



Beta-cyclodextrin Grafted with Poly (ϵ -caprolactone) for Ibuprofen Delivery System



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THE aim of this study is to synthesize a polymeric composite based on grafted beta-cyclodextrin (β -CD) with poly (ϵ -caprolactone) using ring-opening polymerization (ROP) technique, in presence of ethylene glycol dimethacrylate (EGDMA) and benzoyl peroxide (BP) as crosslinker and initiator, respectively, for drug delivery system (β -CD-PCL). The obtained β -CD-PCL composites were characterized by nuclear magnetic resonance (1H NMR), Fourier transform infrared spectroscopy (FT-IR) and transmission electron microscope (TEM). Ibuprofen (IBU) was used as anti-inflammatory drug model. IBU was loaded onto the resulting materials during the preparation process at different drug concentrations (400, 516, 600, 700 and 1000) mg/L. On the other hand, the kinetics study of the copolymerization was carried out in terms of grafting yields (GY%), grafting efficiency (GE%), and monomer conversion (%). Moreover, *in vitro* IBU release study was investigated in phosphate buffer of pH 7.4 at 37°C. The results indicated that the prepared composites based on grafted β -CD with PCL could be used as a potential hydrophobic drug delivery carrier with sustained release property. Besides, due to the sustained release of IBU from the cavity of the β -CD, it was possible to maintain a constant desired IBU concentration over a period of 24 h, as confirmed by the release steady.

Keywords: β -cyclodextrin, ϵ -caprolactone, Ibuprofen, Ring-opening polymerization, *in vitro* drug release.

Introduction

Hydrogels are hydrophilic polymer networks which are capable of absorbing considerable amounts of water while maintaining the three-dimension structure. Interest in the study of amphiphilic biodegradable copolymers and aliphatic polyesters, such as poly (ϵ -caprolactone) (PCL), has increased due to their controlled biodegradation rates and potential applications in drug delivery [1,2]. Poly(ϵ -caprolactone) (PCL) has excellent biodegradability, biocompatibility and drug permeability so that it can be widely used as a controlled-release drug carrier. However, the application of PCL in the biomedical field is limited due to its strong crystalline potential,

poor hydrophilicity and slow biodegradation rate [3-10]. In addition, cyclodextrins CDs are toroidal shape structures exhibiting high potential to entrap entirely or at least partially a wide variety of branched as well as unbranched drug molecules. The hydrophilic external surface and hydrophobic inner surface makes CD's capable of forming host-guest systems [11]. β -cyclodextrin (β -CD), a cyclic oligosaccharide composed of seven glucose molecules with γ -1,4-glucosidase linkages, which has a micro-environment of a chiral, hydrophilic outside and a hydrophobic interior cavity. Also, it has low molecular weight. In order to increase molecular weight of the product, hydrophilic monomer could be linked with β -CD by chemical crosslinking reactions

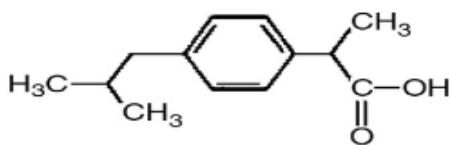
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[12]. Copolymers are widely explored for their ability to self-assemble into micellar aggregates with different morphologies in selective solvents rigid-coil copolymers represent an attractive class of building blocks for the preparation of self-assembled nanostructures [13-15]. Ibuprofen (2(4-isobutylphenyl) propanoic acid) is a non-steroidal anti-inflammatory drug (NSAID) having both analgesic and anti-pyretic activity. It can exist in different crystalline polymorphs and is also poorly water soluble which used regularly as a model drug [16-18]. The drug can be loaded into a hydrogel and then its release may proceed through several mechanisms: diffusion controlled, swelling controlled, chemically controlled and environmentally-responsive release. Drug release is achieved through the macromolecular mesh or the pores and the initial release rate in this case is proportional to the square root of time, rather than being constant and time independent [19-21]. (IBU) as an important NSAID is commonly used to treat rheumatoid arthritis, osteoarthritis and moderate pain. Its use is often limited by frequent side effects affecting the gastrointestinal (GI) tract and ulcerogenic effect. These problems could be reduced from gel graft copolymer composites using (ϵ -caprolactone) (PCL), monomer and β -cyclodextrin to control the IBU drug release. In other words, this work deals with the preparation, characterization and *in vitro* release study of IBU-loaded gel graft copolymers.



Ibuprofen (IBU): α -methyl-4-(2-methylpropyl)-benzene acetic acid

Materials and Methods

Materials

β -Cyclodextrin (Beijing Solarbio Science & Technology Co., PR China) was recrystallized twice from water and dried at 60°C under vacuum before use. ϵ -Caprolactone (CL) was obtained from Acros Organics, 99%. Ethylene glycol dimethacrylate (EGDMA, 98%) (Merck, Germany), and benzoyl peroxide (BP) were used as received. The other chemicals were used without further purification.

Methods

Preparation of β -CD-PCL hydrogels loaded with IBU using ring opening polymerization (ROP) technique

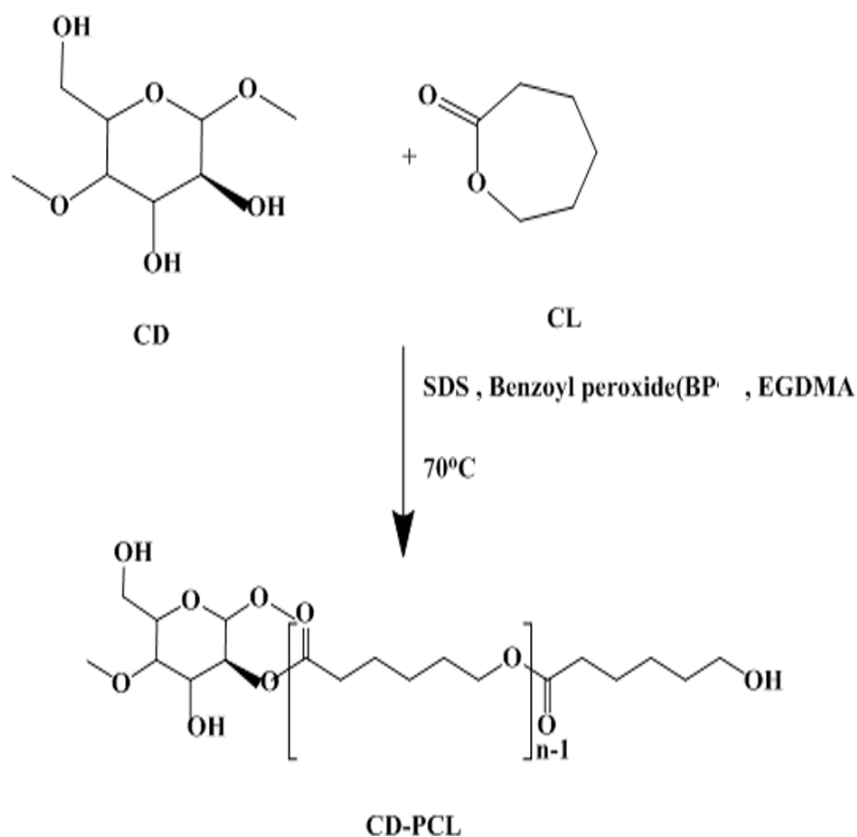
As shown in Scheme 1, the β -CD-PCL hydrogel particles were synthesized *via* ring-opening polymerization, using tin(II) 2-ethylhexanoate, $\text{Sn}(\text{Oct})_2$, as an initiator and catalyst, simultaneously. Briefly, calculated amounts of ϵ -CL (weight ratios of CL to β -CD : 1/1, 1/3, 1/6, 1/10, and 1/20) were dissolved in 10 mL ethanol containing 0.5 wt.% $\text{Sn}(\text{Oct})_2$, 10 mg sodium dihydrogen phosphate (NaH_2PO_4) and 250 mg β -CD under a nitrogen atmosphere. Sodium dodecyl sulphate (SDS) (1 mg) was dissolved in 44 ml H_2O containing different concentrations of benzoyl peroxide (BP) (50, 100, 150, 200, 300 mg) and 0.75 mL of ethylene glycol dimethacrylate (EGDMA) followed by addition of 4 mL solutions at different concentrations of IBU (400, 516, 600, 700, and 1000 mM). The mixture was bubbled with nitrogen gas for 45 min, heated to 70°C, under stirring for 20 h. The resulting mixture was cooled to room temperature and transferred to a beaker with 5 wt% CaCl_2 solution in order to break the emulsion. Particles were isolated by centrifuging the product at 6000 rpm speed for 15 min and washed with distilled water and then the particles were collected. The resulting particles were immersed again in distilled water for 2 days in order to remove any unreacted monomers and crosslinker then dried under vacuum at 40 °C for 24 h.

In vitro drug release

20 mg of dried β -CD-PCL samples loaded with IBU were suspended into 10 mL of phosphate-buffer (pH 7.4), at 37°C. Dissolution tests were performed at different time intervals. Aliquots of 1 mL were withdrawn and replaced by fresh buffer, then, added to 5 mL of the dissolution medium, and the IBU content was determined by UV-visible spectrophotometer at 222 nm. The absorbance was recorded and the amount of ibuprofen released was determined using calibration curve based on the standard solution [22].

Characterization

The FT-IR spectra of the samples were taken with a Vertex 70 Model (Germany) FT-IR spectrometer. $^1\text{H-NMR}$ spectra of the β -CD, and



Scheme 1. Ring-opening copolymerization technique for preparation of polymeric hydrogel composite based on ϵ -CL and β -CD in presence of EGDMA crosslinker and BP initiator.

CD-PCL copolymers were recorded on a Bruker DPX 300 MHz. Deuterated dimethylsulphoxide (DMSO- d_6) was used as the solvent. The UV-spectra of the samples were taken with a T60 Model (England) UV- spectrophotometer at voltage of AC 95-260 V. The TEM- images of the samples were taken with JEOL transmission electron microscope JEM-1230.

Kinetics study of the copolymerization process

The grafted sample was then subjected to soxhlet extraction for 4 h using chloroform to remove any homopolymer, and then the residue was reweighed after drying to a constant weight. The grafting yield (GY%), grafting efficiency (GE%) and amount of homopolymer were calculated according to the following equations [23, 24]:

$$\text{Grafting yield (GY\%)} = \frac{W_1 - W_0}{W_0} \times 100 \quad (1)$$

$$\text{Homopolymer (H\%)} = \frac{W_2 - W_1}{W_3} \times 100 \quad (2)$$

$$\text{Grafting efficiency (GE\%)} = \frac{W_1}{W_2} \times 100 \quad (3)$$

Where W_0 , W_1 are the weights of the initial matrix and the grafted one, respectively. Whereas W_2 is the weight of crude product before extraction and W_3 is the weight of monomer.

Results and Discussion

Characterization of the prepared materials

The FTIR spectrum of β -CD (Fig. 1a) exhibited intense band at 3411cm^{-1} due to O-H stretching vibration, while the stretching vibration of the -CH and - CH_2 - groups appeared in the $2800\text{-}3000\text{cm}^{-1}$ region, the peak at 1651cm^{-1} could be ascribed to the bending vibration of CH_2 , while the peaks around $937\text{-}532\text{cm}^{-1}$ indicated the presence of α -(1,4) glucopyranose of β -CD. On the other hand, the FTIR spectrum of PCL (Fig. 1b) exhibited intense absorption band for the stretching of the ester carbonyl group at 1732cm^{-1} . Besides, the stretching vibration of the -CH and - CH_2 - groups appeared in the region $2880\text{-}2947\text{cm}^{-1}$ [25-27].

The FT-IR spectrum of the prepared β -CD-PCL composite, as shown in Fig. 1c, showed

strong peaks at 2851-2925 corresponding to the stretching vibration of C-H groups which had high intensities due to the formation of

CH₂ in the polymerization process during the polymerization of CL monomer, while the -OH stretching vibration band of β-CD appeared in

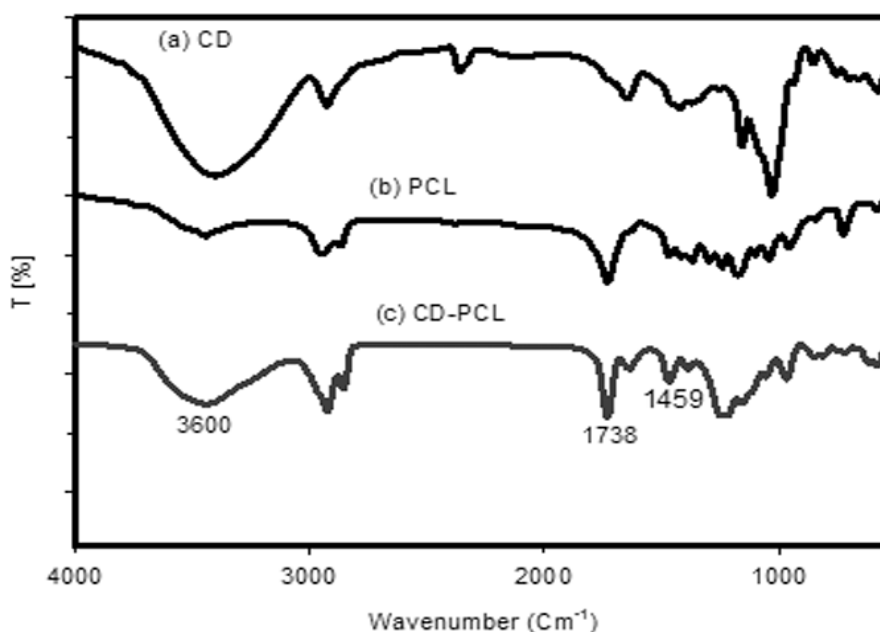


Fig. 1. FT-IR spectra of (a) β-CD, (b) PCL, and (c) CD-PCL.

the range of 3600 cm⁻¹. The C=O stretching of the ester group due to the interaction between C=O of ε-CL monomer and -OH of β-CD was confirmed by characteristic peak at 1738 cm⁻¹, which might be overlapped with the C=O stretching vibration band of the ester group of EGDMA. Moreover, the strong peak due to the bending vibration of -CH₂-O-CH₂- group of EGDMA was appeared at 1459 cm⁻¹ [28].

The synthesized β-CD-PCL polymeric composite was also confirmed by comparing the

¹H-NMR spectrum of β-CD and the prepared β-CD-PCL composite. In the ¹H-NMR spectrum of β-CD (Fig. 2a), It was observed that a series of peaks at 3.36–4.76 ppm were assigned to H-a, H-b, H-c, H-c and H-d of β-CD. Besides, the singlet peak at 5.64 ppm represented anomeric protons (H-e) of α-D-glucopyranosyl residues [25]. ¹H-NMR spectrum of β-CD-PCL composite (Fig. 2) showed peaks at δ= 3.45 and 4.43 ppm (β-cyclodextrin). While, the typical peaks ascribed to the characteristic peaks of PCL were observed at δ= 1.29, 1.35, 1.43, 2.16, 4.1, and 4.43 ppm

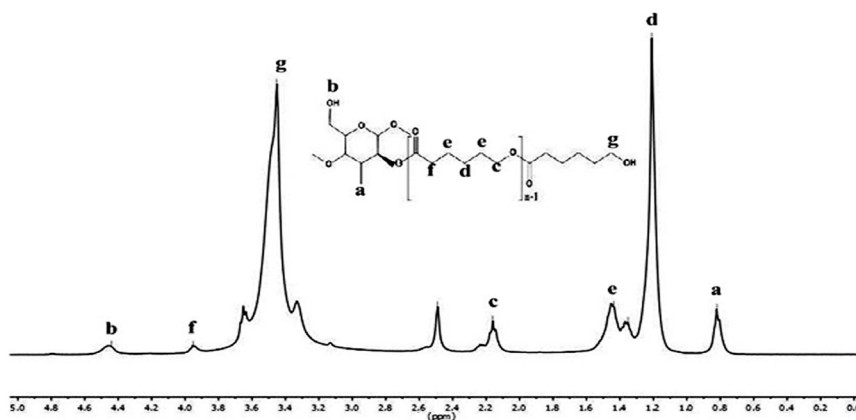


Fig. 2. ¹H-NMR spectrum of the prepared B-CD-PCL composite structure.

corresponding to H-d, H-e, H-c, H-f, and H-b, respectively, indicating the successful coupling between oxo-group of ϵ -CL and hydroxyl group of β -CD [29]. On the other hand, a signal appears at $\delta \sim 4.1$ ppm (H-f) which is consistent with the resonance shift upon the formation of ester linkages. These results proved that the formation

of the desired PCL with the ROP started from the hydroxyl end groups of β -CD and also indicated that all of these groups were active an initiator.

Figure 3a shows TEM images of the IBU-loaded composite. It is clear that IBU drug particles are linked (physically or chemically) with β -CD-PL composite matrix (dark color). In

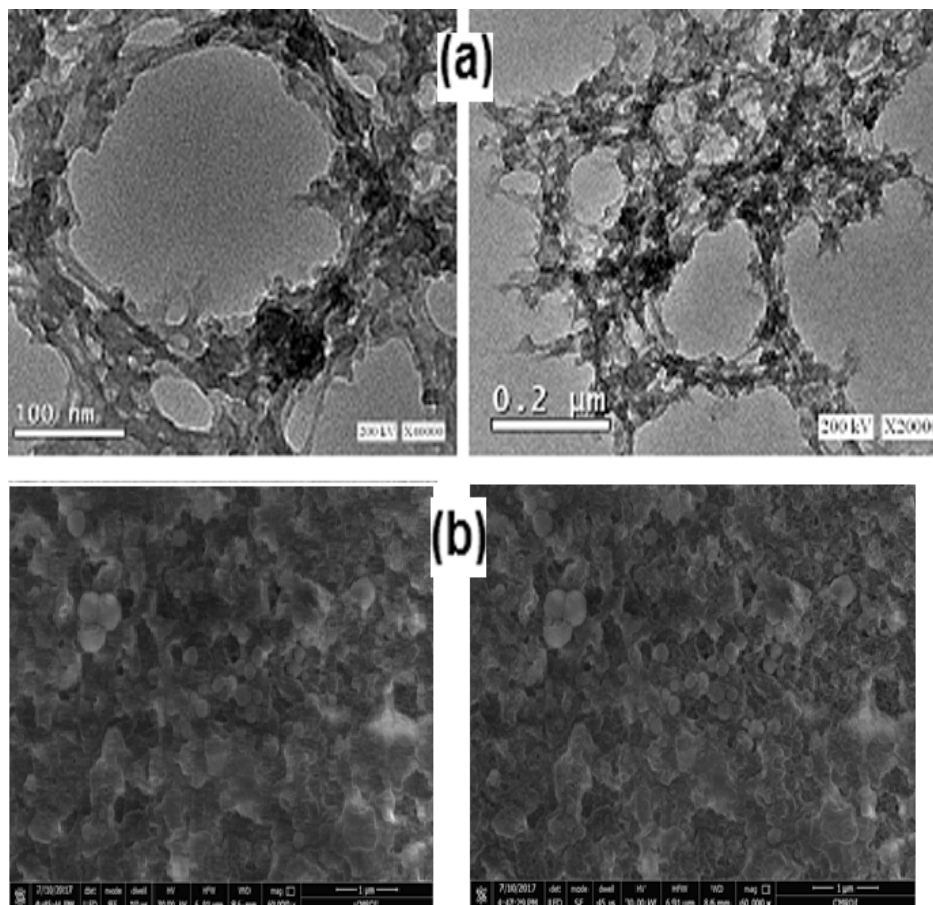


Fig. 3. (a) TEM images and (b) SEM-micrographs of IBU-loaded composite.

addition, β -CD structure has free cavities with micron size, which may lead to retardation in the drug release.

Similarly, Fig. 3b shows SEM-micrographs of IBU-loaded composite. The phase morphology of the prepared materials shows a continuous homogeneous matrix without phasing. Also, the images show the presence of particle aggregates, which proves the presence of IBU drug particles linked with β -CD-PL composite matrix.

Effect of the polymerization parameters on the grafting process

Effect of initiator concentration

The effect of the initiator concentration (BP)

on the graft copolymerization of β -cyclodextrin with ϵ -caprolactone under constant temperature, time, and monomer concentration, is shown in Fig. 4a. Both grafting yield (GY%) and grafting efficiency (GE%) were gradually increased in parallel with initiator concentration, while the homopolymer content (H%) was decreased. The increase in GY% and GE% might be ascribed to the increase of macroradicals generated by the attack of more BP on the available -OH groups of β -cyclodextrin. Moreover, the more active sites of β -cyclodextrin reacted with ϵ -caprolactone monomer. Further the successive increase of the initiator concentration resulted in lowering of the grafting yield and grafting efficiency.

Effect of monomer concentration

As shown in Fig. 4b, the grafting efficiency and grafting yield were found to increase with

an increasing in ϵ -caprolactone concentration until reach maximum. The maximum grafting yield has been found at 226 mM, then after,

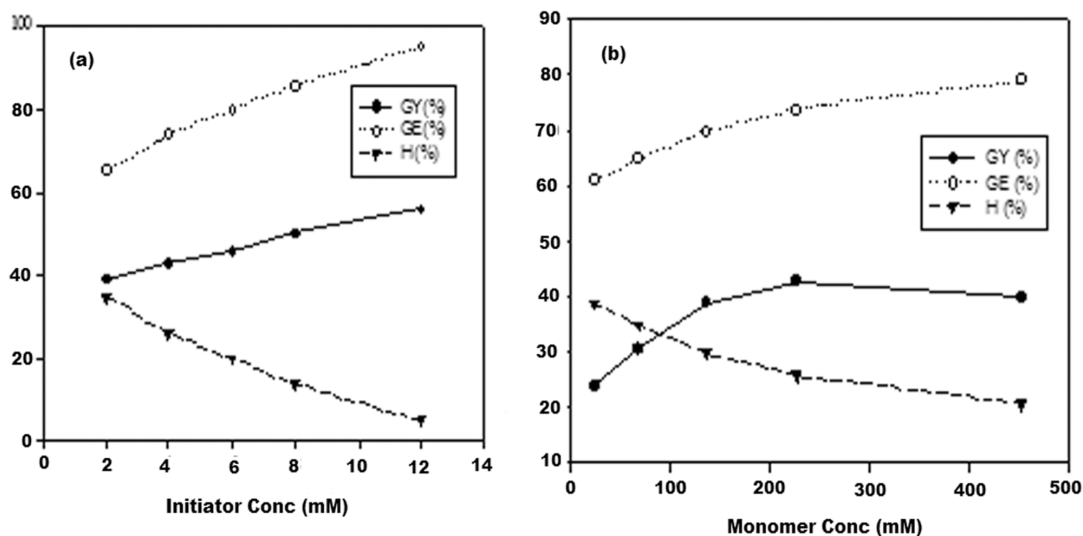


Fig. 4. Effect of the initiator concentrations on copolymerization parameters (a), Effect of monomer concentrations on copolymerization parameters (b).

it was slightly decreased. This decreasing behavior may be attributed to the increase in the ϵ -caprolactone concentration which causes a reduction in the active sites of β -cyclodextrin matrices. Additionally, at high ϵ -caprolactone concentrations, the primary radicals attacked the monomer instead of reacting with the backbone of β -cyclodextrin. Moreover, excess ϵ -caprolactone shielded the grafting process which might inhibit the rate of copolymerization reaction [30-31].

IBU drug release study

The IBU % release from the prepared β -CD-PL composites at various IBU loadings (400, 516,

600, 700 and 1000) mg/L in buffer solution at pH 7.4 and 37°C was recorded as shown in Fig. 5. It was observed that the IBU released was increased with increasing the initial IBU concentrations. However, the amount of IBU released at concentration range 400-600 mg/mL was much lower than that the other concentrations (700 and 1000 mg/mL which had about 32, 41 and 46 %, respectively, over first 5 hrs. On the other hand, the amount of IBU released at concentration range 700-1000 mg/mL was 57 and 61 %, respectively. This release difference can be attributed to the fact that the release rate dependent on the drug concentration. While, the amount of IBU released was reached steady state after 5 hrs. In other

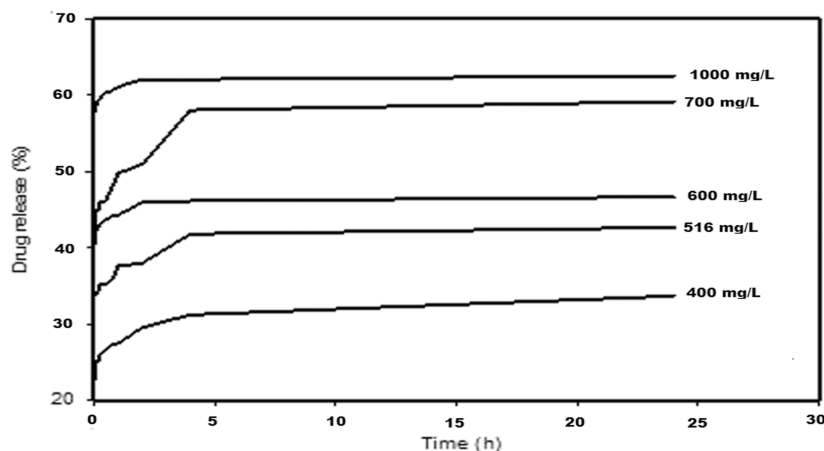


Fig. 5. *In vitro* release profiles of IBU from the CD-PCL with different concentrations at 37°C and pH 7.4.

words, the obvious burst is not observed in the course of IBU release. It can be concluded that the accumulative release of IBU from the prepared polymer carrier was in a controlled manner. It is well known that the hydrophilic material has small contact angle with water which enhances the reaction between the material and the aqueous medium leading to the release of IBU [32]. Burst release could be minimized in case of using β CD/PCL as a delivery system in the first hr. which was probably due to the slow dissolution of the drug adhered onto the surface of the particles.

Conclusion

Hydrogel composites based on β -CD grafted with PCL (β -CD/PCL) were successfully prepared *via* ring opening polymerization reaction as confirmed by structural and morphological investigation techniques (FTIR, ¹HNMR TEM and SEM). The prepared β -CD/PCL composites were tested as drug carriers *via* their successful loading with ibuprofen (IBU) as a model drug (at various concentrations) in order to be used in drug delivery applications. The *in vitro* release study of IBU from the prepared formulations showed gradual and more sustained and controllable release of the IBU drug over the study period (24 hrs). In other words, the presence of the β -CD attached with the PCL polymer has a beneficial effect for the delivery of IBU drug. Based on these results, the β -CD/PCL hydrogel composites could be used for the development of suitable oral drugs with controlled release property e.g. IBU and may be used as a drug carrier for other hydrophilic or hydrophobic drugs in the future.

Acknowledgment

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بيتاسيكلوديكسترين مطعم ببوليمر كابرولاكتون كنظام توصيل لدواء إيبوبروفين

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تهدف هذه الدراسة لتخليق متراكبات بوليمرية مبينه علي تطعيم بيتاسيكلوديكسترين بمونمر كابرولاكتون بواسطة تقنية بلمرة الحلقة المفتوحة في وجود إيثيلين جليكول داي ميثاكريلات وبنزويل بير اوكسيد كعامل تصلد شبكي وبادئ للتفاعل علي التوالي. وإستخدامها كأنظمة توصيل لدواء إيبوبروفين.

تم توصيف المتراكبات المحضره بإستخدام الرنين النووي المغناطيسي للهيدروجين، الأشعه تحت الحمراء، والميكروسكوب الإلكتروني النافذ. تم إستخدام إيبوبروفين كنموذج دواء مضاد للحساسيه وتحميله بتركيزات مختلفه (٤٠٠، ٥١٦، ٦٠٠، ٧٠٠ و ١٠٠٠) ملليجرام/ليتر مع دراسة ديناميكية إفراز الدواء في وسط مائي عند درجة اس هيدروجيني حوالي ٧,٤ ودرجة حراره ٣٧ درجة مئوية.

من ناحيه اخري، تمت دراسة ديناميكية البلمره التساهميه لمونمر كابرولاكتون عن طريق دراسة تأثير تركيزات كل من بادئ التفاعل والمونمر علي النسبه المئوية لكل من ناتج وكفاءة البلمره التساهميه.

أثبتت النتائج إمكانية تحضير متراكبات بلمرية بواسطة تقنية تطعيم بيتاسيكلوديكسترين وإستخدامها كحوامل لتوصيل الدواء بتركيزات مختلفه في خلال فتره زمنيه ٢٤ ساعه.