Carbohydrate Polymers 76 (2009) 46–50

Contents lists available at ScienceDirect

Carbohydrate Polymers

journal homepage: www.elsevier.com/locate/carbpol

Investigation diffusion mechanism of β-lactam conjugated telechelic polymers of PEG and β-cyclodextrin as the new nanosized drug carrier devices

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ARTICLE INFO

Article history:
Received 12 June 2008
Received in revised form 17 September 2008
Accepted 18 September 2008
Available online 30 September 2008

Keywords:
Cyclodextrin
β-Lactam
Drug release
Fickian diffusion
Prodrug

ABSTRACT

Six new prodrugs including conjugated telechelic polymer of β-cyclodextrin-poly (ethylene glycol)-β-cyclodextrin (β-CD-PEG- β-CD) and or parent β-cyclodextrin (β-CD) were designated as the new drug carrier agents containing β-lactam antibiotics such as ampicillin (AMP), amoxicillin (AMO) and cephalexin (CEP) prodrugs for potentially local administration pharmaceutical applications. Investigation of the drug release dynamics in buffered media with pH 7.4 showed that the drug released through the prodrug matrix with slightly deviation, follows Fickian diffusion mechanism. Using equation "$\log (M_t/M_\infty) = \log k + n \log t$" it has revealed that the synthesized prodrugs 5a–c, 6a–c have the "n" values 0.333, 0.334, 0.390, 0.540, 0.514 and 0.473, respectively. In fact, the prodrug 6c showed the least deviation from Fickian diffusion mechanism.

1. Introduction

In the last few decades synthetic macromolecules as the prodrugs containing variety of pharmaceutical materials have received considerable attentions (Hastings, 1985; Entezami, Nasir Tabrizi, & Davaran 1996; Namazi & Adeli, 2003; 2005a; 2005b; Namazi, Bahrami, & Entezami 2005). Polymers are widely used as carrier agents for this purpose due to possibility that these kind of materials can be synthesized and could have remarkable properties ranged from rigid and hydrophobic systems to the highly hydrophilic and flexible biomaterials when they are in contact with the physiological fluids (Roman & Madruga, 1989). On the other hand, controlled release systems can optimize the safety and convenience because they could be designed to deliver a drug molecule at a specific rate and for a specific period of time even at a desired location.

Cyclodextrins (CDs), as the cyclic oligosaccharides are chemically and physically stable molecules and are formed by the enzymatic modification of starch (Slominska, Szostek, & Grzeskowiak 2002). CDs have cavity with nanosize dimensions in their structures (~0.4–0.8 nm and ~0.8 nm as the height and diameter, respectively), are able to form inclusion complexes with a wide variety of suitable sized organic compounds in their cavities. As the result of complexation of suitable size compounds with cyclodextrins, the apparent solubility of the molecules can be altered. The stability of the including compounds in the presence of light, heat and oxidizing conditions is increased and volatility of compounds is decreased (Szejtli, 1988). These capabilities of CDs have been used in the pharmaceutical and foods (Bhandari, D'Arcy, & Thi Bich 1998), cosmetics (Lentini & Zecchino, 1996) and toiletry (Lindauer, Ira, Hill, & Liberman 1984) industries. They can also be used as processing aids to isolate compounds from natural sources and to remove unwanted compounds (Shaw & Buslig, 1988). In the pharmaceutical industry they act both as the complexing and also conjugating agents to increase the aqueous solubility of poorly water-soluble drugs, in order to increase their bio-availability and stability. In addition, CDs can be used to reduce or prevent gastro-intestinal or ocular irritation, reduce or eliminate unpleasant smells or tastes, prevent drug–drug or drug-additive interactions, or even to convert oils and liquid drugs into micro-crystalline or amorphous powders (Hirayama, Usami, Kimura, & Uekama 1997). Their derivatives specifically β-CD derivatives have been used for controlled drug release systems (Stella & Rajewski, 1997). Pharmaceutically useful β-CD derivatives are: hydrophilic derivatives (methylated, hydroxyalkylated, branched 6-glucosyl and -maltosyl), hydrophobic derivatives (ethylated and peracylated), ionizable derivatives (carboxyalkyl, carboxymethyl, sulfates, alkylsulfonates). Many controlled release in oral drug delivery systems (immediate release, delayed release, prolonged release and modified release) and cyclodextrin-based site-specific drug delivery prodrugs have been prepared (Hirayama & Uekama, 1999).

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doi:10.1016/j.carbpol.2008.09.023

Polymer containing CDs also have designated and synthesized for drug delivery systems. Caleceti, Salmaso, and Semenzato (2004) prepared a supramolecular prodrug jointed of β-CD, PEG and folic acid and studied its tumor targeting activity.

β-lactam antibiotics are used clinically for the treatment of broad range of bacterial infections (Mandell, Dougles, & Bennet 1990). Amino-hydroxybenzylpenicillin (AMO) was a semi synthetic, orally absorbed, broad-spectrum antibiotic (Fig. 1). It is now widely used in a standard eradication treatment of gastric infections e.g. helicobacter pyloriinfection combined with an acid-suppressing agent (Vakil & Cutler, 1999). AMP and CEP were also used widely for the treatment of infections (Queiroz, Santos, Monterio, Gibson, & Knowles 2001).

Most drugs can be administrated by a variety of routes, broadly defined as local and systemic (Somayaji, Jariwala, Jayachandran, Vidyalakshmi, & Dudhani 1998). Drugs administered systemically are absorbed into the blood stream and distributed throughout the host patient via the circulatory system, which can result in bacterial resistance (Somayaji et al. 1998; Soskolne et al. 1997). When administered locally, they limit the adverse effects of systemic administration and there is a higher concentration of medication reaching the targeted site (Somayaji et al. 1998). Queiroz et al. (2001) prepared sodium ampicillin and was adsorbed onto hydroxyapatite and glass-reinforced hydroxyaptite composites as a potential pharmaceutical formulation for periodontitis, taking into account similar purpose ampicillin-loaded methylpyrrolidinone chitosan microparticles were described (Giunchedi, Genta, Conti, Muzzarelli, & Conte, 1998). Calcium phosphate based implantable cements containing active drugs which can locally release drug "in situ" after implantation have been designed and prepared in the recent years, for example Vallet-Regi et al. synthesized CEP containing gypsum and apatite/gypsum cements and studied kinetics of the drug release from the cement (Vallet-Regi, Doadrio, Arcos, & Caban 2004). In the previous work we reported the synthesis of versatile telechelic polymer of β-CD and parent β-CD as the naturally occurring nanostructure compounds containing three β-lactam antibiotics AMO, AMP and CEP (Namazi & Kanani, 2007). Here we report evaluation of diffusion mechanism of the synthesized supramolecular prodrugs based on β-lactam conjugated telechelic polymers of poly(ethylene glycol) and β-cyclodextrin which could potentially be used in different ways.

2. Experimental

2.1. Materials

β-CD (Fluka) dried in oven at 90 °C for 8 h. ρ-Toluenesulfonic acid (TSA) were purified by conventional methods before use. *N*, *N*-dimethylformamide (DMF) (Fluka) and pyridin were dried and distilled under reduced pressure. AMP, AMO, and CEP antibiotics were purchased from the Zakariia Co. (Iran), dialysis membrane D7884 from Sigma (retains molecular weights greater than 2000 and releases smaller than 1200). Other reagents and solvents purchased from Merck. Pyridine and DMF refluxed over and subsequently distilled from calcium hydride and barium oxide, respectively, before use.

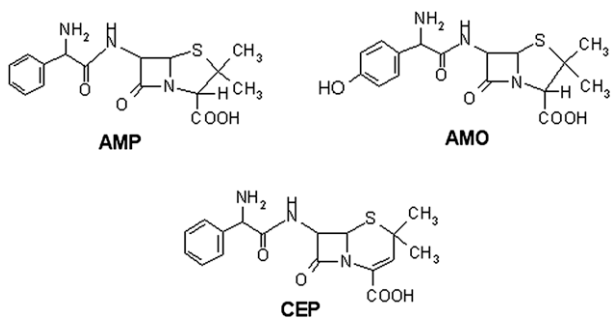

Fig. 1. Schematic structure of AMP, AMO and CEP.

Spectra were recorded on the following instruments: FT-IR spectra, Shimadzu 4200 FT-IR; NMR, Bruker 400 MHz (DMSO-d_6); UV spectra, Shimadzu 265FW UV–Vis spectrophotometer. Differential Scanning Calorimeter (DSC) thermograms were recorded with a Perkin-Elmer DSC-7 differential scanning calorimeter.

2.2. Synthesis

All synthesized prodrugs are numbered as shown in Table 1.

2.2.1. Mono-6-O-tosyl-β-CD (1)

β-CD (6.0 g, 5.29 mmol) was dried at 110 °C under high vacuum for 8 h and then dissolved in pyridine (60 mL). The resulting solution was cooled in an ice bath and treated with a solution of *p*-toluenesulfonyl chloride (1 g, 5.25 mmol) in pyridine (6 mL). The mixture was stirred at room temperature under nitrogen for 12 h. Then pyridine was evaporated under a reduced pressure at 40 °C to obtain a viscose material, then diethyl ether (100 mL) was added. The white precipitate was recrystallized in distilled water three times. Yield, 35% (2.3 g, 1.85 mmol); mp 170 °C.

2.2.2. Telechelic polymer of β-CD-PEG-β-CD (2)

A solution of PEG (M_W 2000, 2 g, 1 mmol) in 20 mL dry DMF was placed in a round-bottom flask equipped with a reflux condenser, dropping funnel, argon inlet and magnetic stirrer. Sodium hydride (0.24 g, 10 mmol) was added and the mixture was stirred at room temperature for 1 h and at 50 °C for additional 2 h. The mixture was cooled and filtered off under argon atmosphere. A solution of mono-6-*O*-tosyl-β-CD (5.15 g, 4 mmol) in DMF (10 mL) was added to the solution at room temperature in 15 min through a dropping funnel, and then it was stirred for 2 h at room temperature and for an additional 12 h at 40 °C. The obtained product was precipitated in diethyl ether. After decantation, the precipitate was dissolved in methanol and reprecipitated in diethyl ether. For further purification the above process repeated three times. The precipitate was dissolved in diluted sodium hydroxide solution (0.5 M, 20 mL) and was neutralized using hydrochloric acid to achieve pH 7.0. The mixture was filtered and 5 mL of the filtrate was subjected to dialysis using a dialysis bag (against 250 mL external distilled water) for 24 h. The solvent was removed overnight by blowing a stream of air over the surface. The resulted product was washed with dichloromethane, chloroform and ethanol, respectively, for a 58% yield.

2.2.3. Synthesis the first group of β-CD-PEG-β-CD prodrugs (5a–c)

Antibiotics AMP, AMO and CEP chemically attached to telechelic polymer 2 through two steps.

Step 1: The amine group of the antibiotic drug molecule was protected then was activated with dicyclohexylcarbodiimide (DCC). For protecting the amine group of drug molecules it was converted to ammonium salt using a solution of hydrochloric acid. In each case drug (0.47 mmol) was placed in a round-bottom flask

Table 1
Numbering of prepared prodrugs

Carrier	Drug		
	AMP	AMO	CEP
β -CD-PEG- β-CD	5a	5b	5c
β -CD	6a	6b	6c

and a solution of hydrochloric acid having pH 3.0 (40 mL) was added with stirring at 0 °C for 20 min. Stirring was stopped after 30 min and water was evaporated by blowing a stream of air over its surface in 24 h. Resulting salt was dissolved in DMF with moderate heating; anhydrous sodium sulfate (0.50 g) was added and stirred for 15 min. The mixture was filtered and DCC (0.165 g, 0.472 mmol) and DMF (0.01 g, as a catalyst) were added to the filtrate and the mixture was stirred for 30 h at room temperature (solution A).

Step 2: Reaction of the protected and activated drug with telechelic polymer 2: telechelic polymer 2 (0.5 g, 0.012 mmol) was dissolved in 5 mL DMF at room temperature (solution B). This solution was added to solution A and stirring was continued for 12 h then the mixture was filtered. Diethyl ether (150 mL) was added to the filtrate; and upper layer of precipitate was decanted. Water (50 mL) was added and after stirring at room temperature for 4 h the solution was filtered. The filtrate was membrane dialyzed twice. The solvent was evaporated by a stream of air over its surface for 24 h. The residue was washed with alcohol (ethanol for 5a and methanol for 5b and 5c) then the product was dried at 40 °C.

2.2.4. Synthesis the second group of prodrugs (6a–c)

For comparison the properties of two group prodrugs, the second group of prodrugs was synthesized *via* linking the drugs to parent β-CD in a similar synthesis route to the first group of prodrugs.

2.3. Drug release procedure

The synthesized six prodrugs were separately subjected to drug release by the following procedure: 30 mg of finely powdered prodrug added to a dialysis bag containing 10 mL phosphate buffer solution with pH 7.4. The prodrug in the dialysis bag was immersed in 50 mL of the same buffered media that was continuously rotated with stirring rate of 50 rpm at 37 °C. At different intervals, a 10 mL sample was withdrawn and the equivalent volume of the solution at the same temperature was added to the dissolution vessel. The absorbance values of the samples were determined using UV (258 nm, 274 nm and 260 nm for AMP, AMO and CEP, respectively). The related concentrations (mol/L) were calculated using calibration profiles based on concentration versus absorbance using previously designed and standardized curves of absorbance for known concentrations. All release tests were run in triplicate and their average values are reported here.

3. Results and discussion

3.1. Characterization of synthesized compounds

Structural characterization of synthesized compounds was performed using ^{1}H NMR, FT-IR and UV spectroscopic and other common methods. The solubility of the prepared prodrugs (mg/mL) were examined in distilled water. The data for the solubility and other characters of all synthesized prodrugs are shown in Table 2.

In each case, the average number of the attached drug molecules was calculated from the integration of related protons in the ^{1}H NMR spectrum using Eq. (1) whereas the parameters Ave, IV_2, IV_1, P and C are the average numbers of the attached drug molecules, integration value of the peaks for aromatic protons of the drug residue, integration value of the peaks for anomeric protons of β-CD, aromatic protons of the drug molecule and total anomeric protons of CD molecules, respectively.

$$\text{Ave.} = \frac{IV_2 \div P}{IV_1 \div C} \quad (1)$$

For example in case of 5a there are four parameters IV_2, IV_1, P and C with values 27.57, 14.55, 5.0 and 14.0, respectively, and thus related average (ave.5a) was resulted as 5.3 (note that each molecule of compound 2 contains two β-CD residue and thus having total of 14 anomeric protons).

3.2. Drug release charts

It is known that a direct correlation exists between the time of the β-lactam concentrations which are maintained above the therapeutic concentration and the clinical outcomes. And it has been confirmed that continuous infusion for β-lactams, has clinical advantages over an intermittent mode of administration. Furthermore, a smaller total antibiotic dose is required to achieve the same pharmacodynamic endpoint by continuous infusion in comparison to intermittent infusion (Drusano, 1988; Roosendaal, Bakker-Woundenberg, Berg, & Michel 1985). In drug delivery systems after water absorbtion the drug diffuses out of prodrug. The diffusion of water in hydrogels and other similar drug delivery systems was classified into three different types based on the relative rates of diffusion and polymer relaxation. This classification of the diffusion of water can also be used to classify the drug release profiles from the prodrugs (Peppas & Korsmeyer, 1987). These systems are as follows:

1. Case I diffusion (or simple Fickian diffusion): this kind of diffusion occurs when the rate of diffusion is much less than that of polymer relaxation. Meanwhile, when the drug is loaded into the prodrugs by equilibrium swelling in a drug solution, drug release from the swollen system follows Fick's law. Drug release from Case I systems is dependent on $t^{1/2}$.
2. Case II diffusion (relaxation-controlled transport): this kind of diffusion occurs when diffusion is very rapid compared to the relaxation process. In Case II systems, diffusion of water through the previously swollen shell is more rapid than the swelling-induced relaxation of polymer. Therefore, in this system the rate of water penetration is controlled by the polymer relaxation. For film specimens, the swelling zone moves into the membrane at a uniform rate and the weight gain increases in direct proportion to time. If the prodrugs contain a water-soluble drug, the drug is essentially immobile in a glassy system, but diffuse out when prodrug swells by absorbing water.
3. Case III (non-Fickian or anomalous diffusion): in this system the diffusion and relaxation rates are comparable. Drug release depends on two simultaneous rate processes, water migration into the device and drug diffusion through continuously swelling prodrugs which is highly complicated.

Fickian, Non-Fickian and Case II diffusion mechanism of the drugs from the prodrug matrix can be calculated from the Eq. (2).

Table 2
Characteristic data of the prodrugs 5a–c, 6a–c (mg/ml of water)

Drug or prodrug	5a	5b	5c	6a	6b	6c
Water solubility (mg of prodrug/ml of water)	0.44[a]	[b]	[b]	1	0.46	[b]
The average number of the attached drug molecules	5.30	6.04	5.72	7.27	8.19	3.36

[a] Forms a cloudy suspension.
[b] Not soluble in distilled water.

$$M_t/M_\infty = kt^n \quad (2)$$

where M_t/M_∞ is the fractional release of drug in time t, 'k' is the constant characteristic of the prodrug system, and 'n' is the diffusion exponent characteristic of the release mechanism. For Normal Fickian diffusion, Case II diffusion and Non-Fickian diffusion the values of 'n' are 0.5, 1.0 and 0.5–1.0, respectively (Ritger & Peppas, 1987).

Fig. 2 illustrates comparison of drug release at pH 7.4 from the synthesized prodrugs.

PEG as a biocompatible polymer was introduced to the backbone of prodrugs in order to increase the hydrophilicity of the final prodrugs. As shown the members of group 1 prodrugs (5a–c) release the drug faster than the group 2 (6a–c). This behavior demonstrates that prodrugs of group 1 dissolve faster in release media probably due to having hydrophilic chain of PEG. On the other hand in case of group 2 prodrugs members, aggregation of carrier molecules is contingent following contact with solution medium. In initial 5 h prodrugs 5c and 6b show the fastest and slowest drug release behavior, respectively.

Eq. (2) can be lineared to the form Eq. (3):

$$\log(M_t/M_\infty) = \log k + n \log t \quad (3)$$

Profiles of Log M_t/M_∞ versus Log t in case of all drugs released from mentioned prodrugs are plotted in Fig. 3.

Generally only the first 60% of released drug data have been used in mathematical evaluations. Experimental data were analyzed by nonlinear least-squares regression. The values n, k and R^2 have been evaluated for the release studies of AMP, AMO and CEP from the Fig. 3 and the obtained results are shown in Table 3. The values of k are between 0.358 and 0.528. Drug release of all prodrug systems have satisfactory fitness with Eq. (1) (R^2 has value greater than 0.99) excluding 6b. It is clear from Table 3 that n has the values from 0.333 (5a) to 0.541 (6a).

It must be noted that the synthesized prodrugs in this work are not swellable in contact with release media and in similar conditions the threshold of n value between Fickian and non-Fickian mechanism must be assumed 0.45 instead of 0.5. (Gao, Gu, & Ping 2007). Therefore, diffusion process related to these prodrugs with slightly deviation follows the Fickian mechanism. As seen, the average number of the attached drug molecules is decreased through order of 6b > 6a > 5b > 5c > 5a > 6c (Table 2). And in comparison with R^2 values in Table 3 reveals that deviation is considerably related to the average number of the attached drug molecules in prodrugs. Therefore, comparing the data in Tables 2 and 3 reveals that 6c has the lowest attached drug molecules and thus the least deviation from the Fickian mechanism.

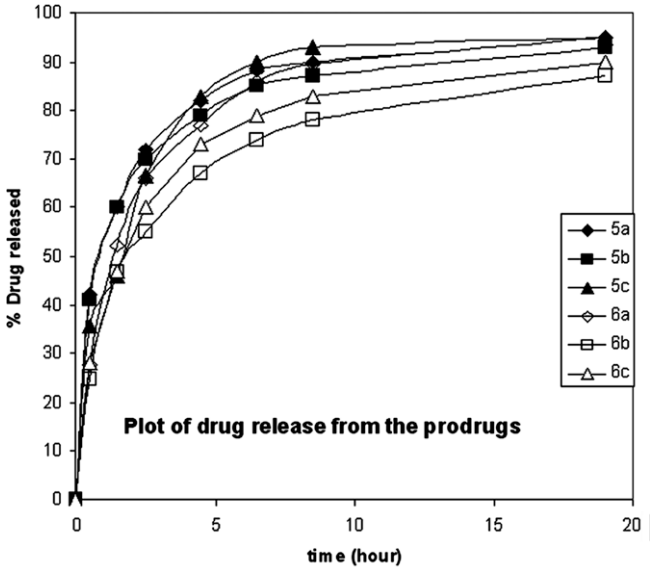

Fig. 2. Plot of drug release from the prepared prodrugs.

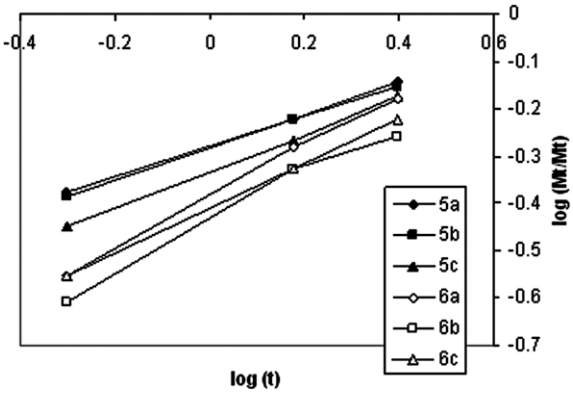

Fig. 3. Profiles of Log M_t/M_∞ versus Log t in case of all drugs released from prepared prodrugs.

Table 3
The calculated values of n, k and R^2 for the synthesized prodrugs 5a–c, 6–c

Prodrug	Parameter		
	n	k	R^2
5a	0.333	0.527	0.999
5b	0.334	0.518	0.999
5c	0.390	0.465	0.999
6a	0.540	0.409	0.997
6b	0.514	0.358	0.983
6c	0.473	0.388	1.000

4. Conclusions

From the foregone discussion it is concluded that AMP, AMO and CEP based prodrugs have potentiality to act as drug delivery devices. Also from the drug release dynamics it is concluded that the drug released through the prodrug matrix with slightly deviation, follows Fickian diffusion mechanism and the rate of drug diffusion and the rate of polymer chain relaxation are comparable. Meanwhile, drug release depends on two simultaneous rate processes, water migration into the device and drug diffusion through prodrugs. Experimental results showed that drug release mechanism in the prodrugs is highly related to the average number of the attached drug molecules. Drug release properties of these new synthesized prodrugs in comparison with literature data also revealed that they are potentially suitable candidates for local antibiotic therapy such as: dental, bone and joint infections.

Acknowledgements

Authors greatly acknowledge the University of Tabriz for financial supports of this project and also we thank Dr A. Ansarin for his help in proofreading of the article.

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