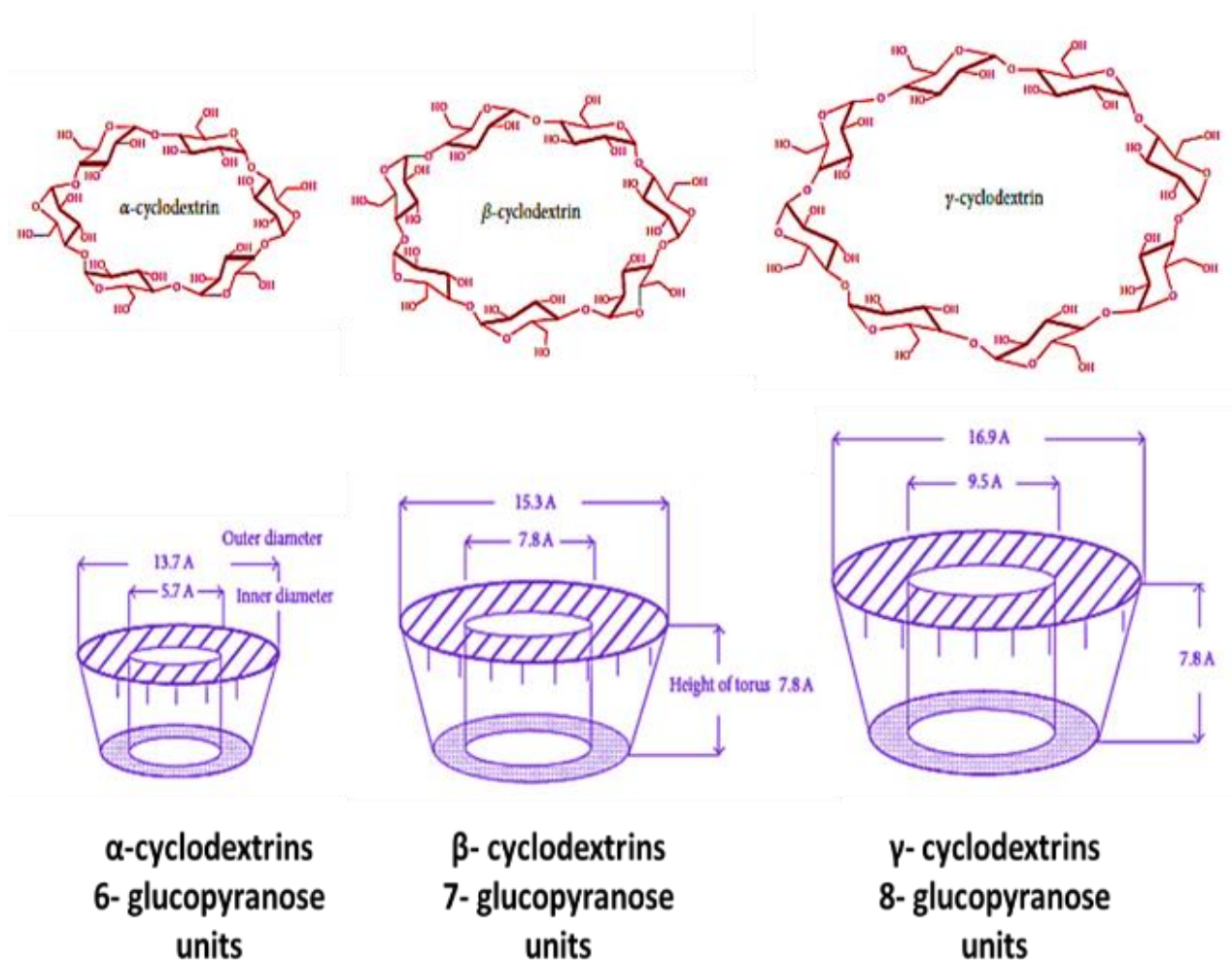


Figure 1. Types of Cyclodextrins

The novel concept, would allow entrapment of water soluble cyclodextrin ICs of water insoluble drugs such as PTX in aqueous core of liposomes. The extent of loading efficiency depends on the entrapment of drug into CD cavity, the concentration of ICs in solution during liposomal formulation and the method of preparation of liposomes. This strategy has been explored by some of the researches to encapsulate water insoluble drugs in aqueous compartment of liposomes and seems to be promising in improving drug to lipid molar ratio and loading efficiency as compared to conventional incorporation of drugs in lipid phase. (32-35) herein, a suitable alternative is to encapsulate drug as CD complex in the aqueous core. Incorporation of lipophilic drug in form of water soluble complex only in core though improves the stability of the system but present limitation in the amount being loaded as the volume of aqueous compartment is very low compared to the volume of bilayer. Such strategy has

been widely used to accommodate a variety of lipophilic drug and has shown improved physicochemical and pharmaceutical properties compared to the conventional liposomes.

4. Cyclodextrin-Based Nanocarriers of Anticancer Drugs

The use of pharmaceutical carriers provides a loom, which is more time and cost-effective than new drug development. (26)

Cellular/molecular biology has contributed to advancement in chemotherapy and gene therapy of cancer, optimistically avoiding the toxic doses of nonspecific agents. The development of new delivery system or new administration schedules offer less expensive, but more effective treatment with negligible/rare side effects. (11-13)

Progress in nanotechnology and Nanoparticles with the size of about 100-

10,000 times smaller than human cells offer unique interaction with biomolecules, which may revolutionize cancer diagnosis and treatment. They have engorged surface area-volume ratio and can overcome both cellular

and noncellular mechanisms of resistance, thereby increasing selectivity of drug towards cancer cell and reducing toxicity towards normal tissues. (9,11,36-38)

Table 2. Examples of Cyclodextrin-enhanced solubility and dissolution

Improvements	Drug
β -cyclodextrin	Nimesulide, sulfomethiazole, lorazepam, Ketoprofen, Griseofulvin, ibuprofen
α -cyclodextrin	Praziquantel
γ -cyclodextrin	Omeprazole, digoxin
HP- β -cyclodextrin	Albendazole, Ketoprofen, Itraconazole, Carbamazepine, Phenytoin, Rutin
DM- β -cyclodextrin	Naproxen, Campotothesin
SBE-- β -cyclodextrin	Danazol, Fluasterone, Spironolactone
RM- β -cyclodextrin	ETH-615, Tacrolimus
Randomly acetylated amorphous - β -cyclodextrin	Naproxen

5. Conclusion

Cyclodextrins are water soluble macromolecules made by protein degradation of starch which are biocompatible in nature with hydrophilic outer surface and lipophilic cavity. Due to this feature, CDs form inclusion complexes with a wide variety of hydrophobic compounds and change the physicochemical and biological properties of guest molecules. Cyclodextrin consists of (α -1,4)-linked α -D-glucopyranose unit with a lipophilic central cavity and the structures of various CDs. CD extensively explored as carrier containers to deliver drugs efficiently. However, the applications of cyclodextrin in clinical setting are yet to be proven for cancer therapeutics.

Acknowledgements

I would like to express my gratitude to Himalayan Journal of Health Sciences who gave me the opportunity to publish the article.

Financial Disclosure statement:

The author received no specific funding for this work.

Conflict of Interest

The author declares that there is no conflict of interest regarding the publication of this article.

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