High-efficiency loading and controlled release of highly water-soluble drug, pravastatin sodium by use of cross-linked β-cyclodextrin

Yatendra Kumar, Betty Philip, Kamla Pathak
Department of Pharmaceutics, Rajiv Academy for Pharmacy, NH#2, P.O. Chhattikara, Mathura-281 001, India.

INTRODUCTION
The primary method of accomplishing a controlled release has been through incorporating the biologically active agents within polymers. Generally, controlled release dosage forms have been designed on the basis of polymers. Therefore, to obtain a suitable barrier for achieving controlled release, the cross-linking of polymers is a substantial approach. Cross-linking is the process of chemically joining 2 molecules by a covalent bond. Cross-linking reagents contain reactive ends to specific functional groups (primary amines, hydroxyl, and others) on proteins, carbohydrates, or other molecules. Chemical cross-linking allows good control of molecular weight between cross-links by the amount of cross-linking agents added to the solution. This makes it possible to control the cross-linked structure and reduce the number of entanglements.

The chemical modification of cyclodextrins (CDs), cyclic oligosaccharides containing glucopyranose units attached by α-(1→4)-glucoside bonds has been extensively investigated in order to improve the physicochemical properties of CDs, such as water solubility, hygroscopicity, surface activity, and so on, and the modified CDs have been applied as drug carriers for enhancing drug efficacy. The majority of the literature citations report the use of CL β-CD as a carrier for delivery of poorly water-soluble drugs, and very scarce reports are available for using the carrier for water-soluble drugs. The purpose of this study is to prepare and characterize CL β-CD microparticles using emulsification phase separation method followed by chemical cross-linking by epichlorohydrin and to achieve maximum loading of the hydrophilic drug, pravastatin sodium (PS) within CL β-CD so as obtain its controlled release.

PS, an antihyperlipoproteinemic drug that inhibits HMG Co-A reductase is freely soluble in water with log P (octanol/water) of −0.23 is effective in low dose of 10–40 mg. Short plasma half-life (1.3–2.6 h), low bioavailability (17%), and fluctuations in blood levels makes it a model drug for the present study.
The controlled release of PS has the potential to enhance its therapeutic properties by offering the advantage of less-frequent dosing with decreased fluctuation in the blood levels during the dosing interval.

**MATERIALS AND METHODS**

**Materials**

PS was gifted by Cadila Pharmaceuticals Ltd (Ahmedabad, India). β-CD was supplied by S Merck (Mumbai, India) and epichlorohydrin was purchased from G.S. Chemicals (New Delhi, India). Tween 80, potassium dihydrogen orthophosphate LR, and ethanol (95%), sodium hydroxide, concentrated hydrochloric acid, glacial acetic acid, and heavy and light liquid paraffin (Qualigens Fine Chemicals, Mumbai, India) were used as received.

**Methods**

**Preparation of cross-linked β-cyclodextrin microparticles**

The emulsification phase separation or polymerization method was used for the preparation of CL β-CD microparticles. β-CD solution (7.5% w/v) in 100 mL of 0.1 M NaOH was used as an internal phase. The external phase was the mixture of light and heavy liquid paraffin in the ratio 1:1 in which the designated amount of span 60 was dissolved. The internal phase was gradually added to paraffin mixture and was emulsified by stirring it at 250 rpm for 5 min. The cross-linking agent epichlorohydrin was added dropwise in the emulsion and stirring continued until the microparticles of β-CD were solidified. The produced microparticles were filtered and washed 3 times alternatively with acetone and water for complete removal of residual solvent or cross-linking reagent and dried in oven for 24 h at 60°C. The dried product was collected, weighed, and subjected to evaluation.

**Evaluation of CL β-CD microparticles**

**Melting point and solubility studies**

The melting point of β-CD and CL β-CD microparticles was determined by digital automelting point apparatus (HICON Enterprises, New Delhi, India). For the solubility evaluation, 50 mg of CL β-CD microparticles was taken in a test tube and 5 mL of different solvents, such as water, acetone, alcohols, acetonitrile, DMSO, 1 M NaOH, 0.1 M HCl, PEG 400, PG, methanolic HCl, methanolic NaOH, n-hexane, and DMF, were added separately in each test tube. The test tubes were mechanically shaken in a water bath maintained at 25°C for 5 min and visually observed for complete dissolution of CL β-CD microparticles. The experiment was repeated for β-CD that was used as reference.

**Degree of cross-linking**

The method for determination the degree of cross-linking was based on the method used by Sugiura.[10] The degree of cross-linking was determined with the help of elemental analysis through elemental analyzer Elementar vario EL III (Germany), by calculating the percentage of carbon in sample of CL β-CD microparticles using following equation:

\[
C% = \frac{12.011 \times [42 + (6 + n) m]}{(\text{MW of epichlorohydrin} \times m + (\text{MW of β-CD} \times n))} \times 100
\]

where m and n are the degree of cross-linking and number of methylene moiety of cross-linking reagent, respectively.

**Swelling index**

Compacts of CL β-CD microparticles weighing 100 mg were placed in a dessicator for 48 h. The disk was placed on a mini-glass plate (2 × 4 cm) of known weight, which was transferred onto a Petri dish containing 20 mL distilled water at room temperature. After 12 h, the glass plates with the hydrated disks were removed, dried by blotting with tissue paper, and weighed. The degree of swelling or swelling index (SI) was determined by dividing the amount of water absorbed by sample (mg) by the amount of dry sample (mg).

**Micromeritic studies**

The micromeritic studies of β-CD powder and CL β-CD microparticles were performed by determination of bulk density and tapped density by cylinder method. On the basis of these properties, flow property determinants, such as Carr’s index and Hausner’s ratio were derived from density determinations. The angle of repose was determined by static funnel method, and particle size distribution was studied by optical microscopy.[11]

**Optimization of PS loading in CL β-CD microparticles**

The incorporation of drug within CL β-CD microparticles was done by active drug loading through incubation process. A known amount of CL β-CD microparticles was placed in 11.2 mM drug solution for 40 h with constant magnetic stirring of 100 rpm. The process variables, temperature, and pH of loading vehicle were optimized using 2² factorial design [Table 1]. Phosphate and borate buffers of variable strength were used for varying the pH of incubation medium. At the end of the incubation period, the amount of drug loaded in CL β-CD microparticles was determined by calculating the fraction of drug remaining in the pH of incubation media that was estimated spectrophotometrically (Shimadzu 1700 Pharmaspec, Kyoto, Japan) at 238 nm. To enhance the drug loading efficiency, different grades of nonionic surfactants, namely, Tween 20, 40, 60, and 80 and span 20, 60, and 80 in concentration of 1% w/v were considered and the drug loaded was analyzed. The surfactant that resulted in highest drug loading was selected for incorporation in the incubation media.

| Batch code | Temperature (°C) | pH  | Drug loading (%) |
|------------|-----------------|-----|------------------|
| C-LB1      | 20              | 4.0 | 86.74 ± 0.77     |
| C-LB2      | 20              | 9.0 | 79.45 ± 0.69     |
| C-LB3      | 40              | 4.0 | 84.97 ± 0.76     |
| C-LB4      | 40              | 9.0 | 76.67 ± 0.89     |
**Scanning electron microscopy**

The topography of β-CD, CL β-CD microparticles, pure PS, and PS-loaded CL β-CD microparticles were examined using a scanning electron microscope (LEO 435 VP, UK). The samples were previously fixed on a brass stub using double-sided adhesive tape and then were made electrically conductive by coating, in a vacuum, with a thin layer of gold (approximately 300 Å), for 30 s. The pictures were taken at various magnifications.

**Fourier transform infrared spectroscopy**

The infrared spectrophotometric study of β-CD, CL β-CD microparticles, pure PS, and PS-loaded CL β-CD microparticles was carried out by preparing KBp pellet and the spectrum was obtained in the range of wave number 400–4000/cm by using FTIR spectrophotometer (8400S Shimadzu, Kyoto, Japan).

**Differential scanning calorimetry**

Differential scanning calorimeter (DSC) measurements were performed on a Perkin Elmer (Pyris Diamond, UK) differential scanning calorimeter with a thermal analyzer. All accurately weighed samples of β-CD, CL β-CD microparticles, pure PS, and PS-loaded CL β-CD microparticles were placed in sealed pans before heating at a scanning rate of 100°C/min, from 25°C and PS-loaded CL

**In vitro release behavior of PS from the loaded CL β-CD microparticles**

The *in vitro* drug release rate studies were performed using USP XXIV dissolution rate test apparatus type I (fabricated basket type, mesh #120). The temperature of the 900 mL dissolution medium stirred at 50 rpm was maintained at 37°C ± 0.5°C. The dissolution medium was 0.1 N HCl, pH 1.2 for initial 2 h and then phosphate buffer pH 7.4 for 6 h. At predetermined time intervals, 5 mL samples were withdrawn, replaced with fresh medium and analyzed spectrophotometrically. Each experiment was conducted in triplicate for the determination of average values. On the basis of percentage drug release in different time intervals, various model-dependent and independent parameters were determined using PCP Disso v2.08 software, Pune, India.

## RESULTS

**Characterization of CL β-CD microparticles**

### Degree of cross-linking

CL β-CD microparticles were prepared and the degree of cross-linking, a molar ratio of a cross-linking residue to a β-CD residue, was calculated using the results of the elemental analysis of carbon in the microparticles of β-CD. The degree of cross-linking was determined to be 4.2, which means that 4.2 cross-linking residues can bind to one β-CD residue and generate microparticles that are suitable for drug loading.

**Melting point, solubility, and swelling index**

The β-CD showed the melting phenomenon at 256°C corresponding to the literature value,[12] but CL β-CD microparticles did not show any melting up to 300°C. The cross-linking process altered the physicochemical properties of β-CD; therefore, it failed to melt at the melting point of β-CD. Qualitative analysis of solubility revealed that β-CD was soluble in water and other tested solvents, but CL β-CD did not show any sign of solubility in the tested solvents. The SI of prepared CL β-CD microparticles was found to be 98.37% at the end of 12 h. Thereafter CL β-CD microparticles started to disintegrate slowly and signs of fragmentation were observed.

**Micromeritic studies**

The results of various rheologic properties of β-CD microparticles are summarized and compared with β-CD powder in Table 2. Due to increment in size by cross-linking process, the microparticles displayed a decrease in angle of repose, Carr’s index, and Hausner’s ratio that denoted better flow properties as compared with β-CD powder.

**Optimization of PS loading in CL β-CD microparticles**

Temperature and pH are 2 crucial experimental conditions that can alter the drug loading efficiency. The effect of these process variables on percentage drug loading are summarized in Table 1. Low pH (4.0) and low temperature (20°C) were identified as the favorable conditions for the process of active drug loading. At pH 4.0, the drug molecules were less ionized in comparison to borate buffer pH 9 and were more likely to get loaded within CL β-CD. On the other hand, at a relatively high temperature (40°C), the mobility of loaded drug molecule increases within cavities in CL β-CD, due to which the efficiency of entrapment decreased, therefore more amount of PS was loaded in CL β-CD microparticles at 20°C. As the extent of drug loading was very low, surfactants were incorporated in the incubation media. The effect of various nonionic surfactants on the extent of drug loading are shown in Table 3 and maximum percentage drug loading with Tween 80 clearly guided its selection as loading facilitator for PS. Thus active drug loading of PS was carried out at 20°C, pH 4.0 in the presence of 1% w/v Tween 80 to achieve maximum drug loading.

**Characterization of PS-loaded CL β-CD microparticles**

**Scanning electron microscopy**

The morphology of β-CD, CL β-CD microparticles, PS, and PS-loaded CL β-CD microparticles was characterized by scanning electron microscopy [Figure 1]. The β-CD molecules appeared

---

**Table 2: Micromeritic properties of β-CD powder and CL β-CD microparticles**

| Characteristic          | β-CD powder | CL β-CD microparticles |
|-------------------------|-------------|------------------------|
| Bulk density (g/cc)     | 0.523 ± 0.54 | 0.494 ± 0.89           |
| Tapped density (g/cc)   | 0.754 ± 0.56 | 0.532 ± 0.87           |
| Carr’s compressibility% | 21.44       | 7.0                    |
| Hausner’s ratio         | 1.441       | 1.076                  |
| Angle of repose         | 23 ± 0.99°  | 16° ± 0.89°            |
| Size distribution       | 7–45 μm     | 425–2500 μm            |
as definite, discrete particles with smooth surface, whereas CL β-CD microparticles appeared as an agglomeration of several β-CD molecules with highly irregular, 3-dimensional structures. It was likely that fusion of β-CD molecules occurred during the polymerization reaction via chemical cross-linking leading to aggregation. The morphologic characteristics were observed for the CL β-CD microparticles with impressions of solvent evaporation on the surface of the microparticles. It is vivid from SEM photograph that the irregular crystals of PS [Figure 1c] went into molecular solution during incubation and the PS molecules got entrapped in cross-linked matrices of β-CD microparticles. Thus the micrograph of PS-loaded CL β-CD microparticles [Figure 1d] showed the absence of solvent impressions that could be faintly recognized on the CL β-CD microparticles [Figure 1b]. The residuals of solvent on the surface of CL β-CD microparticles disappeared probably due to molecular deposition of PS during incubation. The comparable morphology reveals that strong loading did take place in PS-loaded CL β-CD microparticles.

**Fourier transform infrared spectroscopy**

The FTIR spectra of β-CD shows a broad O–H stretching vibration band at 3450/cm, a sharp hydrogen-bonded O–H stretching vibration at 3299/cm, and a C–O stretching vibration band at 1159/cm [Figure 2]. The CL β-CD microparticles demonstrated 2 strong characteristic peaks at 1043/cm and 3379/cm that were due to the asymmetric carbonyl (C–O–C) stretching and hydrogen-bonded O–H stretching, respectively.[13] Absence of characteristic peak of nonhydrogen-bonded O–H stretching vibration band at 3450/cm observable in the IR spectrum of β-CD microparticles proves that all free primary alcoholic groups of β-CD were utilized in the cross-linking process. The FTIR spectrum of the PS-loaded CL β-CD microparticles was superimposition of the spectral patterns of PS and CL β-CD microparticles.

**Differential scanning calorimetry**

As shown in Figure 3a the sharp, symmetrical endothermic peak (ΔH = 14.69 J/g) corresponding to the melting point of β-CD is located at 260°C that could not be observed in the thermogram of CL β-CD microparticles (3b) suggestive of chemical cross-linking of β-CD. The thermogram of PS in pure form depicted a sharp, symmetrical endothermic peak (ΔH = 18.43 J/g) at 169°C (3c) corresponding to its melting point that was observed at 162°C with slightly lower ΔH of 17.41 J/g (3d). No new peak was observed in the DSC curve of PS-loaded β-CD microparticles indicating no degradation of the drug during processing.

**In vitro drug release**

The in vitro drug release profiles of PS from PS-loaded CL β-CD microparticles presented in Figure 4 are significantly different from the profile of drug alone. In the pure form, 45.15% PS was dissolved within 30 min and followed by 92.53% and 98.12% in the 2nd and 4th h, respectively. On the other hand, the release of PS from all the CL β-CD microparticles was considerably reduced with a maximum of 8.07%–23.11% release in the acidic media followed by gradual release of more than 95% in pH 7.4 from all the batches. The release rate controlling effect

| Nonionic surfactant | Drug loading (%) ± S.D |
|---------------------|------------------------|
| Span20              | 80.79 ± 0.89           |
| Span 60             | 78.12 ± 0.91           |
| Span 80             | 75.56 ± 0.65           |
| Tween 20            | 81.43 ± 0.69           |
| Tween 40            | 83.27 ± 0.78           |
| Tween 60            | 83.97 ± 0.84           |
| Tween 80            | 85.44 ± 0.61           |
was maximum in case of C-LB 1 with 98.07% CDR in 8 h and least controlling effect was documented in case of C-LB 4 with 95.01% being released in 6 h. Upon visual observation of swelling behavior of C-LB1–C-LB4 during the in vitro release studies, it was observed that fragmentation of swollen C-LB4 started at 6th h followed by C-LB3 at 7th h, C-LB2 at 8th h, and no sign of fragmentation could be observed for C-LB1 at the end of 8th h. This explains why C-LB1 was able to control the release in a better manner in comparison to the rest of the drug-loaded microparticles.

**Release kinetics of PS from loaded batches of CL β-CD microparticles**

In order to obtain meaningful information, the drug release profiles were fitted to various kinetic models. Table 4 summarizes the correlation coefficients for different release kinetic models of drug-loaded CL β-CD microparticles. Model with higher correlation coefficient was judged to be a more appropriate one for the dissolution data. The in vitro release profile for pure drug best fitted first order during the initial 2 h and thereafter it leveled off. The release data of C-LB2–C-LB4 either fitted matrix or Peppas model, whereas the profile of C-LB1 fitted zero-order model with r² value of 0.9910. This indicated that apart from cross-linked polymer properties, the additional process variables affected the drug release behavior more prominently. The release data was also used to determine model-independent parameters and the t½ and t¼ were maximum for batch C-LB1. Another important model-independent parameter, dissolution efficiency (DE), was also determined. The DE in the initial and later dissolution period DE_{t<0.5h} and DE_{t>0.5h}, respectively, was evidently least from C-LB1 than rest of the batches.

**DISCUSSION**

In order to achieve cross-linking of the native β-CD, emulsion phase separation was accomplished followed by interfacial cross linking of β-CD. In the first step, oil in water emulsion consisting of an aqueous phase-containing cyclodextrin develops, that roughly produces droplets of 10–35 μm. These when cross-linked, under suitable processing conditions separate as microparticles. The microparticles produced were freed of any residual cross-linking agent by repeated washings and characterized. The degree of cross-linking that prominently depends on the concentration of cross-linking reagent used in the process, was determined to be 4.2, which means that 4.2 cross-linking residues can bind to one β-CD residue. It has been documented that a degree of cross-linking in the range of 3–6 is appropriate for the loading guest molecule(s) in β-CD. Thus, the microparticles generated are suitable for drug loading. As a result of the cross-linking, changes in physicochemical properties are anticipated that were confirmed by physicochemical experimentation.

Thus a cross-linked polymer was obtained that could neither be melted by heating nor dissolved in commonly used solvents and can be used as an inert carrier for drug delivery. However, the cross-linked carrier did not solubilize but exhibited swelling properties. Polymerization of β-CD through the cross-linking process induces capability to absorb water and swell and hence offers a possibility for the cross-linked polymer to be used as a controlled release system. This is quite in contrast to β-CD that was soluble in distilled water up to the saturation point and any further quantity added, did not go into the solution but settled at the bottom and remained as a solid without swelling, and hence does not lend itself to be used as a carrier for extended/sustained release.

As a consequence of cross-linking that caused changes in physical properties, the rheologic properties that could affect processing were also expected. Although β-CD exhibits favorable rheologic characteristics, CL β-CD offered superior flow properties of the powder material largely due to increase
in particle size that resulted in reduction in interparticle friction, and hence a reduction of \( \tau \) in the angle of repose. The improvement was further expressed by favorable derived rheologic parameters compiled in Table 2. The numerical values of Carr’s compressibility index and Hausner’s ratio suggest the amenability of the developed product for tabletting.[11]

The CL β-CD microparticles were then subjected to active drug loading of PS through incubation. The core reason for selection of active drug loading through incubation process was the oxidizing nature of epichlorohydrin, which oxidizes or distorts the drug molecules, and changes its properties. Active loading of PS in CL β-CD microparticles was performed through the incubation process in which the process variables temperature and pH were optimized for the maximum drug loading. At pH 4.0, the drug molecules were less ionized in comparison to borate buffer pH 9 and were more likely to get loaded within CL β-CD. On the other hand, at a relatively high temperature (40°C), the mobility of loaded drug molecule increases within cavities in CL β-CD, due to which efficiency of entrapment decreased, therefore more amount of PS was loaded in CL β-CD microparticles at 20°C. One major problem in the present experiment was the hydrophobic nature of prepared cross-linked network in the drug-loading process that did not favor loading of hydrophilic PS. Therefore, incorporation of nonionic surfactant in the incubation medium was accomplished that can reduce interfacial tension between the PS molecule and the CL β-CD. The preference of nonionic surfactant over cationic or anionic surfactant was based on the avoidance of potential interactions. Thus inclusion of Tween 80 as the loading facilitator in the incubation media resulted in 85.44% ± 0.61% loading of PS. Thus the maximum active drug loading of PS could be accomplished at 20°C, pH 4.0 in the presence of 1% w/v Tween 80.

For visualization of drug loading, SEM micrographs were analyzed and it was observed that faint impressions of solvent evaporation on the CL β-CD were utilized in the cross-linking process.[13] The DSC thermograms were used to analyze the entrapment of PS in the matrix of CL β-CD microparticles and to examine any structural changes in the CL β-CD. Absence of any new peak in the DSC curve of PS-loaded β-CD microparticles when compared to reference thermograms was indicative of stability of drug in the system. Conclusively, the DSC study corroborated the results of FTIR and confirmed the absence of any chemical interaction between the drug and CL β-CD and elucidated physical entrapment as the possible mechanism of drug loading that can affect drug release.

The microparticles of CL β-CD notably decreased the dissolution rate of PS. The cross-linked network of β-CD molecules in the microparticles retarded the release of PS, as the hydrophobic character of cross-linked residue did not facilitate penetration of dissolution media into the microparticles, thus limiting dissolution of drug. It has been documented in the literature that the insoluble or cross-linked polymer tends to decrease the wettability of cross-linked network and reduces the penetration of dissolving media.[16] The release rate controlling effect was maximum in case of C-LB1 with 98.07% CDR in 8 h that is attributable to higher swelling ability than rest of the batches that resulted in the formation of a wider diffusional path length. Although the base microparticle is same in all the batches, probably the processing variables of active drug loading played a significant role on the swelling behavior, and hence the release. Consequently, the in vitro release profile of nonfragmenting C-LB1 fitted zero-order model with \( r^2 \) value of 0.9910. The release data were also analyzed by model-independent release parameters and \( t_{50}\) and \( t_{80}\) were found to be maximum for batch C-LB1, guiding its selection as the best batch. Another important model-independent parameter: DE defined as the area under the dissolution curve up to a certain time \( t \), expressed as the percentage of the area of the rectangle described by 100% dissolution in the same time was also computed. As DE takes into account the entire dissolution profile as a whole, as opposed to \( t_{50}\) values, this approach employs a more realistic and meaningful method of comparison as well as interpretation of in vitro release data for various formulations.[17] The DE in the initial and later dissolution period \( DE_{0-4 h} \) and \( DE_{0-6 h} \), respectively, was evidently least from C-LB1 than rest of the batches. Conclusively, the cross-linked polymeric structure is the controlling determinant for the modulation in release of the highly water-soluble drug.

**CONCLUSIONS**

CL β-CD microparticles were successfully prepared and characterized. The microparticles could be efficiently loaded with a highly water-soluble drug PS with the help of a loading facilitator. The developed controlled release of PS has the potential to enhance its therapeutic properties by offering the advantage of less-frequent dosing with decreased fluctuation in the blood levels during the dosing interval.

**REFERENCES**

1. Pariot N, Edwards-Levy F, Andry MC, Levy MC. Cross-linked β-cyclodextrin microcapsules: Preparation and properties. Int J Pharm 2000;211:19-27.
2. Pariot N, Edwards-Levy F, Andry MC, Levy MC. Cross-linked
1. Wise DL. Handbook of Pharmaceutical Controlled Release Technology. New York: Marcel Dekker; 2005. p. 18-57.

2. Sugiura I, Komiyama M, Toshima N, Hirai H. Immobilized \( \beta \)-cyclodextrins. Preparation with various crosslinking reagents and the guest binding properties. Bull Chem Soc Japan 1989;62:1643-50.

3. Martin A. Physical chemical principles in the pharmaceutical sciences. 4th ed. New Delhi: BI Waverly Private Limited; 1999.

4. Rowe RC, Sheskey PJ, Weller PJ. Pharmaceutical excipients. London: Pharmaceutical Press; 2001.

5. Clarke’s Analysis of Drugs and Poisons. London: Pharmaceutical Press; 2005.

6. Zhao D, Zhao L. Synthesis and properties of water insoluble \( \beta \)-cyclodextrin polymer cross-linked by citric acid and PEG 4000. Carbohydrate Polymers 2009;20:125-30.

7. Horiuchi Y, Abe K, Hirayama F, Uekama K. Release control of theophylline by \( \beta \)-cyclodextrin derivatives: Hybridizing effect of hydrophilic, hydrophobic and ionizable \( \beta \)-cyclodextrin complexes. J Control Release 1991;15:177-83.

8. Tenreiro CR., Lorenzo CA, Perez AR, Concheiro A, Torres Labandeira JJ. New cyclodextrin hydrogels cross-linked with diglycidylethers with a high drug loading and controlled release ability. Pharm Res 2006;23:121-30.

9. Trotta F, Cavalli R. Characterization and applications of new hyper cross-linked cyclodextrins. Composite Interfaces 2009;16:39-48.

10. Ikeda Y, Kimura K, Hirayama M, Arima H, Uekama K. Controlled release of a water-soluble drug, captopril, by a combination of hydrophilic and hydrophobic cyclodextrin derivatives. J Control Release 2000;66:271-80.

11. S. Chand; 2000.

12. Korenaga EP, Sugiura I, Komiyama M, Uekama K. Properties of \( \beta \)-cyclodextrin polymer and its pharmaceutical use. Pharm. Sci. Technol. Today 2002;5:105-10.

13. Clarke’s Analysis of Drugs and Poisons. London: Pharmaceutical Press; 2005.

14. Gowariker VR, Viswanathan NV, Sreedhar J. Polymer science. New Delhi: New Age International Publishers; 1989.

15. Velaz I., Isasi JR, Sanchez M., Uzqueda M., Ponchel G. Structural characteristics of some soluble and insoluble \( \beta \)-cyclodextrins polymers. J Incl Phenom Macrocyclic Chem 2007;57:65-8.

16. Banakar UV. Pharmaceutical dissolution testing. New York: Marcel Dekker Inc; 1992.

17. Costa P, Lobo JM. Modeling and comparison of dissolution profiles. Eur J Pharm Sci 2001;13:123-33.

Source of Support: Nil, Conflict of Interest: None declared.
Received: 15-11-10, Accepted: 02-12-10