Review Article

Available online at www.JGTPS.com

ISSN: 2230-7346
Journal of Global Trends in Pharmaceutical Sciences
Volume 4, Issue 2, pp -1099-1106, April- June 2013

BETA (β) CYCLODEXTRINS AS DRUG DELIVERY VEHICLES – AN OVERVIEW

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Journal of Global Trends in Pharmaceutical Sciences

ABSTRACT

Cyclodextrins are torus like molecules with a central core; the ring like structure is responsible for their properties which have been well explored in the areas and have been the topic of current research. There are many types of cyclodextrins based on the number of glucose units (α – 6, β – 7, γ – 8 glucose units). Among them the β cyclodextrin has many applications in the field of pharmacy like drug delivery vehicles, solubility enhancers, protein and peptide drug delivery, stabilizers etc and others like food, agriculture, cosmetics etc. Not only the naturally obtaining Cyclodextrins but also their derivatives produced by chemical means also possess specific properties which are tailor suited and meeting the needs of the present trends in drug delivery. Here the β cyclodextrins and its derivatives as drug delivery vehicles have been discussed.

Keywords: cyclodextrins, β cyclodextrin, drug delivery vehicles.

INTRODUCTION

Cyclodextrins (CDs) are cyclic oligo saccharides composed of atleast six D (+) glucopyranose units. These are linked by α (1-4) bonds[1]. The cyclic structures with less than 6 units cannot be performed due to steric hindrance. The CDs with greater than 9 units are difficult to purify. Recently Endo etal established procedure for isolation and purification for large ring CDs ie δ CD (9 glucose units) [2, 3, 4]. The naturally occurring CDs are α, β, γ with 6, 7, 8 glucose units respectively. The torus like molecular structure is shown in the figure 1[1]. The α, β, γ CDs differ in their ring size and physicochemical properties which are shown in table 1[5, 6].

The CDs contain hydroxyl groups that can be modified chemically to obtain derivated cyclodextrins which had shown improved physicochemical properties. Some of the chemically modified derivatives are given in table 2. The major characteristic of CDs is the formation of the inclusion complexes. The characterization and factors influencing inclusion complex formation are discussed by Rajeswari challa et al[7].

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Classification

Various kinds of CDs derivatives such as hydrophilic, hydrophobic and conic derivatives are developed to improve the physicochemical properties. Some of them are listed in table 3[8].

Table 1: Physico chemical properties of Cyclodextrins

CD	Glucose units	Mol wt	Aqueous solubility 25⁰c (%w/w)	Cavity diameter (A⁰)	Cavity volume (A⁰)³	Crystal water content (%w/w)
α	6	972	12.7	4.7-5.3	174	10.2
β	7	1135	1.88	6.0-6.5	262	13.2-14.5
γ	8	1297	25.6	7.5-8.3	427	8.13-17.7

Table 2: Chemical derivatives of Cyclodextrins

Hydroxyl ethyl β CD	HE β CD
Hydroxyl propyl β CD	HP β CD
Sulfobutyl ether β CD	SBE β CD
Methyl β CD	M β CD
Dimethyl β CD	DM β CD
Randomly dimethylated β CD	RDM β CD
Randomly methylated β CD	RM β CD
Carboxy methyl β CD	CM β CD
Diethyl β CD	DE β CD
Tri o methyl β CD	TRIME β CD
Tri o ethyl β CD	TE β CD
Tri o butyl β CD	TB β CD
Tri o valeryl β CD	TV β CD
Di o hexanoyl β CD	DH β CD
Glucosyl β CD	G1 β CD
Maltosyl β CD	G2 β CD
2 Hydroxy 3- trimethyl ammonio propyl β CD	HTMAP β CD

APPLICATIONS IN PHARMACY

1. Improvement in the pharmaceutical Properties of drug

The inclusion complex formation leads to alteration of many physicochemical properties of the guest molecules like solubility, penetration, absorption etc[9].

Bioavailability

The oral bioavailability is a major limitation for majority of the drugs. There are many research articles showing the increased solubility of the class II drugs. The outer side of the torus structure is hydrophilic and inside is hydrophobic so they can accommodate hydrophibic drugs in the core and increase in the solubility as the external surface is hydrophilic. Some of the examples of the drugs that are tried are

β CD – Meloxicam[10], Imatinib[11], Omeprazole[12], Sildenafil[13], Ginseng Saponin[14], Naftinine[15], Ozonide and anti malarials[16], Nelfinavir[17], Gossypol[18], Celecoxib[19, 28], Valdecoxib[20, 24], Benzocaine[21], Flurbiprfen[22], Quercetin[23], Prednisolone[25], Tricloslan[26], Risperidone[27], 3 Hydroxy flavone[29], Triamterene[30], Fumidine[31], Furan Derivatives[32], Z Glu Tyr and related compounds[33], Ampicillin[34], Rofecoxib[35, 38], Natamycin[36], Bisabolol[37], Diclofenac[39], Ketoconazole[53], Gliclazide[54], palcitaxel[57]

Table 3: Possible uses of cyclodextrins and their derivatives

Derivative	Characteristic	Possible uses
Hydrophilic derivatives		
Methylated β CD		
1. ME β CD	Soluble in cold water and in organic solvents	Oral, dermal
2. DM β CD	surface active hemolytic	Mucosal
3. TM β CD	soluble in water, low hemolytic	Parenteral, oral, mucosal
4. DMA β CD		
Hydroxy alkylated β CD		
1. 2 HE β CD	Amorphous mixture with different d-s (encapsin)	Parenteral, oral, mucosal
2. HP β CD	Highly water soluble (>50%)	Parenteral, oral, mucosal
3. HP β CD	Low toxicity	Parenteral, oral, mucosal
4. 2,3 DHP β CD		Parenteral, oral, mucosal
Branched β CD		
1. G1 β CD	High water soluble	Parenteral, oral, mucosal
2. G2 β CD	Low toxicity	Parenteral, oral, mucosal
3. GVG β CD		Parenteral, oral, mucosal
Hydrophobic derivatives		
Alkylated β CD		
1. DE β CD	Water insoluble, soluble in organic solvents, surface active	Oral, subcutaneous
2. TE β CD		Slow release
Acylated β CD	Water insoluble, soluble in organic solvents	
1. TA β CD	Mucoadhesive	Oral, subcutaneous
2. TB β CD	Formation of films	Slow release
3. TV β CD		Slow release
4. TO β CD		Slow release
Ionizable derivatives		
Anionic β CD		
1. CME β CD	Pk_a = 3 to 4 soluble at pH > 4	Oral, dermal, mucosal (delayed release enteric)
2. β CD sulfate	Pk_a > 1, water soluble	Oral, soluble
3. SBE 4- β CD	water soluble	Parenteral, oral
4. SBE 7- β CD	water soluble	Parenteral, oral
5. Al β CD sulfate	water insoluble	Parenteral (slow release)
6. org 25969	water soluble	Parenteral

α CD – Meloxicam[10], Sildenafil[13], Naftifine[15], Celecoxib[19], Retinoic acid[40], Prednisolone[25], Risperidone[27], 3 hydroxy flavones[29], Z Glu Tyr and related compounds[33]
γ CD - Meloxicam[4], Sildenafil[13], Naftinine[15], Celecoxib[19], Prednisolone[25], Risperidone[27], Z Glu Tyr and related compounds[33], Natamycin[36]
HP β CD - Meloxicam[4], Sildenafil[13], Progesterone[41], Ginseng Saponin[14], Valsertan[42], Celecoxib[19], Quercetin[23], Retinoic acid[40], Valdecoxib[24], Tricloslan[26], Risperidone[27], Camptothecin[43], Ampicillin[34], Furosemide[44], Natamycin[36], Acitrtin[45], Fentanyl[46], Artemisinin[47], Ketoconazole[48, 53], Caprofen[49], Acyclovir[52], Hydrocortisone[57], Palcitaxel[57], Nicardipine[58]
RM β CD – Imatinib[11], Triclosan[26], Acitretin[45], Hydrocortisone[57]
M β CD – Omeprazole[12], Naftifine[15]
PM β CD - Progesterone[41]
SBE β CD – Progesterone[41], Ozonide and antimalarials[16], Quercetin[23], Rofecoxib[35], Fentanyl[46], Danazol[51]
G1 β CD – Prednisolone[25]
G2 β CD – Prednisolone[25], Fentanyl[46]
HE β CD – Flurbiprofen[22], Hydrocortisone[57], Palcitaxel[57]
DM β CD – Disoxanil[50]
CM β CD – Hydrocortisone[57]
SBE γ CD – Prednisolone[25]

Stability

The stability of the labile drugs was increased. Many examples of the drugs that are reported in the literature showed increased stability of the guest molecule. Complexation of Digoxin with γ CD suppressed the acid degradation hydrolysis and also increased the bioavailability[55]. The complexation of Carmofur (a masked compound of 5 FU) with β CD improved its solubility and stability in the GI tract[56]. Better stability of various drugs like Hydrocortisone, Phenytoin, Naproxen, Adenine arabinoside, Adenosine, Ibuprofen, Diazepam, Hydrochlorthiazide have been reported[57]. DM β CD has shown the increased stability and bioavailability of Insulin[59]. Generally CDs cannot enter the cytoplasm but extracellularly added ME β CD had shown some effects.

2. Release control

1. Immediate release[63, 64, 65]

Many drugs like Prostaglandins, Steroids, Non steroidal anti inflammatories, Benzodiazepines, Anti diabetics, Fat soluble vitamins, Nifedipine, Itraconazole, Cyclosporin, Tacrolimus the aqueous solubility and dissolution rate are increased.

2. Prolonged release

Hydrophilic CDs such as Ethylated CDs act as slow release carriers of water soluble drugs like Isosorbide dinitrite, Diltiazem HCl, 5 Fluorouracil[63, 64, 65].

3. Protein and peptide formulation

The oral bioavailability of poorly water soluble drug cyclosporin A is improved by the hydrophilic CDs[66]. Insulin solutions containing the SBE 4 β CD when injected into the dorsal subcutaneous tissues of rats, the plasma immune reactive insulin level rapidly increased and higher levels were maintained for atleast 8hr[67]. The sustained action of Ruserelin was achieved by ethylated β CDs[68]. Sulfated β CD had stabilized and sustained the release of bFGF[69]. HP β CD had significantly inhibited adsorption of insulin on glass containers and polypropylene tubes by interaction with hydrophobic regions of the peptide[70]. HP β CD was effective in reduction of aggregation of rhGH[71, 72].

4. β CD in transdermal drug delivery[73]

The β CD have many applications as transdermal drug delivery vehicles some of them are shown in table 4.

Table 4: Uses of β Cyclodextrins in transdermal drug delivery

Improvement	Drugs
Stability	Tixoxtrol 17–butyrate 21-propionate, Bethamethasone
Release/Permeation	4 Biphenyl acetic acid, Chloramphenicol, Ciprofloxacin, Ethyl 4 bi phenyl acetate, Flurbiprofen, Hydrocortisone, Indomethacin, Nitroglycerine, Norfloxacin, Piroxicam, Prednisolone, Prostaglandin E1, Sulfanilic acid
Local irritation	Chlorpromazine HCl, Tretinoin

β CD derivatives in transdermal route[73]

The β CD derivatives have many applications as transdermal drug delivery vehicles some of them are shown in table 5.

Table 5: Uses of derivatives of β Cyclodextrins in transdermal drug delivery

DM β CD	Release or permeation	4 biphenyl acetic acid, Ethyl 4 bi phenyl acetate, Indomethacin, Prednisolone, Sulfanilic acid
	Local irritation	Chlorpromazine
RM β CD	Release or permeation	Acitretin, Hydrocortisone, Piribedil, S - 9977
HP β CD	Release or permeation	4 biphenyl acetic acid, Dexamethasone, 17 β Estradiol, Ethyl 4 bi phenylyl acetate, Hydrocortisone, Liarozole, Miconazole
G2 β CD	Release or permeation	Hydrocortisone
β CD Polymer	Release or permeation	Tolnaftate, Indomethacin
DE β CD	Release or permeation	Nitroglycerine
CM β CD	Release or permeation	Hydrocortisone
CME β CD	Release or permeation	Prostaglandin E_1

5. Cyclodextrins in rectal drug delivery[73]

The β CD have many applications as rectal drug delivery vehicles some of them are shown in table 6.

Table 6: Uses of β Cyclodextrins in rectal drug delivery

β CD	Stability	AD 1590, Carmofur, Ethyl 4 biphenyl acetate
	Release or permeation	4 biphenyl acetic acid, Ethyl 4 biphenyl acetate, Naproxen
DM β CD	Release or permeation	4 biphenyl acetic acid, Carmofur, Diazepam, Ethyl 4 biphenyl acetate, Flurbiprofen, Insulin
	Local irritation	4 biphenyl acetic acid, Ethyl 4 biphenyl acetate
TM β CD	Release or permeation	Carmofur, Diazepam, Flurbiprofen
HP β CD	Release or permeation	4 biphenyl acetic acid, Ethyl 4 biphenyl acetate, Diazepam
βCD polymer	Selective transfer into Lymphocytes	Carmofur

CONCLUSION

β CDs have many applications in the field of pharmacy as drug delivery vehicles, solubilizers, stabilizers etc. The CDs are not only drug carriers but also possess many other applications like in cosmetics, veterinary, food sciences etc. The clear importance of β CDs as drug delivery systems has been reviewed.

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