Chapter

Effect of Cyclodextrin Derivatization on Solubility and Efficacy of Drugs

Syed Haroon Khalid, Mehreen Bashir, Sajid Asghar, Tauqeer Hussain Mallhi and Ikram Ullah Khan

Abstract

Cyclodextrins (CDs) possess cyclic structure having (α-1,4)-linked glucopyranose units making them less vulnerable to enzymatic degradation as than the linear dextrins. Commonly used natural CDs are α-CD, β-CD, and ɣ-CD with truncated cone-like appearance having lipophilic central cavity and hydrophilic exterior surface. The problem of low aqueous solubility of natural CDs can be addressed by reacting them with various reagents to produce water-soluble derivatives. CD derivatives can be categorized in many ways depending upon their substituents, biological activity, polarity, and size. The derivatization of natural CDs produces noncrystalline and amorphous forms with higher water solubility that are physically and microbiologically stable for prolonged time period. Variety of methods can be used to determine average degree of substitution for a modified CD. Dissociation by dilution is considered as major release mechanism of drugs from complex. It is essential to optimize the amount of CDs for a given preparation because they can either retard or promote drug delivery through biological membrane.

Keywords: natural cyclodextrins, cyclodextrin derivatives, inclusion complex, poorly soluble drugs

1. Introduction

Cyclodextrins (CDs), first isolated by Antoine in 1891, are categorized as cyclic oligosaccharides in which glucose units are repeatedly connected through α-1,4-glycosidic linkages. Their unique property is the availability of various hydroxyl groups that serve as active site to form a variety of derivatives and linkages. CDs possess the capability of forming inclusion complexes with various molecules by incorporating them in their inner hydrophobic cavity, which not only alters the biological and physicochemical properties but also expands their magnitude of application [1–3].

Inclusion complexation is basically the formation of hydrogen bonds and Van der Waals' and hydrophobic interactions along with removal of water molecules [4, 5]. CDs are getting popular as food additives, owing to their solubilizing and protecting properties; they can be effectively used for incorporating vitamins, flavors, fragrances, essential oils, and dyes. They not only provide the controlled

release of drugs and other incorporated molecules but also mask the obnoxious taste and odor [6–9].

The order of water solubility for commonly used cyclodextrins is as follows: β-CD (18.5 gL^{-1}) < α-CD (145gL^{-1}) < γ-CD (232 gL^{-1}). The crystal state of natural CDs indicates strong molecular bonding (high crystal lattice energy) which in turn results in low aqueous solubility. β-CD has limited application as a solubilizing agent due to its low aqueous solubility, despite low cost, ease of availability, and appropriate cavity size. The most likely justification of lower solubility of β-CD is inadequate hydration by water molecule due to intramolecular hydrogen bond interaction offered by optimally arranged secondary hydroxyl groups [10]. Another possible elucidation of low aqueous solubility is the formation of aggregates that leads to unfavorable interactions with the hydrogen bonded structure of water molecule as proposed by Colman and coworkers [11]. β-CD shows Bs-type behavior in phase solubility graph when added to the aqueous drug solution or suspension due to precipitation of respective CD inclusion complex.

The solubilizing power of parent CDs can be enhanced by adopting many different strategies, but the most interesting of them is the derivatization of CDs. The hydroxyl groups of CDs can be substituted to yield a variety of derivatives with significantly high aqueous solubility [12–14]. This chapter discusses the various strategies to functionalize the CDs and the resultant improvement in the aqueous solubility of formed complexes.

2. Functionalized CDs

Parent CDs can be modified through structural modifications by incorporating hydrophilic moieties that will ultimately result in significant increase in aqueous solubility. Furthermore, the inclusion complexes formed by modified CDs have higher complexation efficiencies than that of parent CDs. Rekharsky and Inoue reported various examples of thermodynamic parameters of inclusion complexes involving derivatized CDs [5].

It is noteworthy that derivatization of CDs does not always enhance the complexation. The inhibition and promotion of complexation solely depends upon the type of substituents. Although the strong electrostatic force of attraction between the cationic substituents and organic anion was predicted to promote complexation, paradoxical effect was observed when the complexation of 2-naphthalene sulfonate was reduced with polyamine derivatives of β-CD. An unfavorable entropic effect may be involved that results in decrease in complexation [15]. On the other hand, a favorable electrostatic interaction occurs that leads to formation of zwitterionic corona by substituting both cationic and anionic groups at the primary face that will ultimately enhance the complexation of amino acids [16].

The interdependence of numerous molecular parameters including type of substituent at the CDs, contribution of hydrophobic, and charge character of the guest moiety and competitive self-complexation (possible inclusion complexation of substituent moiety inside the core of CD) was discussed in detail by Kean and his coworkers [17]. While dealing with ionic species, electrostatic effects are usually dominated which exert a paradoxical effect. Based on this status quo, the inclusion complexation of charged CD with organic ions must be evaluated on the basis of electrostatic interactions. The properties of modified CDs are governed by the location of hydroxyl groups on the parent CDs that are going to be substituted. Three different hydroxyl groups that exert different reactivities are located on the glucose repeating unit of a CD molecule, including one primary hydroxyl group attached to

C6 (at the narrow side) and two secondary hydroxyl groups attached to C2 and C3 (at wider side).

Most common derivatives of CDs are discussed in this section.

2.1 Methyl derivatives of CDs

There is variety of ways to perform methylation of native cyclodextrins:

Formerly methyl derivatives were synthesized by using either methyl iodide or dimethyl sulfate [18]. These two reagents are highly toxic and unsafe so may be detrimental to the environment as well as human being. Based on this status quo, it is mandatory to seek new and novel synthetic method to replace these toxic chemicals.

Dimethyl carbonate being eco-friendly could be an attractive alternate in this scenario [19]. The synthesis involves addition of β-CD in dimethylformamide solution followed by stirring until clear solution is obtained. Potassium carbonate is added as catalyst followed by dropwise addition of dimethyl carbonate, and mixture is allowed to stir for the next 48 hours. The catalyst and dimethyl carbonate are removed to produce syrupy consistency. At the end, this concentrate is treated with acetone followed by its removal by filtration. Finally, the product is treated with ether two to three times, and after filtration white powdered product is obtained as indicated in **Figure 1**.

An important feature of methyl β-CD is its degree of substitution that has marked effect on drug solubilization, so it must be carefully investigated [20]. **Table 1** gives the use of methyl derivatives of β-CD with effect on solubility and efficacy of various drugs.

This pharmaceutically significant methylated derivative of β-CD has the following advantages:

- Easy availability (as dry powder/aqueous solution 50%)
- Good water solubility
- Cost-effective
- High inclusion capacity for hydrophobic drugs

2.2 Hydroxypropyl CDs

The replacement of hydroxyl groups of CD by 2-hydroxypropyl moiety can be done by the reaction of CD with propylene oxide in an alkaline aqueous solution (**Figure 2a**) [31]. An isopropylene (oligomeric hydroxypropylene) side chain is formed for high degree of substitution (**Figure 2b**).

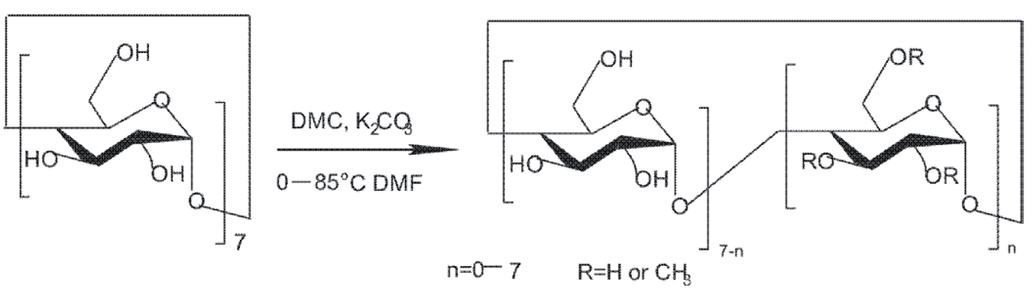

Figure 1.
Synthesis of methyl β-CD [21].

Author	Drug	Additives (if used)	Effects
Schipper et al. [22]	Insulin	—	Improved nasal absorption
Schipper et al. [23]	Salmon calcitonin	—	Enhanced nasal penetration
Sigurdsson et al. [24]	Dexamethasone	—	Localized drug delivery to anterior eye segment
Soares-Sobrinho et al. [25]	Benznidazole	PVP, HPMC	Enhanced solubility, reduced toxicity
Mathiron et al. [26]	Midazolam	—	Improved solubility, protective effect on drug degradation
Chao et al. [27]	Ofloxacin	—	Significant increase in solubility, improved pharmacological efficacy
Vieira et al. [28]	Efavirenz	PVP	Improved dissolution profile, increased stability
Rassu et al. [29]	Deferoxamine mesylate	—	Improved bioavailability, avoidance of systemic exposure
Terauchi et al. [30]	Simvastatin	—	Improved solubility, effective bone regeneration therapy

Table 1.
Effect of methyl derivatives of β-CD on solubility and efficacy of drugs.

The characterization of finally synthesized hydroxypropyl derivatives involves determination of average number of substituents on the cyclodextrin molecule (degree of substitution). According to latest US and European pharmacopoeias, the acceptable range for DS is 2.8–10.5 for HPβCD. Degree of substitution can be measured by a variety of techniques including near-infrared reflectance spectroscopy, nuclear magnetic resonance (NMR), microcalorimetric titration [33], mass spectrometry (MS), differential scanning calorimetry (DSC) [34], and reductive-cleavage and methylation analysis.

Encapsin™ and Molecusol™ are the trade names of commercially available form of hydroxyalkyl derivative (2-hydroxypropyl-β-CD). Various clinical trials have been performed with this derivative besides its use in technological, toxicological, and pharmaceutical experiments [35]. Being the most thoroughly studied derivative, FDA has approved Sporanox™ by Janssen using the same derivatives as molecular carrier. The hydroxypropyl derivative of β-CD and ɣ-CD have been widely used for solubility enhancement and leading to increase in efficacy of various drugs as illustrated in **Tables 2** and **3**.

2.3 Sulfoalkylated CDs

Almost more than 180 articles had focused on the preparation and use of charged (anionic) CD derivatives by the end of July 1998.The glucopyranose unit present in the native CD ring could be directly substituted with charged moiety, or a neutral spacer group may be used for the insertion [49]. Such functional groups can be inserted at different degrees of substitution (DS) and have variable sizes, so the final product of modified CD derivative may be influenced by electronic and steric factors.

The sulfopropyl and sulfobutyl derivatives of beta-CDs are produced by reacting native CD with propane sultone and butane sultone, respectively, in an alkaline aqueous solution as shown in **Figure 3**.

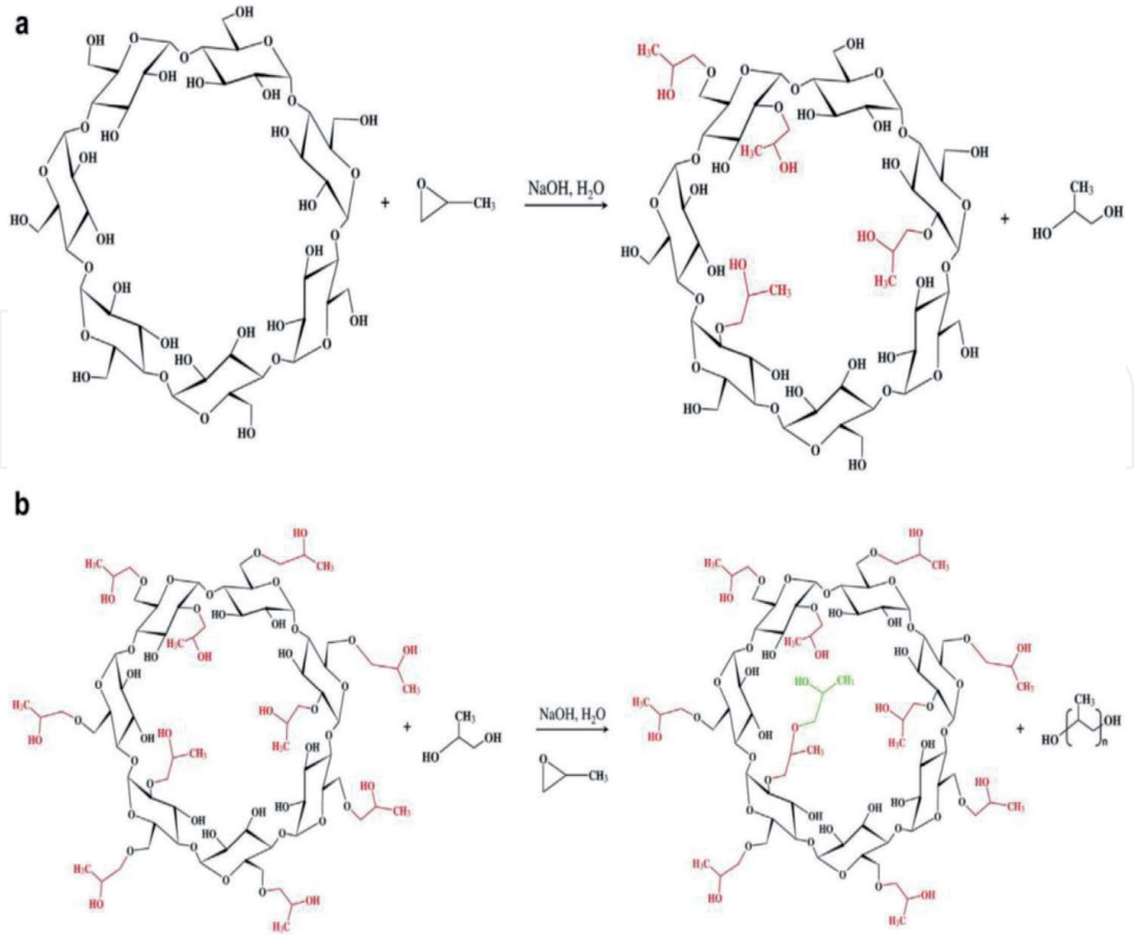

Figure 2.
Reaction scheme for HPβCD synthesis: (a) low DS, (b) high DS [32].

Author	Drug	Other additives (if present)	Effects
Kaur et al. 2004 [36]	Acetazolamide	PVA, PVP, HPMC, Carbopol 940	Improved solubility, effective drug permeation, improved corneal transport
Chowdary et al. [37]	Celecoxib	PVP, HPMC, PEG	Improved solubility, higher CE by ternary complexation
El-Maradny et al. [38]	Meloxicam	PVP, L-ARG	Improved solubility, quick pain relieving effect, faster drug release with ternary complex
Manali Shah et al. [39]	Etoricoxib	PVP, L-ARG	Enhanced dissolution profile, improved oral bioavailability
Asbahr et al. [40]	Finasteride	PVP, chitosan	Positive effect on drug solubility, inc. in bulk of formulation so can be used in solid dosage forms
Mummidi and Jayanthi [41]	Isradipine	PVP, HPMC, PEG	Marked increase in solubilizing efficiency, improved dissolution with ternary complexes
Pacheco et al. [42]	Albendazole	PVA	Enhanced solubility, improved intrinsic dissolution rate
Jadhav and Pore [43]	Bosentan	Arginine (ARG)	Enhanced solubility and dissolution profile

Table 2.
Effects of HPβCD on solubility and efficacy of drugs.

Author	Drug	Other additives (if present)	Effects
Zhou et al. [44]	Baicalein	—	Higher drug absorption, better stability, enhanced release profile
Soica et al. [45]	Oleanolic acid, ursolic acid	—	Enhanced aqueous solubility, marked antiproliferative activity
Misiuk and Jasiuk 2014 [46]	Bupropion	—	Improved release, rapid absorption, enhanced encapsulation efficiency
Misiuk et al. [47]	Ceftazidime	—	Improved aqueous solubility, improved stability as suggested by NMR study
Wathoni et al. [48]	Curcumin	—	Increased solubility, enhanced antioxidant activity

Table 3.
Effects of HPγCD on solubility and efficacy of drugs.

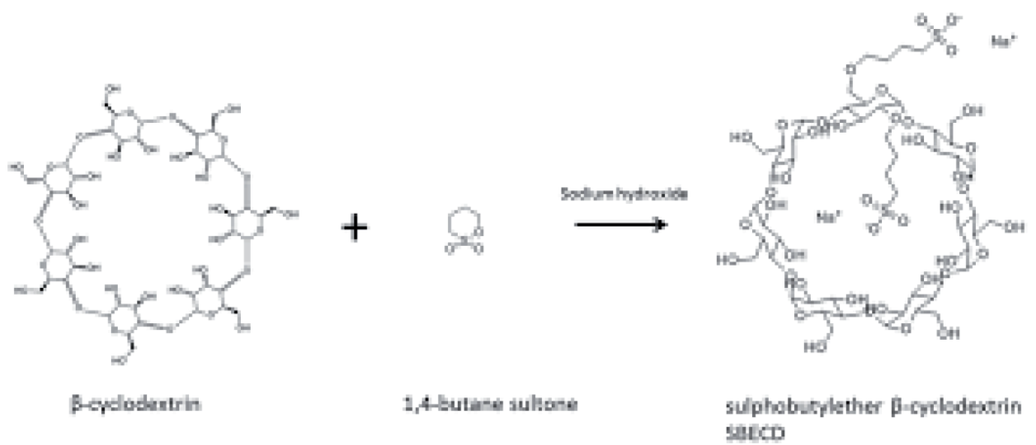

Figure 3.
Synthesis of SBE-β-CD [50].

Sulfobutylated β-CD with seven substituents is considered as suitable derivative and is commercially available under the trade name of Captisol™ by CyDex. Resveratrol is complexed with sulfobutylether derivatives of β-CD and increased the anticancer activity with increase in solubility of resveratrol as well [51].

2.4 Sulfated CDs

A class of water-soluble CD derivatives having anti-angiogenic, biological, and anticancer properties is sulfated CDs. As the tumor growth is dependent on angiogenesis, the use of these derivatives could be a unique approach for the treatment of solid tumors, as reported by Folkman et al. in early 1970 [52]. In addition to these properties, they also possess antilipemic, antiviral, and anti-inflammatory effects [53].

Reaction of CD in absolute dimethylformamide with pyridine sulfur trioxide gives better yield of sulfated derivatives of CDs [54]. Besides their use as solubility enhancers, these derivatives also provide protection against gentamicin-induced nephrotoxicity and have no hemolytic properties, so can be effectively used in clinical studies [55]. **Figure 4** presents the scheme of preparation of sulfated β-CD.

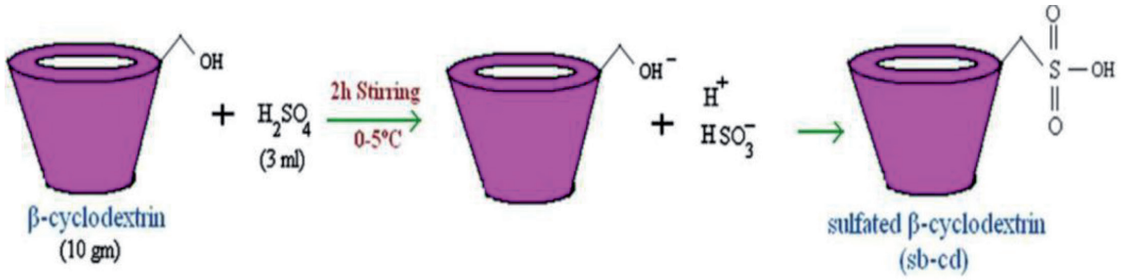

Figure 4.
Synthesis of sulfated β-CD [56].

2.5 Guidelines regarding synthesis of CD derivatives

The following guidelines should be strictly followed during the synthesis of CD derivatives in order to get the better solubility and complexing ability:

- Although the substituents at primary hydroxyl side may influence other uses, they do not exert much effect on the complexation. The pH of the medium is decisive that either the secondary hydroxyl side or primary side will be substituted. Moderately basic medium will favor secondary hydroxyl substitution, whereas primary hydroxyl side will get substituted in strong basic medium [57].

- To avoid the deformation of cavity shape, avoid the bulky substitution which may crowd each other. Although the CD torus is made of anhydroglucose repeating units which are quite rigid, they are connected to each other through single glycosidic bonds. As torus is stabilized by hydrogen bonds between the secondary hydroxyls on adjacent glucose unit, the stabilizing effect of hydrogen bonding is diminished by secondary hydroxyl substitution. Finally, the anhydroglucose units may tilt out the defined torus shape due to introduction of steric strain between substituting units present on the adjacent anhydroglucose residues [35].

- The water-soluble CDs are used either in solid form or in concentrated solution state. Some substituting groups have the tendency to incorporate in the core of CDs, so they compete with active drug molecules for inclusion complexation. Therefore, it is mandatory to select those substituents that are unable to fit in the cavity of CDs [58].

- A glucopyranose unit of cyclodextrin ring contains how many substituted hydroxyl groups are defined as its degree of substitution. One mole of glucopyranose unit contains three reactive hydroxyl groups so the maximum possible numbers of substituents are 18, 21, and 24 for α-, β-, and γ- CDs, respectively. Controlling the degree of substitution is important in producing the desired properties in functionalized CDs.

3. Conclusion

Using different functional groups, modified CDs could play a pivotal role in improving limited drug stability and boosting aqueous solubility and dissolution behavior of drugs with poor water solubility. In order to use full potential of CDs as

a drug delivery carrier, the nature and degree of functionalization play an important role. However, the future research should focus on the use of green chemistry for CDs' functionalization, and the attention should also be paid to the toxicokinetic profiling of the modified CDs to establish their safety and efficacy at the same time.

Conflict of interest

There is no conflict of interest among the listed authors.

Author details

Syed Haroon Khalid[1*], Mehreen Bashir[1], Sajid Asghar[1], Tauqeer Hussain Mallhi[2] and Ikram Ullah Khan[1]

1 Department of Pharmaceutics, Faculty of Pharmaceutical Sciences, Government College University, Faisalabad, Pakistan

2 Department of Clinical Pharmacy, Jouf University, Sakaka, Kingdom of Saudi Arabia

*Address all correspondence to: haroonkhalid80@gmail.com and syedharoonkhalid@gcuf.edu.pk

References

[1] Kurkov SV, Loftsson T. Cyclodextrins. International Journal of Pharmaceutics. 2013;**453**:167-180. DOI: 10.1016/j.ijpharm.2012.06.055

[2] Brewster ME, Loftsson T. Cyclodextrins as pharmaceutical solubilizers. Advanced Drug Delivery Reviews. 2007;**59**:645-666. DOI: 10.1016/j.addr.2007.05.012

[3] Del Valle EM. Cyclodextrins and their uses: A review. Process Biochemistry. 2004;**39**:1033-1046. DOI: 10.1016/S0032-9592(03)00258-9

[4] Acuña-Rougier C, Olea-Azar C. Thermodynamic and geometric study of diasteroisomeric complexes formed by racemic flavanones and three cyclodextrins through NMR. Journal of Inclusion Phenomena and Macrocyclic Chemistry. 2013;**75**:119-136. DOI: 10.1007/s10847-012-0153-5

[5] Rekharsky MV, Inoue Y. Complexation thermodynamics of cyclodextrins. Chemical Reviews. 1998;**98**:1875-1918. DOI: 10.1021/cr970015o

[6] Astray G, Gonzalez-Barreiro C, MejutoJC, Rial-OteroR, Simal-GandaraJ. A review on the use of cyclodextrins in foods. Food Hydrocolloids. 2009;**23**:1631-1640. DOI: 10.1016/j.foodhyd.2009.01.001

[7] Szente L, Szejtli J. Cyclodextrins as food ingredients. Trends in Food Science and Technology. 2004;**15**:137-142. DOI: 10.1016/j.tifs.2003.09.019

[8] Szejtli J, Szente L. Elimination of bitter, disgusting tastes of drugs and foods by cyclodextrins. European Journal of Pharmaceutics and Biopharmaceutics. 2005;**61**:115-125. DOI: 10.1016/j.ejpb.2005.05.006

[9] Loftsson T, Brewster ME, Masson M. Role of cyclodextrins in improving oral drug delivery. American Journal of Drug Delivery. 2004;**2**:261-275. DOI: 10.2165/00137696-200402040-00006

[10] Miyazawa I, Ueda H, Nagase H, Endo T, Kobayashi S, Nagai T. Physicochemical properties and inclusion complex formation of δ-cyclodextrin. European Journal of Pharmaceutical Sciences. 1995;**3**:153-162. DOI: 10.1016/0928-0987(95)00006-Y

[11] Coleman AW, Nicolis I, Keller N, Dalbiez JP. Aggregation of cyclodextrins: An explanation of the abnormal solubility of β-cyclodextrin. Journal of Inclusion Phenomena and Molecular Recognition in Chemistry. 1992;**13**:139-143. DOI: 10.1007/BF01053637

[12] Szejtli J. The properties and potential uses of cyclodextrin derivatives. Journal of Inclusion Phenomena and Molecular Recognition in Chemistry. 1992;**14**:25-36. DOI: 10.1007/BF01041363

[13] Uekama K. Pharmaceutical uses of cyclodextrin derivatives. In: High Performance Biomaterials. A Comprehensive Guide to Medical and Pharmaceutical Applications. Szycher M, editor. Technomic: Lancaster, PA; 1991. pp. 789-806

[14] Szejtli J. Introduction and general overview of cyclodextrin chemistry. Chemical Reviews. 1998;**98**:1743-1754. DOI: 10.1021/cr970022c

[15] Inoue Y, Liu Y, Tong LH, Shen BJ, Jin DS. Calorimetric titration of inclusion complexation with modified. Beta.-cyclodextrins. Enthalpy-entropy compensation in host-guest complexation: From ionophore to cyclodextrin and cyclophane. Journal of the American Chemical Society. 1993;**115**:10637-10644. DOI: 10.1021/ja00076a023

[16] Tabushi I, Kuroda Y, Mizutani T. Artificial receptors for amino acids in water. Local environmental effect on polar recognition by 6A-amino-6B-carboxy- and 6B-amino-6A-carboxy-. Beta.-cyclodextrins. Journal of the American Chemical Society. 1986;**108**:4514-4518. DOI: 10.1021/ja00275a043

[17] Kean SD, May BL, Clements P, Lincoln SF, Easton CJH. Host–guest complexation of aromatic carboxylic acids and their conjugate bases by 6 A-(ω-aminoalkylamino)-6 A-deoxy-β-cyclodextrins† in aqueous solution. Journal of the Chemical Society, Perkin Transactions. 1999;**2**:1257-1264. DOI: 10.1039/A806488A

[18] Yuan LM. Effect of mobile phase additive on chiral separation. Separation and Purification Technology. 2008;**63**:701-705. DOI: 10.1016/j.seppur.2008.06.021

[19] Tundo P, Selva M. The chemistry of dimethyl carbonate. Accounts of Chemical Research. 2002;**35**:706-716. DOI: 10.1021/ar010076f

[20] Gan Y, Zhang Y, Xiao C, Zhou C, Zhao Y. A novel preparation of methyl-β-cyclodextrin from dimethyl carbonate and β-cyclodextrin. Carbohydrate Research. 2011;**346**:389-392. DOI: 10.1016/j.carres.2010.05.028

[21] Available from: http://www.google.com/search?biw=1366&bih=576&tbm=isch&sa=1&ei=PgvvXICpLZHFwQKJgK-YAQ&q=synthesis+of+methyl+%CE%B2-Cyclodextrin&oq=synthesis+of+methyl+%CE%B2-Cyclodextrin&gs 1=img.3...165667.172378..178711...o.o..o.358.2515.ojij5j3.....o....1j2..gws-wiz-img.....ojoi67.kdloQir1DqM#imgrc=qywHXUGYUQO96M:

[22] Schipper NG, Romeijn SG, Verhoef JC, Merkus FW. Nasal insulin delivery with dimethyl-β-cyclodextrin as an absorption enhancer in rabbits: Powder more effective than liquid formulations. Pharmaceutical Research. 1993;**10**:682-686. DOI: 10.1023/A:1018999414088

[23] Schipper NG, Verhoef JC, Romeijn SG, Merkus FW. Methylated β-cyclodextrins are able to improve the nasal absorption of salmon calcitonin. Calcified Tissue International. 1995;**56**:280-282. DOI: 10.1007/BF00318047

[24] Sigurdsson HH, Konráðsdóttir F, Loftsson T, Stefansson E. Topical and systemic absorption in delivery of dexamethasone to the anterior and posterior segments of the eye. Acta Ophthalmologica Scandinavica. 2007;**85**:598-602. DOI: 10.1111/j.1600-0420.2007.00885.x

[25] Soares-Sobrinho JL, Santos FL, Lyra MA, Alves LD, Rolim LA, Lima AA, et al. Benznidazole drug delivery by binary and multicomponent inclusion complexes using cyclodextrins and polymers. Carbohydrate Polymers. 2012;**89**:323-330. DOI: 10.1016/j.carbpol.2012.02.042

[26] Mathiron D, Marçon F, Dubaele JM, Cailleu D, Pilard S, DjedaÏni-pilard F. Benefits of methylated cyclodextrins in the development of midazolam pharmaceutical formulations. Journal of Pharmaceutical Sciences. 2013;**102**:2102-2111. DOI: 10.1002/jps.23558

[27] Chao J, Liu Y, Zhang Y, Zhang J, Zhang Y, Guo Z, et al. Investigation of the inclusion behavior of ofloxacin with methyl-β-cyclodextrin. Journal of Molecular Liquids. 2014;**200**:404-409. DOI: 10.1016/j.molliq.2014.11.015

[28] Vieira AC, Fontes DA, Chaves LL, Alves LD, de Freitas Neto JL, Soares MF, et al. Multicomponent systems with cyclodextrins and hydrophilic polymers for the delivery of Efavirenz. Carbohydrate Polymers. 2015;**130**:133-140. DOI: 10.1016/j.carbpol.2015.04.050

[29] Rassu G, Soddu E, Cossu M, Brundu A, Cerri G, Marchetti N, et al. Solid microparticles based on chitosan or methyl-β-cyclodextrin: A first formulative approach to increase the nose-to-brain transport of deferoxamine mesylate. Journal of Controlled Release. 2015;**201**:68-77. DOI: 10.1016/j.jconrel.2015.01.025

[30] Terauchi M, Inada T, Tonegawa A, Tamura A, Yamaguchi S, Harada K, et al. Supramolecular inclusion complexation of simvastatin with methylated β-cyclodextrins for promoting osteogenic differentiation. International Journal of Biological Macromolecules. 2016;**93**:1492-1498. DOI: 10.1016/j.ijbiomac.2016.01.114

[31] Pitha J, Szabo L, Fales HM. Reaction of cyclodextrins with propylene oxide or with glycidol: Analysis of product distribution. Carbohydrate Research. 1987;**168**:191-198. DOI: 10.1016/0008-6215(87)80025-3

[32] Available from: http://www.google.com/search?q=Reaction+scheme+for+HPBCD+synthesis&source=Inms&tbm=isch&sa=X&ved=0ahUKEwiY-Lj 6cHiAhXBoKQKHdfkBGkQAUIDigB&biw=1366&bih=576#imgrc=fwlmslwWc6M3DM:

[33] Reer O, Müller BW. Determination of the degree of substitution of chemically modified cyclodextrins by a microcalorimetric titration technique. International Journal of Pharmaceutics. 1994;**104**:239-246. DOI: 10.1016/0378-5173(94)90164-3

[34] Novák C, Pokol G, Sztatisz J, Szente L, Szejtli J. Determination of the degree of substitution of hydroxypropylated β-cyclodextrins by differential scanning calorimetry. Analytica Chimica Acta. 1993;**282**:313-316. DOI: 10.1016/0003-2670(93)80216-8

[35] Szente L, Szejtli J. Highly soluble cyclodextrin derivatives: Chemistry, properties, and trends in development. Advanced Drug Delivery Reviews. 1999;**36**:17-28. DOI: 10.1016/S0169-409X(98)00092-1

[36] Kaur IP, Kapil M, Smitha R, Aggarwal D. Development of topically effective formulations of acetazolamide using HP-β-CD-polymer co-complexes. Current Drug Delivery. 2004;**1**:65-72. DOI: 10.2174/1567201043480054

[37] Chowdary KP, Srinivas SV. Influence of hydrophilic polymers on celecoxib complexation with hydroxypropyl β-cyclodextrin. AAPS PharmSciTech. 2006;**7**:E184-E189. DOI: 10.1208/pt070

[38] El-Maradny H, Mortada S, Kamel O, Hikal A. Characterization of ternary complexes of meloxicam-HPβCD and PVP or L-arginine prepared by the spray-drying technique. Acta Pharmaceutica. 2008;**58**:455-466. DOI: 10.2478/v10007-008-0029-9

[39] Shah M, Karekar P, Sancheti P, Vyas V, Pore Y. Effect of PVP K30 and/or L-arginine on stability constant of etoricoxib–HPβCD inclusion complex: Preparation and characterization of etoricoxib–HPβCD binary system. Drug Development and Industrial Pharmacy. 2009;**35**:118-129. DOI: 10.1080/03639040802220292

[40] Asbahr AC, Franco L, Barison A, Silva CW, Ferraz HG, Rodrigues LN. Binary and ternary inclusion complexes of finasteride in HPβCD and polymers: Preparation and characterization. Bioorganic & Medicinal Chemistry. 2009;**17**:2718-2723. DOI: 10.1016/j.bmc.2009.02.044

[41] Mummidi V, Jayanthi V. Effect of hydrophilic polymers on isradipine complexation with hydroxypropyl β-cyclodextrin. Drug Development and Industrial Pharmacy. 2013;**39**:970-977. DOI: 10.3109/03639045.2012.686508

[42] Pacheco PA, Rodrigues LN, Ferreira JF, Gomes AC, Veríssimo CJ, Louvandini H, et al. Inclusion complex and nanoclusters of cyclodextrin to increase the solubility and efficacy of albendazole. Parasitology Research. 2018;**117**:705-712. DOI: 10.1007/s0043

[43] Jadhav P, Pore Y. Physicochemical, thermodynamic and analytical studies on binary and ternary inclusion complexes of bosentan with hydroxypropyl-β-cyclodextrin. Bulletin of Faculty of Pharmacy, Cairo University. 2017;**55**:147-154. DOI: 10.1016/j.bfopcu.2016.12.004

[44] Zhou Q, Zhong L, Wei X, Dou W, Chou G, Wang Z. Baicalein and hydroxypropyl-γ-cyclodextrin complex in poloxamer thermal sensitive hydrogel for vaginal administration. International Journal of Pharmaceutics. 2013;**454**:125-134. DOI: 10.1016/j.ijpharm.2013.07.006

[45] Soica C, Oprean C, Borcan F, Danciu C, Trandafirescu C, Coricovac D, et al. The synergistic biologic activity of oleanolic and ursolic acids in complex with hydroxypropyl-γ-cyclodextrin. Molecules. 2014;**19**:4924-4940. DOI: 10.3390/molecules19044924

[46] Misiuk W, Jasiuk E. Study of the inclusion interaction of HP-γ-cyclodextrin with bupropion and its analytical application. Journal of Molecular Structure. 2014;**1060**:272-279. DOI: 10.1016/j.molstruc.2013.12.056

[47] Misiuk W. Investigation of inclusion complex of HP-γ-cyclodextrin with ceftazidime. Journal of Molecular Liquids. 2016;**224**:387-392. DOI: 10.1016/j.molliq.2016.10.009

[48] Wathoni N, Motoyama K, Higashi T, Okajima M, Kaneko T, Arima H. Enhancement of curcumin wound healing ability by complexation with 2-hydroxypropyl-γ-cyclodextrin in sacran hydrogel film. International Journal of Biological Macromolecules. 2017;**98**:268-276. DOI: 10.1016/j.ijbiomac.2017.01.144

[49] Rajewski RA. Development and evaluation of the usefulness and parenteral safety of modified cyclodextrins. 5332-5332. Order No. DA9110909 from: Diss Abstr Int B; 1991

[50] Available from: http://www.google.com/search?q=synthesis+of+SBE-%CE%B2-CD&source=Inms&tbm=isch&sa=X&ved=oahUKEwjWytO6sHiAhVFr6QKHYXyDXoQAUIDigB&biw=1366&bih=576#imgrc=gsB7mNy3Gv4-EM:

[51] Venuti V, Cannavà C, Cristiano MC, Fresta M, Majolino D, Paolino D, et al. A characterization study of resveratrol/sulfobutyl ether-β-cyclodextrin inclusion complex and in vitro anticancer activity. Colloids and Surfaces. B, Biointerfaces. 2014;**115**:22-28. DOI: 10.1016/j.colsurfb.2013.11.025

[52] Folkman J, Weisz PB, Joullie MM, Li WW, Ewing WR. Control of angiogenesis with synthetic heparin substitutes. Science. 1989;**243**:1490-1493. DOI: 10.1126/science.2467380

[53] Anand R, Nayyar S, Pitha J, Merril CR. Sulphated sugar alpha-cyclodextrin sulphate, a uniquely potent anti-HIV agent, also exhibits marked synergism with AZT, and lymphoproliferative activity. Antiviral Chemistry and Chemotherapy. 1990;**1**:41-46. DOI: 10.1177/095632029000100107

[54] Pitha J, Mallis LM, Lamb DJ, Irie T, Uekama K. Cyclodextrin sulfates: Characterization as polydisperse and amorphous mixtures. Pharmaceutical Research. 1991;**8**:1151-1154. DOI: 10.1023/A:1015854402122

[55] Shiotani K, Irie T, Uekama K, Ishimaru Y. Cyclodextrin sulfates in parenteral use: Protection against gentamicin nephrotoxicity in the rat. European Journal of Pharmaceutical

Sciences. 1995;**3**:139-151. DOI: 10.1016/0928-0987(95)00008

[56] Available from: http://www.google.com/search?biw=1366&bih=576&tbm=isch&sa=1&ei=DA7vXI3jAcPUsAfFxbqwDw&q=synthesis+of+sulfated+beta+Cyclodextrin&oq=synthesis+of+sulfated+beta+Cyclodextrin&gs1=img.3...98943.106317..106999...0.0..0.287.2376.0j5j6.....0....1j2..gws-img.....35i39j0.-K9CA2MG-vc#imgrc=HuSGnVpvSKSLsM:

[57] Pitha J, Rao CT, Lindberg B, Seffers P. Distribution of substituents in 2-hydroxypropyl ethers of cyclomaltoheptaose. Carbohydrate Research. 1990;**200**:429-435. DOI: 10.1016/0008-6215(90)84208-C

[58] Harata K, Rao CT, Pitha J, Fukunaga K, Uekama K. Crystal structure of 2-O-[(S)-2-hydroxypropyl] cyclomaltoheptaose. Carbohydrate Research. 1991;**222**:37-45. DOI: 10.1016/0008-6215(91)89004-Y