Polym. Bull. (2012) 69:1–13
DOI 10.1007/s00289-011-0684-8

ORIGINAL PAPER

Cyclodextrin-based low molecular weight polymers as encapsulates for nonpolar drug molecules

Indrajit Shown · Weon Baek-Ko · C. N. Murthy

Received: 14 July 2011 / Revised: 7 September 2011 / Accepted: 27 November 2011 /
Published online: 13 December 2011

Abstract Low molecular weight water-soluble polymers containing maltose and cyclodextrin (CD) in the main chain were synthesized and used for slow release of a water-soluble drug. These low molecular weight polymers were synthesized from CDs (β-, γ-, and HP-β-CD) and maltose using the differential reactivity of a triazine linker through a single pot polycondensation reaction under controlled conditions. The low molecular weight polymers were characterized by ^{1}H-NMR, FT-IR spectroscopy, XRD analysis, TGA, ESI-mass, and aqueous solubility determination; and were confirmed to be linear. In addition, the inclusion complex formation of Efavirenz (an anti-HIV drug) with the CD–maltose polymer was confirmed from FT-IR and UV–Vis spectroscopy. Comparison of the stability of drug-inclusion complexes of different CD–maltose polymers with that of the parent CDs using the phase solubility studies indicated that the polymers were better at inclusion of the drug. The release performances of Efavirenz with the polymers were investigated through conventional dissolution studies with similar results. The results are explained based on the expansion of the nonpolar cavity due to functionalization of the parent CD.

Keywords Cyclodextrin polymer · Water soluble · Polycondensation reaction · Linear

Electronic supplementary material The online version of this article (doi: 10.1007/s00289-011-0684-8) contains supplementary material, which is available to authorized users.

I. Shown · C. N. Murthy (✉)
Applied Chemistry Department, Faculty of Technology and Engineering,
The M. S. University of Baroda, Kalabhavan, P.O. Box 51, Vadodara 390001, India
e-mail: chivukula_mn@yahoo.com

W. Baek-Ko
Department of Chemistry, Sahmyook University, Seoul, South Korea

Introduction

Cyclodextrins (CDs) are truncated cone-shaped cyclic oligosaccharides with a hollow nonpolar internal cavity, produced from the active enzymes, glycosyltransferases, upon amylase [1]. The supramolecular chemistry of CDs has been the subject of extensive investigations because of its well-known property of host–guest complex formation with a number of organic and nonpolar drug molecules [2–5]. This has been widely used to improve drug stability, solubility, dissolution, and in formulation applications [6, 7].

A number of CD derivatives have been developed to overcome the drawbacks (cytotoxicity and nephrotoxicity) of the parent CDs [8–11]. Other than these CD derivatives, CD-based polymers are of recent interest due to their high water solubility and reduced toxicity as compared with the parent CDs. It has been reported that CD-based polymers can increase the bioavailability [12–14]. These have a large number of potential applications, like controlled release of a soluble substance across a membrane [15] and also partitioning of organic molecules in an aqueous two phase systems [16]. There are also a few reports that show that the polymeric form can increase the stability constants of the inclusion complexes [17–19].

The synthesis of polymeric materials with natural building blocks such as saccharides and carbohydrate molecules has potential for various biomedical applications such as biological recognition [20] and protein–cell interactions [21]. There are several reports available for the synthesis of polymeric materials with saccharides as side-chain moiety with different reactions based on the ester, amide, and ether formations [22–28]. Novel lactose-based β-CD copolymer has been reported for potential environmental and biomedical applications [29–31].

Efavirenz ((*S*)-6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one) is a nonnucleoside reverse transcriptase inhibitor drug of human immunodeficiency virus type-1. However, Efavirenz has an extremely low aqueous solubility (approximately, <10 μg/mL at 25 °C). As a result, its bioavailability appears to be limited. One recent strategy appears to be very promising toward the development of liquid aqueous Efavirenz formulation for the improved pediatric HIV pharmacotherapy [32]. Chiappetta et al. incorporated Efavirenz into the core of linear and branched poly(ethylene oxide)–poly(propylene oxide) block copolymer micelles to improve the aqueous solubility and the oral bioavailability of this drug. The low aqueous solubility of poorly water-soluble drugs has been enhanced by complexation with the CD-based polymers, which simultaneously offers the advantages of the amorphous state and CD-type complexation without toxic effects [33–35]. Previously we had reported γ-CD-based polymers as drug carrier systems [36]. Though γ-CD has a bigger cavity than that of β-CD, the expansion of the cavity by a simple single pot synthesis of a series of low molecular weight maltose-based CD polymer by the polycondensation reaction with an aromatic linking agent under mild conditions has not been attempted before. Thus, the physicochemical properties of the modified CD were characterized using various techniques including ^{1}H-NMR, FT-IR, TGA, X-ray powder diffractometry (XRD), ESI-mass, and aqueous solubility determination. Using Efavirenz as a model drug,

we report the investigations on the CD–maltose polymer as drug carriers and their drug release pattern in vitro. The phase solubility studies of CD–maltose polymer/drug-inclusion complexes were examined and compared with the CD molecules.

Experimental

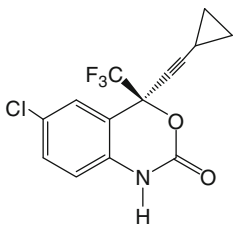
Materials

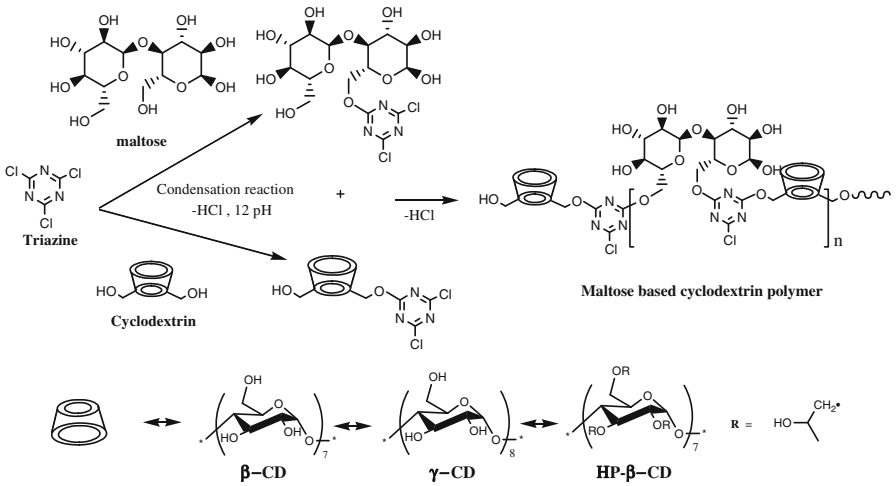
β-Cyclodextrin (β-CD) was provided by Sigmanet Pvt. Ltd., Mumbai as a gift. γ-cyclodextrin (γ-CD) and hydroxypropyl-β-CD (HP-β-CD) were purchased from Sigma Chemical Company and used as received. Cyanuric chloride, maltose, and other chemicals were purchased from local markets and used without further purification. Efavirenz (Fig. 1) was obtained from Ranbaxy Ltd. (Indore, India) as a gift sample and used as received.

Synthesis of CD polymers

Maltose-based CD polymers were synthesized by one-step condensation polymerization. The reaction is given in Scheme 1. In a typical synthesis procedure, 0.5 mol of CD, 0.5 mol of maltose, and 1 mol cyanuric chloride were taken in three flasks separately and dissolved in distilled water at pH 12. The CD solution (10 mL) was taken in a round bottom flask and kept in ice bath with continuous stirring and the temperature maintained between 0 and 5 °C. To this 10 mL of cyanuric chloride solution was added drop wise with the help of a pressure equalizing funnel into the CD solution. During addition, the temperature was maintained between 0 and 5 °C. After complete addition, the maltose solution was added to this flask. The reaction was continued with stirring, temperature was maintained between 0 and 5 °C for 4–5 h. Stirring was continued for another 12 h while the contents were allowed to attain ambient temperature (30 °C). The polymerization was stopped by neutralization with 0.1 N HCI solution. The solution obtained was dialyzed for 24 h with a membrane of molecular weight cut-off 3,500. Residual unpolymerised and merely substituted CD was separated in order to investigate the properties of the high molecular weight polymer fraction. The solution obtained was directly freeze-dried to get an off-white fluffy product (yield 43%). The details of the polymers are given in Table 1.

Fig. 1 Structure of Efavirenz





Scheme 1 Synthesis of the maltose-based CDs polymers

Table 1 Molecular weight data of maltose-based CDs polymers

Samples	Mole ratio			ESI-mass (M_n)
	CD	CC	Maltose	
M-β-CD-poly	0.5	1	0.5	5284 ± 2.05
M-γ-CD-poly	0.5	1	0.5	7311 ± 6.21
M-HP-β-CD-poly	0.5	1	0.5	7418 ± 5.37

Analysis

^{1}H-NMR spectra were recorded on a Bruker spectrometer operating at 400 MHz at room temperature. Samples were prepared in DMSO-d_6 (maltose-based β-CD polymer)/D_2O (Maltose-based γ-CD and maltose-based HP-β-CD polymer) containing TMS as an internal chemical standard. FT-IR spectra were taken on a Shimadzu (8400S) instrument. The blend of the Efavirenz with CD–maltose polymer at 10:90 (w/w) ratios was manually ground for 10 min using a mortar and pestle.

The TG analysis of the CD–maltose polymer was done on a Shimadzu TGA-50 system with a heating rate of 10 °C/min in the temperature range of 50–700 °C. XRD patterns were taken on a computer-controlled RIGAKU-DMAX-2200.

Aqueous solubility of CD polymer

A polymer sample (0.6 g) was added to 0.5 mL of distilled water to ensure the solution reaching saturation. The solution was mechanically shaken for 4 h and then incubated overnight at room temperature. This solution was then filtered through a microfilter-syringe. The filtrate was dried in an air drying oven for sufficient period until a constant weight was reached. The solubility was estimated in terms of the

weight of sample in the saturated solution and solution volume. This was repeated to get constant values with in an error of ±0.05 g.

Solubility studies

The solubility measurement of Efavirenz was carried out by adding 100 mg of Efavirenz to 10 mL of pH 6.8 phosphate buffer solution (PBS) of CD–maltose polymer. The percentage of the polymer was varied from 1 to 7% (w/v). All solutions were prepared in a glass container which was shaken at a constant temperature (25 °C) until equilibrium was achieved (72 h). An aliquot was withdrawn and the Efavirenz concentration was determined by measuring the ultraviolet absorbance of the saturated solutions at 247 nm wavelength and compared with the calibration curve for Efavirenz. The apparent binding constant of the Efavirenz/CD–maltose polymer complexes were calculated from the slope and intercept of the straight line obtained by plotting the concentration of Efavirenz versus maltose concentration in solution. The phase solubility diagram is shown in Fig. 7 and the binding constant was calculated using the following equation [37].

$$K_{1:1} = \frac{\text{Slope}}{\text{Intercept}(1 - \text{Slope})}$$

Dissolution studies

For dissolution studies, Efavirenz/CD–maltose polymer complexes were prepared by adopting the procedure described by Arias et al. [38] and Mura et al. [14]. Efavirenz with CD–maltose polymer at 10:90 (w/w) ratio was manually ground using a mortar and pestle for 10 min. PBS of pH 6.8 was employed as dissolution medium at 37 ± 0.5 °C. The sample powder prepared with the polymer was added to 75 mL of water in a 150-mL beaker and stirred at 100 rpm with a glass three-blade propeller centrally immersed in the beaker 20 mm from the bottom. At appropriate time intervals, suitable aliquots were withdrawn with a filter-syringe (pore size 0.45 μm). Efavirenz concentration in the PBS was obtained by UV–Vis spectrophotometer measurements (after calibration) at certain periods of time.

Results and discussion

Synthesis

The low molecular weight CD–maltose polymers were synthesized by a one pot condensation reaction. The first step was the preparation of dichlorotriazine sodium salt from the dispersion of cyanuric chloride in water. In the second and the final step of the condensation reaction, two chlorine groups of dichlorotriazine covalently react with two CD (primary –OH) under alkaline conditions and low temperature (5–30 °C). Preparation of the dichlorotriazine sodium salt reduced the degree of substitution (DS) of the reactive groups from DS = 1.0–0.4 due to a precomplexation effect that

contains only 2–3 triazine groups per CD molecule [36, 39]. With a higher degree of substitution, the solubility of the synthesized CD–maltose would be reduced to form insoluble by cross-linking. With these optimized conditions, highly water-soluble oligomers were synthesized with low cross-linking reactions. This was confirmed from the aqueous solubility data shown in Table 2. The low DS per CD moiety insures low cross-linking of the polymers. The molecular weights of the polymers measured by the ESI-mass are shown in Table 1. The β-CD, γ-CD, and HP-β-CD–maltose polymers have number average molecular weight (M_n) of 5284, 7311, and 7418, respectively. These low weights indicate that there are approximately 4–5 CD units per chain.

^{1}H NMR spectroscopy

The spectra are shown in Fig. 2. Maltose-based β-CD copolymers show peaks at δ 4.83 (C^1H), δ 4.49 ($C^{6'}H$), δ 4.30 (C^5H), δ 3.65 (C^2H, C^3H), δ 3.56 (C^6H), and δ 3.35 (C^4H). The peak at 5.0 ppm assigned to the anomeric proton attached to the C-1 of the glucose unit and two broadened peaks between 3 and 4.5 ppm correspond to the protons in pyranose rings. When maltose is one of the components of the chain, a shoulder at δ 3.30 ppm appears. This shoulder in spectra may be due to a different chemical environment after polymerization with β-CD triazine, as compared with β-CD triazine homopolymer. This signal that is absent in the latter indicates the reaction of the maltose primary hydroxyl with the triazine. Similarly the NMR spectrum for the γ-CD polymer was found to match with the corresponding peaks. This is shown in supporting information (Fig. S4).

Figure S4 shows the NMR spectrum of the maltose-based γ-CD copolymer with peaks at δ 5.01 (C^1H), δ 4.18 ($C^{6'}H$) δ 3.83 (C^5H), δ 3.77 (C^6H), δ 3.51 (C^2H, C^3H), and δ 3.44 (C^4H). The shoulder around δ 3.30 ppm appears because maltose is one of the components of the main polymeric chain. Similarly the spectra for HP-β-CD copolymer with maltose shows peaks at δ 5.15 (C^1H), 4.24 ($C^{6'}H$), δ 3.91 (C^5H), δ 3.84 (C^5H), δ 3.62 (C^2H, C^3H), and δ 3.51 (C^4H), respectively, with the shoulder at around δ 3.30 ppm. This can be seen in supporting information (Fig. S4).

Infra-red spectroscopy

The FT-IR spectra for the maltose-based CD (β-, γ-, and HP-β-CD) polymers, Efavirenz and the inclusion complex are shown in Fig. 3 and the supporting

Table 2 Aqueous solubility of maltose-based CDs polymers at 25 °C

Samples	Aqueous solubility (mg/mL)	Solubility relative to CD
β-CD	18.5 ± 0.05	1.0
M-β-CD-poly	136.2 ± 0.05	7.4
γ-CD	232 ± 0.05	1.0
M-γ-CD-poly	938 ± 0.05	4.0
HP-β-CD	410 ± 0.05	1.0
M-HP-β-CD-poly	1250 ± 0.05	3.0

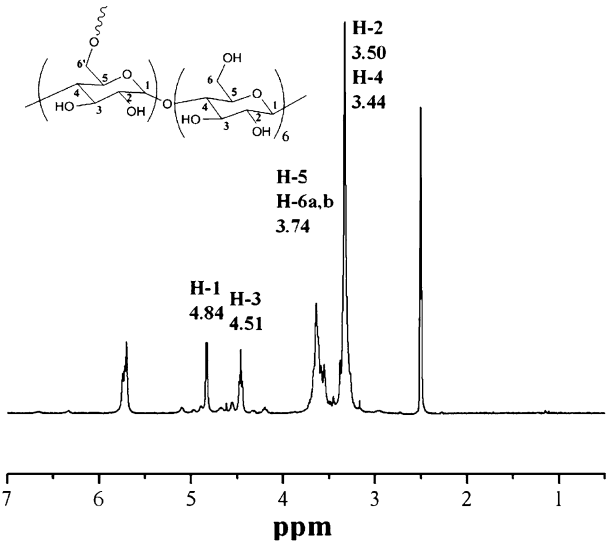


Fig. 2 ^{1}H NMR spectrum of maltose-based β-CD polymer

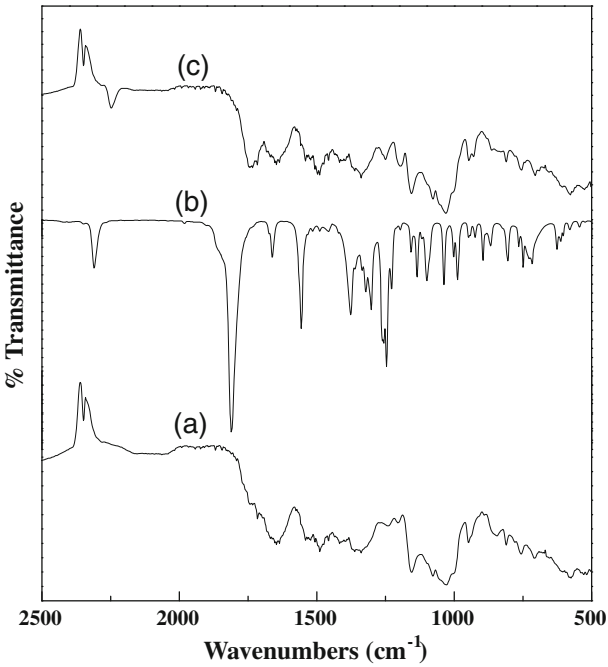


Fig. 3 FT-IR spectra of (*a*) maltose-based β-CD polymer, (*b*) Efavirenz, and (*c*) maltose-based β-CD polymer/Efavirenz

information (Figs. S5 and S6). Apart from the typical absorption peaks of C–H stretching (2,890–2,880 cm^{-1}) and bending (1,480–1,280 cm^{-1}) from normal alkanes for the CD moiety, the maltose-based CD (β-, γ-, and HP-β-CD) polymers (Figs. 3a, S5a, S6a) also show a characteristic C=N stretching at 1,750–1,766 cm^{-1}. This confirms the formation of polymer with the addition of the triazine as a part of the polymer chain. Figures 3b, S5b, and S6b show the spectra for Efavirenz with a typical exocyclic triple bond stretching at 2,260 cm^{-1}. In the complex of Efavirenz/maltose-based CD (β-, γ-, and HP-β-CD) polymer (Figs. 3c, S5c, S6c), the spectra show that the peaks of Efavirenz almost disappear, whereas the characteristic peaks of the parent CDs remain strong. The band at about 1,000 cm^{-1} is broadened and slightly shifted due to the superposition of the band associated with stretching of the Efavirenz. In the complex, we observe a shift of the Efavirenz characteristic peak from 2260 to 2243, 1753 to 1740, and 1242 to 1235 cm^{-1}. These results indicate the modification of environment of Efavirenz due to the formation of drug/CD (β-, γ-, and HP-β-CD)–maltose polymer complex. If it were not so, then the spectra would resemble that of a physical mixture of Efavirenz and the maltose-based-CD (β-, γ-, and HP-β-CD) polymers with no shift in the characteristic bands.

Thermal analysis

Figure 4 shows thermogravimetric plots of the polymers. In CDs (β-, γ-, and HP-β-CD), the mass loss was observed in three different temperature regions. In the pristine CDs, the first mass loss around 103–107 °C is due to the loss of moisture, the second and third mass loss at 300 and 360–367 °C, respectively, due to decomposition after melting of glucose in CD. In the case of the maltose-based CD polymer, the first mass loss is around the same temperature, but the second mass

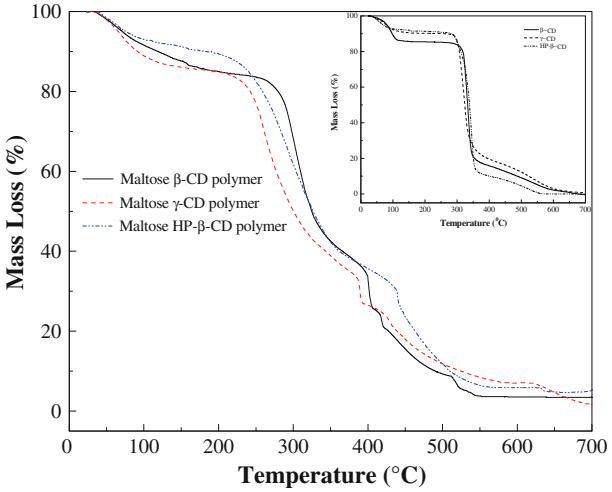


Fig. 4 TGA curves of the maltose-based CDs polymers (*inset* TGA curves of the β-, γ-, and HP-β-CDs)

loss is at 248 °C and the third mass loss at 320 °C. Beyond 390 °C, it is due to the decomposition of the glucose in monomer and the triazine linker.

X-ray powder diffractometry (XRD)

The XRD patterns of the maltose-based CD (β-, γ-, and HP-β-CD) polymers are shown in Fig. 5. It was observed that the maltose-based CDs (β-, γ-, and HP-β-CD) polymers does not have typical 2θ values of the parent CDs. It can be seen that the maltose-based copolymers have a different structure than that of the parent CDs [β-CD ($2\theta = 9°$, 12.5°, 19.6°, 23.0°, 27.0°, 34.8°), HP-β-CD ($2\theta = 9.6°$, 20.1°, 23.0°, 25.0°, 27.0°), and γ-CD ($2\theta = 12.5°$, 19.6°, 23.0°, 27.0°)] with the total suppression of the crystalline nature of the parent CDs (β-, γ-, and HP-β-CD). These XRD data show that the CDs (β-, HP-β-, and γ-CD) are modified due to the condensation reaction and converted to amorphous polymers. All the polymers showed no characteristic crystalline peaks, but showed small humps at around 20°, thus, indicating their amorphous nature.

Aqueous solubility of CD–maltose

The aqueous solubility of the CD polymers is shown in Table 2. It can be seen that after polymerization there is significant enhancement of the aqueous solubility. The solubilities of the maltose-based CD polymers are higher than that of the parent CDs. The low aqueous solubility of the parent CD is attributed to the intermolecular hydrogen bonding between the secondary hydroxyl groups, which are unfavorable to the interaction between CD and surrounding water molecules. The introduction of triazine groups via condensation polymerization disrupts the intermolecular hydrogen bonding, thus, increasing the aqueous solubility. In the case of saccharide-based polymers, maltose provides the unique chemical functionality of water solubility along with the flexibility of the linear polymeric chain. The enhanced water solubility of the maltose-based CD polymers also is one indication of the absence of any significant cross-linking. If the polymer were highly cross-linked, the solubility would not be as many times of the original CD. There is an almost three- to sevenfold increase in the solubility on polymerization.

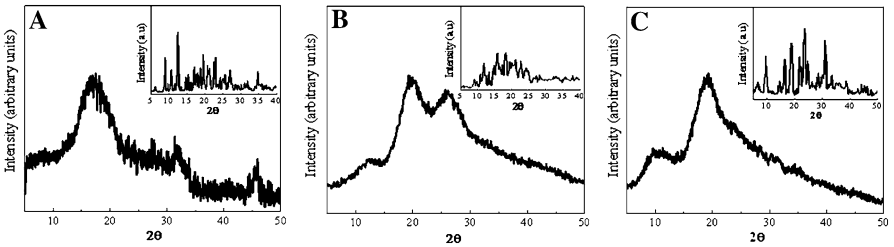


Fig. 5 XRD of **a** maltose-based β-CD polymer (*inset* β-CD), **b** maltose-based γ-CD polymer (*inset* γ-CD), **c** maltose-based HP-β-CD polymer (*inset* HP-β-CD)

Host–guest interaction in aqueous solution

The confirmation of the host–guest interaction was obtained from UV absorbance studies. The Efavirenz drug shows an absorbance at around 247 nm in methanol and is water-insoluble, whereas maltose-based β-CD polymer shows no absorbance in this region. The spectra (Fig. 6) of the inclusion complex in water showed the typical absorbance peak corresponding to the Efavirenz drug implying that the drug has been encapsulated in the CD cavity. The various cavity sizes of the β-, γ-, and HP-β-CDs offer a nonpolar environment for the drug and thus it has been "solubilized" in water. The improved water solubility of Efavirenz is shown in Fig. 7. In the phase solubility studies by linear relationship between dissolved drug

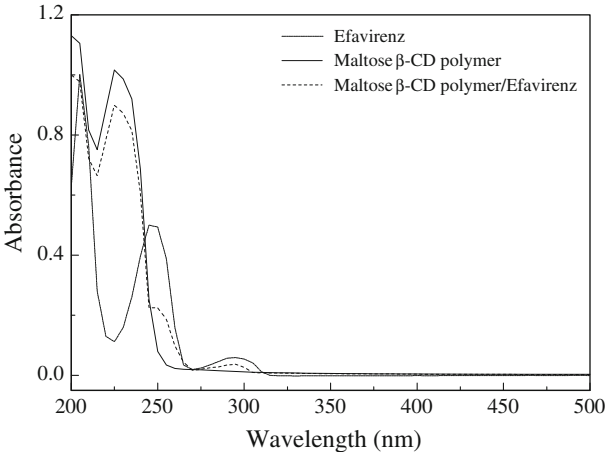


Fig. 6 UV–Vis spectra of Efavirenz in methanol and maltose-based β-CD polymer and Efavirenz–maltose-based β-CD polymer in water

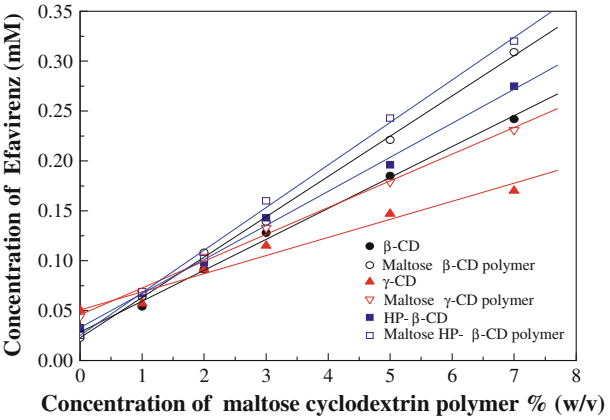


Fig. 7 Phase solubility diagrams of Efavirenz in CDs and maltose-based CDs polymers

concentration and amount of solubilizing agent, we calculated the binding constants of the drug-inclusion complexes at 25 °C ($K_{1:1\ (\beta\text{-CD})} = 1.1 \times 10^3 \pm 0.8 \times 10^{-3}$ mol^{-1}, $K_{1:1\ (\text{M-}\beta\text{-CD-P})} = 1.9 \times 10^3 \pm 0.7 \times 10^{-3}$ mol^{-1}, $K_{1:1\ (\gamma\text{-CD})} = 3.6 \times 10^2 \pm 0.15 \times 10^{-2}$ mol^{-1}, $K_{1:1\ (\text{M-}\gamma\text{-CD-P})} = 5.9 \times 10^2 \pm 0.09 \times 10^{-2}$ mol^{-1}, $K_{1:1\ (\text{HP-}\beta\text{-CD})} = 1.1 \times 10^3 \pm 1 \times 10^{-3}$ mol^{-1}, $K_{1:1\ (\text{M-HP-}\beta\text{-CD-P})} = 1.8 \times 10^3 \pm 1 \times 10^{-3}$ mol^{-1} calculated according to the molecular weight of CD repeating unit). From the phase solubility plot, the slope of the diagram is less than one, thus, the inclusion complex should be of 1:1 stoichiometry. These results show the maltose-based CD polymers to have better complexing properties or binding constants compared to the parent CDs. This can be attributed to the cooperative action in binding by the maltose units and polymer chains. The adjacent maltose units and polymer chain act like arms of the CD cavities to facilitate the drug inclusion that is helpful for the complexing of large molecules.

Dissolution studies

Figure 8 shows the dissolution profiles of the co-ground complexes of the Efavirenz with the synthesized CD–maltose and compared with the Efavirenz/CDs. Efavirenz/CD–maltose samples show better dissolution rates and higher cumulative release (almost 98–99% release for the maltose–β-CD and maltose–HP-β-CD polymer and 60–70% in case of the maltose–γ-CD polymer) of the drug. This is due to the highly hydrophilic nature of the polymers, lowering the interfacial tension between the highly water insoluble drug and water. These results are also in agreement with the binding constants calculated for the complexes. The highly amorphous nature of the synthesized polymers and the co-ground procedure of the preparation of drug complexes results in the enhanced cumulative release of the drug.

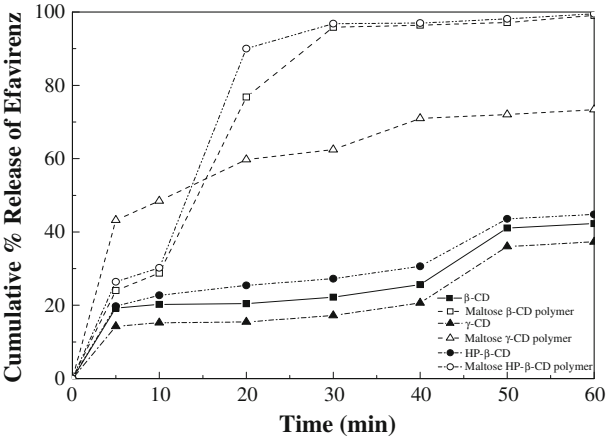


Fig. 8 Dissolution curves of Efavirenz with CDs and ground products with maltose-based CDs polymers

Conclusions

In this study, water-soluble maltose-based low molecular weight CDs polymers were synthesized and characterized. As a linking agent, cyanuric chloride was chosen because of the ease of functionalization without the loss of the complexing properties of the CDs. The maltose-based oligomers have potential as highly water soluble, biocompatible materials. The inclusion complexation of CD–maltose with Efavirenz significantly enhances the water solubility and drug-inclusion stability of Efavirenz, thus, opening possibilities of using these as carriers for other water-insoluble drugs. The polymerization process is simple and carried out at ambient temperature and is more controlled than the existing epichlorohydrin CD polymerization process.

Acknowledgment One of author (IS) wishes to acknowledge The M. S. University of Baroda, Vadodara, for providing financial support.

References

1. Atwood JL, Davies JED, Macnicol DD, Vogtle F (1996) Comprehensive supramoleculer chemistry, vol 3 (cyclodextrins), 1st edn. Elsevier Science Ltd., New York
2. Monti S, Sortino S (2002) Photoprocesses of photosensitizing drugs within cyclodextrin cavities. Chem Soc Rev 31:287–300
3. Murthy CN, Geckeler KE (2001) The water-soluble β-cyclodextrin–[60]fullerene complex. Chem Commun 13:1194–1195
4. Murthy CN, Choi SJ, Geckeler KE (2002) Nanoencapsulation of [60]fullerene by a novel sugar-based polymer. J Nanosci Nanotechnol 2:129–132
5. Bortolus P, Marconi G, Monti S, Mayer B, Koehler G, Grabner G (2000) Interaction of 4-hydroxybiphenyl with cyclodextrins: effect of complex structure on spectroscopic and photophysical properties. Chem Eur J 6:1578–1591
6. Mura P, Faucci MT, Bettinetti GP (2001) The influence of polyvinylpyrrolidone on naproxen complexation with hydroxypropyl β-cyclodextrin. Eur J Pharm Sci 13:187–194
7. Renard E, Deratani A, Volet G, Sebille B (1997) Preparation and characterization of water soluble high molecular weight β-cyclodextrin-epichlorohydrin polymers. Eur Polym J 33:49–57
8. Bost M, Laine V, Pilard F, Gadelle A, Defaye J, Perly B (1997) The hemolytic properties of chemically modified cyclodextrins. J Incl Phenom Macrocycl Chem 29:57–63
9. Weisz PB, Kumor K, Macarak EJ (1991) Protection of erythrocytes against hemolytic agents by cyclodextrin polysulfate. Biochem Pharmacol 42:1502–1503
10. Szejtli J (1998) Introduction and general overview of cyclodextrin chemistry. Chem Rev 98:1743–1753
11. Shiotani K, Uehata K, Irie T, Uekama K, Thompson DO, Stella VJ (1995) Differential effects of sulphate and sulfobutyl ether of β-cyclodextrins on erythrocyte membranes in vitro. Pharm Res 12:78–84
12. Szeman J, Ueda H, Szejtli J, Fenyvesi E, Machida Y, Nagai T (1987) Complexation of several drugs with water-soluble cyclodextrin polymer. Chem Pharm Bull 35:282–288
13. Fenyvesi EJ (1988) Cyclodextrin polymers in the pharmaceutical industry. J Incl Phenom Macrocycl Chem 6:537–545
14. Mura P, Faucci MT, Maestrelli S, Furlanetto S, Pinzauti S (2002) Characterization of physicochemical properties of naproxen systems with amorphous β-cyclodextrin-epichlorohydrin polymers. J Pharm Biomed Anal 29:1015–1024
15. Harata K, Morimoto S, Tsuda K (1984) US Patent 4:432,802
16. Ekberg B, Sellergren N, Olsson L, Mosbach K (1989) The synthesis of water-soluble polymers of β-cyclodextrin and their use in aqueous two-phase systems. Carbohydr Polym 10:183–188

17. Harada A, Furue M, Nozakura S (1976) Cyclodextrin-containing polymers. 2. Cooperative effects in catalysis and binding. Macromolecules 9:705–710
18. Szejtli J (1984) Highly soluble β-cyclodextrin derivatives. Starch-Starke 36:429–432
19. Li J, Xiao H, Jiehue L, Zhong YP (2004) Drug carrier systems based on water-soluble cationic β-cyclodextrin polymers. Int J Pharma 278:329–342
20. Furuike T, Nishi N, Tokura S, Nishimura SI (1995) Synthetic glycoconjugates. 6. Preparation and biochemical evaluation of novel cluster-type glycopolymers containing Gal .beta.(1.fwdarw.4)Glc-NAc (N-Acetyllactosamine) residue. Macromolecules 28:7241–7247
21. Lis H, Sharon N (1998) Lectins: carbohydrate-specific proteins that mediate cellular recognition. Chem Rev 98:637–674
22. Nishimura SI, Matsuoka K, Furuike T, Ishii S, Kurita K, Nishimura KM (1991) Synthetic glycoconjugates. 2. n-Pentenyl glycosides as convenient mediators for the syntheses of new types of glycoprotein models. Macromolecules 315 24:4236–4241
23. Nishimura SI, Matsuoka K, Kurita K (1990) Synthetic glycoconjugates: simple and potential glycoprotein models containing pendant N-acetyl-D-glucosamine and N,N'-diacetylchitobiose. Macromolecules 23:4182–4184
24. Roy R, Tropper FD, Romanowska A (1992) New strategy in glycopolymer syntheses. Preparation of antigenic water-soluble poly(acrylamide-co-p-acrylamidophenyl .beta.-lactoside). Bioconjug Chem 3:256–261
25. Aoi K, Tsutsumiuchi K, Aoki E, Okada M (1996) First synthesis of glycopeptide macromonomers and graft-type sugar-containing polymers with glycopeptide side chains. Macromolecules 29:4456–4458
26. Kobayashi K, Kamiya S, Enomoto N (1996) Amylose-carrying styrene macromonomer and its homo- and copolymers: synthesis via enzyme-catalyzed polymerization and complex formation with iodine. Macromolecules 29:8670–8676
27. Fraser C, Grubbs RH (1995) Synthesis of glycopolymers of controlled molecular weight by ring-opening metathesis polymerization using well-defined functional group tolerant ruthenium carbene catalysts. Macromolecules 28:7248–7255
28. Chen X, Dordick JS, Rethwisch DG (1995) Chemoenzymic synthesis and characterization of poly(α-methyl galactoside 6-acrylate) hydrogels. Macromolecules 28:6014–6019
29. Choi SJ, Geckeler KE (2007) A novel polycondensate containing cyclodextrin and lactose: synthesis, metal-complexing properties, and degradation. Polymer 48:1445–1449
30. Shown I, Murthy CN (2009) Grafting of cotton fiber by water-soluble cyclodextrin-based polymer. J Appl Polym Sci 111:2056–2061
31. Heise HM, Kuckuk R, Bereck A, Riegel D (2010) Infrared spectroscopy and raman spectroscopy of cyclodextrin derivatives and their ferrocene inclusion complexes. Vib Spectro 53:19–23
32. Chiappetta DA, Hocht C, Taira C, Sosnik A (2010) Efavirenz-loaded polymeric micelles for pediatric anti-HIV pharmacotherapy with significantly higher oral bioavailaibility. Nanomedicine 5:11–23
33. Ruebner A, Statton GL, James MR (2000) Synthesis of a linear polymer with pendent γ-cyclodextrins. Chem Phys 201:1185–1188
34. Bettinetti G, Gazzaniga A, Mura P, Giordano F, Setti M, (1992) Thermal behaviour and dissolution properties of naproxen in combinations with chemically modified β-cyclodextrins. Drug Dev Ind Pharm 18:39–53
35. Mura P, Liguori A, Bramanti G, Bettinetti GP, Campisi E, Faggi E (1992) Improvement of dissolution properties and microbiological activity of miconazole and econazole by cyclodextrin complexation. Eur J Pharm Biopharm 38:119–123
36. Shown I, Murthy CN (2008) Synthesis and characterization of linear water-soluble γ-cyclodextrin based polymers as drug carrier systems. Supramol Chem 20:573–578
37. Higuchi T, Connors KA (1965) Phase-solubility techniques. Adv Anal Chem Instrum 4:117–212
38. Arias MJ, Moyano JR, Gines JM (1997) Investigation of the triamterenbeta-cyclodextrin system prepared by co-grinding. Int J Pharm 153:181–189
39. Reuscher H, Hirsenkorn RJ (1996) BETA W7 MCT—new ways in surface modification. Incl Phenom Macrocycl Chem 25:191–196