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Synthesis and Characterization of Ibuprofen Delivery System Based on β-cyclodextrin/Itaconic Acid Copolymer

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Abstract

This study aims at preparation and characterization of drug delivery system based on grafted beta-cyclodextrin (β-CD) with itaconic acid (IA) using free-radical copolymerization technique, in the presence of N, N'-methylene bisacrylamide (BIS) and ammonium persulphate (APS) as a crosslinker and an initiator, respectively. The obtained copolymer (CD-PIA) was characterized using Fourier transform infrared spectroscopy (FT-IR), thermogravimetric analysis (TGA), X-ray diffraction patterns (XRD), transmission and scanning electron microscopes (TEM and SEM). Ibuprofen (IBU), as an anti-inflammatory drug model, was loaded during the preparation. The kinetic of the copolymerization was investigated in terms of grafting yield (GY %), grafting efficiency (GE %) and monomer conversion (%). Moreover, *in vitro* IBU release and kinetic of released using the different mathematical models (0-order, first-order and Higushi) were carried out in simulated gastric and intestinal fluids (SGF and SIF at pH 1.2 and 7.4, respectively) at 37 °. The results proved the successful preparation of the target copolymer with irregular spherical-like shape and particle size around 14 - 27.7 nm. After IBU loading, the copolymer exhibited thermal stability with crystalline nature. Also, the study showed that the synthesized copolymer, especially which high IA content is controlled the release of IBU after 4 h. Besides, it could be used as a potential IBU delivery system with sustained-release followed the first-order kinetic over 24 h.

Keywords: β-cyclodextrin, Itaconic acid, Ibuprofen, Free radical copolymerization, *In vitro* drug release

Introduction

Many significant efforts have been devoted to using hydrogels as drug delivery systems [1-6]. They are defined as an effective hydrophilic macromolecular networks. Their affinity to absorb water could be attributed to the presence of the hydrophilic groups [7-9]. Also, the nanogels were employed as drug carriers for nonsteroidal anti-inflammatory drugs (NSAIDs) to serve as an alternative to the normally coated tablets that are offering unfavorable release in the stomach due to unforeseen pH alterations [10-13]. Itaconic acid (IA) is an unsaturated dicarboxylic acid and structurally similar to the petrochemical-derived acrylic and methacrylic acids [14]. Globally, IA and its derivatives have a wide range of applications in the textile industry, lubricant additives, surface-active agents, dye intermediates and resins, as well as in the preparation of some drug carriers in the pharmaceutical industry. The introduction of even small amounts of IA in a polymeric chain promotes the complexation, pH-sensitivity [15] and swelling nature in the prepared hydrogels [16]. It is expected that IA-based hydrogels are exhibited less toxicity due to their natural origin [17-19]. On the other hand, cyclodextrins (CDs) are the most plentiful natural oligosaccharides that have valuable characteristics, including the enhancement of biocompatibility, biodegradability and the poor's bioavailability soluble drugs. The β-CD is a cage-shaped molecule with a hydrophilic exterior and hydrophobic internal cavity that enables it to complex with a non-polar part of an entire guest molecule [20-33]. This complexation overcomes intrinsic limitations of some drug molecules such as low solubility, instability, reducing toxicity and controlling the release of the drug [34,35]. However, its utilization is limited in the formulations due to its low aqueous solubility. To reimburse this issue, the hydrophilic derivatives of the β-CD are interesting [36,37]. Some previous works reported that the β-CD cavity of the macrocycle showed a higher affinity for Ibuprofen (IBU) in the neutral state due to the interactions between the carboxylic proton of the drug and the oxygen at the ring of the β-CD cavity [38-41]. Furthermore, the polymeric grafted β-CD residues represent a unique

class of the host materials with tunable inclusion properties and have recently received much attention in connection with the development of the drug delivery systems. A series of copolymers were synthesized in our study based on the grafted β-CD with IA using N,N'-methylene bisacrylamide (BIS) and ammonium persulfate (APS), *via* free radical copolymerization technique. The nonsteroidal anti-inflammatory drug, Ibuprofen (IBU), was used as a drug model. The *in vitro* cumulative IBU release and kinetic of released were carried out in SGF and SIF with pH 1.2 and 7.4, respectively, at 37° over 24 h.

Materials and methods

Materials

β-cyclodextrin (β-CD), which was obtained by Sigma-Aldrich, was recrystallized twice from water and dried at 60 ℃ under vacuum before use. Itaconic acid (IA), ammonium persulfate (APS) and N,N'-methylene-bis-acrylamide (BIS) were obtained by Acros organics. All other reagents and chemicals were used as received.

Methods

Synthesis and IBU loading of CD-PIA copolymers

CD-PIA copolymers were prepared by free-radical copolymerization technique in the aqueous solution. Sodium dodecyl sulfate (SDS, 100 mg) and various amounts of ammonium persulfate (100, 150, 200 and 300 mg, APS) was dissolved in 100 mL of an aqueous medium, then β-CD (0.5 gm) and methylene bisacrylamide (0.075 g, BIS) were added together with different ratios of IA (2/1, 1/1 and 1/2) and fixed amount of IBU (100 mg, 4.85 mM). The mixtures were bubbled with nitrogen gas for 45 min, then heated to 70 ° under constant stirring (800 rpm) overnight. The mixtures were cooled down to room temperature and the particles were isolated by centrifuging at 6,000 rpm for 15 min. The resulting materials were washed with double distilled water, dried and kept for further investigation (**Table 1**).

Table 1 Chemical composition of CD-PIA copolymers.

Sample	Chemical composition (Wt %)		
	β-CD	IA	APS
CD-PIA1	45	23	18
CD-PIA2	37	37	15
CD-PIA3	27	54	11

Characterization

The FT-IR spectra of the samples were recorded by a Vertex 70 Model (Germany) FT-IR spectroscopy using KBr pellets under the condition: scan resolution: 4 cm^{-1}, scan rate: 2 mm/s, number of scans: 32, range: 400 - 4,000 cm^{-1} and mode: Transmission. ^{1}H-NMR spectra were recorded on a Bruker DPX 300 MHZ. The UV spectra of the samples were carried out by T60 Model UV-spectrophotometer (UK). Thermogravimetric analysis was investigated using Perkin Elmer Pyris TGA/ DTG-60H. X-ray diffraction patterns (XRD) were carried out by Rigaku Miniflex with Cu (Kα 30 kV, 15 mA, λ = 1.54178 Å) radiation. The TEM images of the samples were recorded using JEOL transmission electron microscope JEM-1230. While the SEM-micrographs were investigated using JEOL analytical scanning electron microscope JSM-6510LA.

Kinetics of the copolymerization process

The grafted polymer had been transferred to soxhlet for 8 h using isopropyl alcohol to remove any homopolymer and the precipitate was reweighed after drying. The grafting yield (GY %), grafting efficiency (GE %) and homopolymer (HP %) were calculated from the following equations [42]:

$$(GY\ \%) = [\text{Weight of the grafted polymer}/\text{Weight of the substrate}]\times 100 \quad (1)$$

$$(GE\ \%) = \{\text{Weight of the grafted polymer}/[\text{Weight of the grafted polymer} + \text{Weight of the homopolymer}]\}\times 100 \quad (2)$$

$$(HP\ \%) = W_3 - W_2/W_3\times 100 \quad (3)$$

whereas, W_2 and W_3 is the weight of the grafted polymer before and after extraction.

In vitro IBU release and kinetic of released

20 mg of dried CD-PIA copolymer samples were suspended into 10 mL of phosphate buffer pH 7.4 containing 5 % of SDS (sink conditions) at 37 ℃. Dissolution tests were performed at different interval times..

Aliquots of 1 mL were withdrawn and replaced by fresh buffer and the IBU content was determined by UV absorption at λ 222 nm. The absorbance was recorded and the amount of IB released was calculated from the calibration curve based on the standard solution.

Results and discussion

Physicochemical characterization of the prepared copolymers

The FTIR spectrum of β-CD **(a)** is characterized by O-H stretching broad vibration band around 3,411cm^{-1}, while the characteristic bands appeared at 2,925 and 2,882 cm^{-1} correspond to the aliphatic stretching of -CH_2 and -CH- groups, respectively. The characteristic band also appeared around 1,651 cm^{-1} indicating the bending vibration of CH_2 group. Several peaks were observed at the finger print region around 937 - 532 cm^{-1} due to the aliphatic -CH deformation of the glucopyranose ring of β-CD [43,44]. On the other hand, the FTIR spectrum of IA **(c)** illustrated characteristic sharp band at 1,705 cm^{-1} assigned to C=O stretching of the carboxylic groups as well as characteristic bands at 2,880 - 2,947 cm^{-1} correspond to the aliphatic stretching -CH and -CH_2 groups [45]. Besides, the characteristic peak appeared at 3,484 cm^{-1} corresponding to the carboxylic acid's O-H stretching vibration. The FTIR spectrum of CD-PIA copolymer is presented in **(b)**. It can be noticed that the characteristic peak around 3,694 - 3,411 cm^{-1} assigned to O-H stretching vibration of β-CD moiety, while, A new 2 strong peaks appeared at 1,726 and 1,685, indicating the overlap between C=O stretching vibration of the carboxylic and the amidic carbonyl groups of BIS. The characteristic peak corresponding to -NH deformation bond in the amide group of BIS has appeared at 1,533 cm^{-1}.

Table 2 FTIR-ATR interpretation of the prepared scaffolds.

Peak (cm^{-1})	Interpretation
3,694 - 3,411	O-H (str)
2,925	CH_2 (str, Alkyl)
2,882	CH (str, Alkyl)
1,726 - 1,705	C=O (str)
1,636	C=C (str)
1,651	CH_2 (bending, Alkyl)
1,685	-C=O (str, amide)
1,420	C-H (in-plane pending)
937 - 532	-CH deformation of glucopyranose

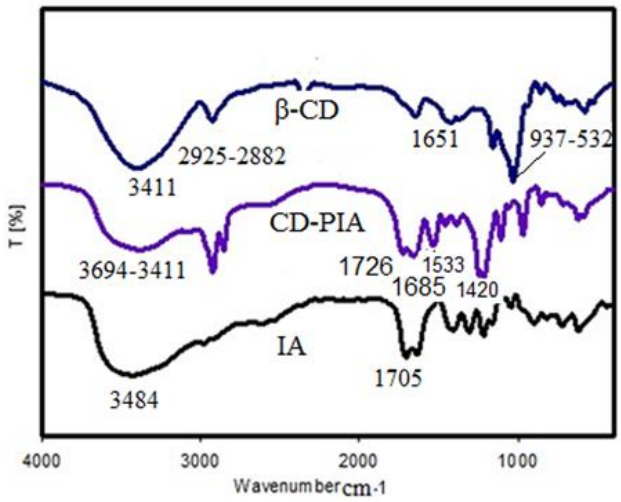
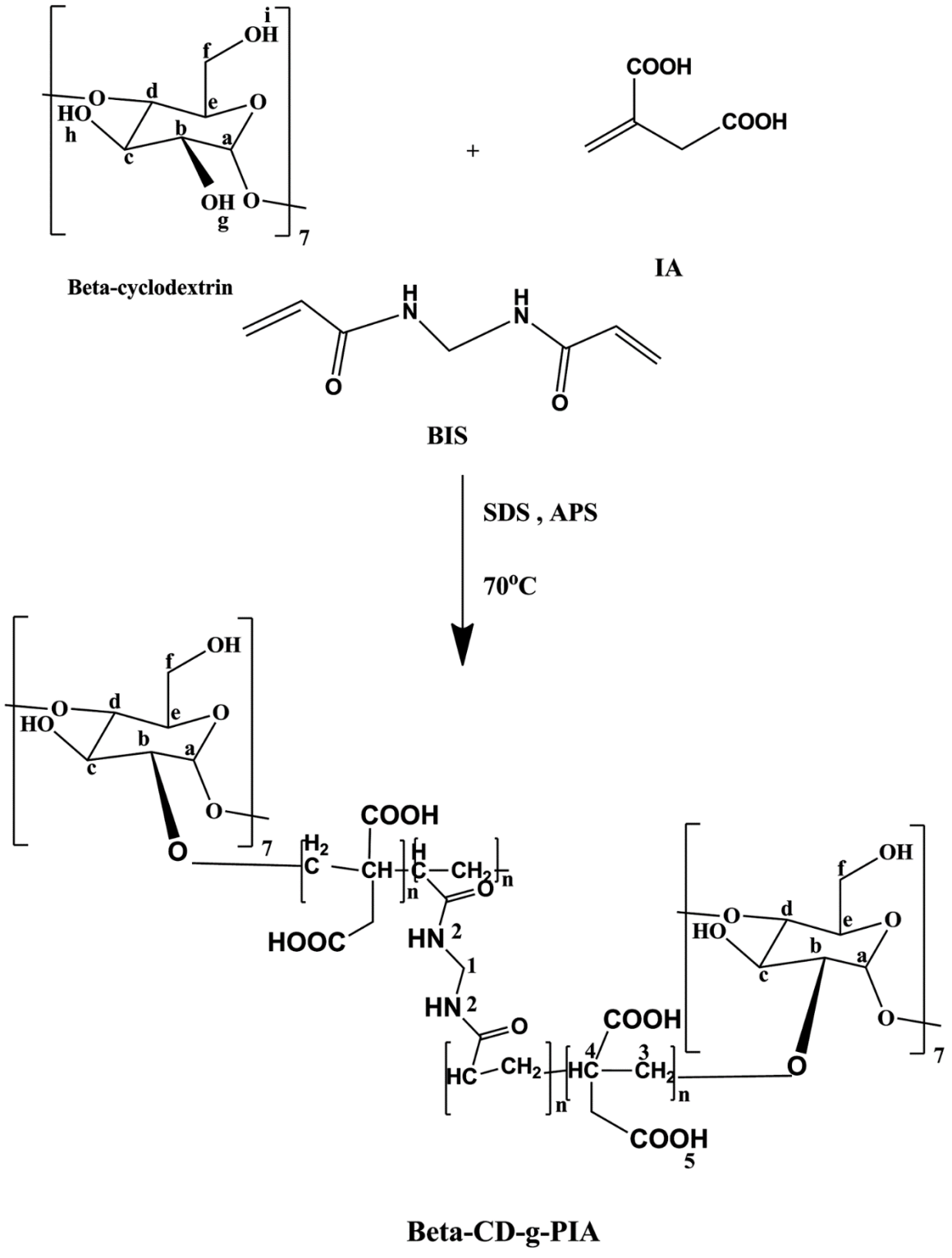


Figure 1 FTIR-ATR spectra of β-CD, CD-PIA copolymer and IA.

These results confirmed that IA was successfully grafted to β–CD using free-radical copolymerization technique (**Scheme 1**).



Scheme 1 Schematic representation of the synthesized CD-PIA copolymer.

Thermogravimetric analysis (TGA) of β-CD (**Figure 2(i)**) is characterized by 2-step degradation. The first degradation step at the temperature range from 25 to 150 ° with weight loss of β-CD around 13.012 % could be ascribed to the release of the water molecules. While the second one appeared at 150 - 450 ° with a weight loss of about 76.064 %. This may be due to the decomposition of the main structure. TGA of the prepared CD-PIA copolymer is shown in **Figure 2(ii)**. It can be observed that the thermal degradation was in 3 stages. The first degradation step appears at the range from 25 to 150 °, which assigned to the release of the unbound water molecules with weight loss of about 15.720 %. This may be due to the grafting of β-CD with IA increased the hydrophilic carboxyl groups content inside the CD-PIA copolymer, which can enhance the copolymer's hydrophilicity and consequently the water-binding ability. The second step at 150 - 450 ° with weight loss of about 39.161 %. This may be due to CD-PIA copolymer's thermal stability enhanced relative to β-CD because of the formation of the complex side chain (PIA) on the copolymer network resulting from the grafting copolymerization process. The last degradation step at 450 - 562 ° with weight loss of about 40 % corresponds to the entire polymeric network's slow carbonization and incineration [46].

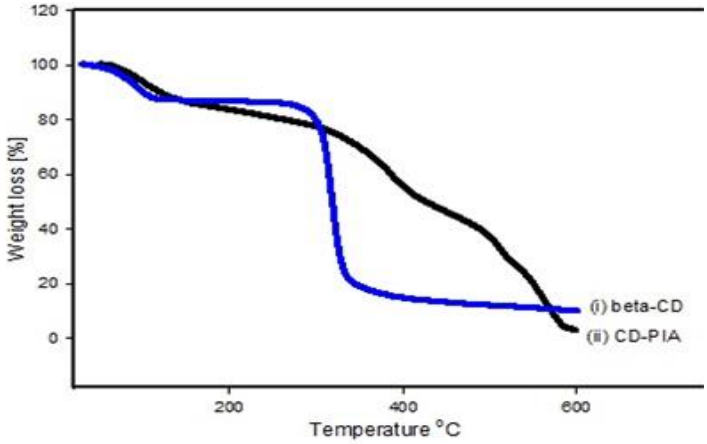


Figure 2 TGA diagrams of (i) β-CD and (ii) CD-PIA copolymer.

Figure 3 shows the XRD diffractogram of the synthesized copolymer after loading with IBU drug (CD-PIA/IBU). It was found that the peaks associated with pure β-CD and IBU appeared at 2θ values (12, 17, 20, 24, 27, 28, 30 and 32 º) and (18, 22, 24 and 25 º), respectively, which are previously reported [47, 48]. Besides, the new signals appeared at 2θ values 68 and 72 º, corresponding to the grafted β-CD with PIA. The increase in the peaks height was observed with the greater amount in the grafted copolymer. It can be concluded that the grafting of β-CD with PIA in the presence of IBU could be obtained with a crystalline structure.

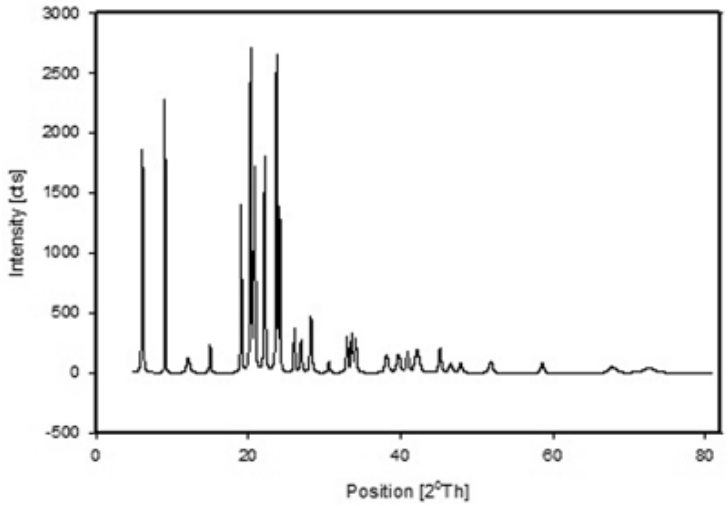


Figure 3 XRD diffraction patterns of CD-PIA copolymer after IBU loading.

TEM images of the synthesized CD-PIA copolymer (**Figure 4**) showed the spherical-like structure with particle size around 14 - 27.7 nm. At high β-CD concentration, the formation of a large number of nuclei leads to smaller PIA crystallite size and vesicles entrapping of IBU, indicating spherical and fairly irregular shape aggregates, which appear as a darker region. It was previously reported that polar functional groups such as -COOH and -OH had been found to be useful for β-CD/IBU complex [49]. Generally, all the findings indicated that CD-PIA nanoparticles had excellent physical stability.

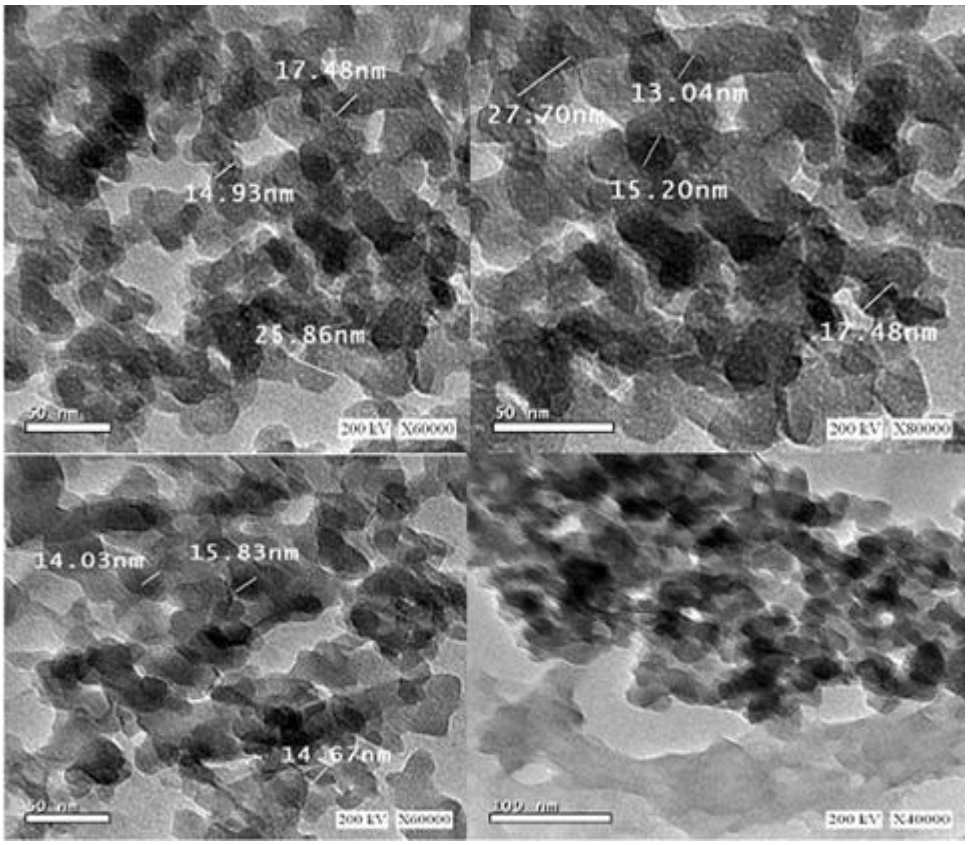


Figure 4 TEM images of CD-PIA copolymer after IBU loading (50 nm scale bar and 200 Kv).

SEM micrograph of the pure IBU is shown in **Figure 5(a)**, which appeared as needle-shaped crystals with a rough surface and high cohesion tendency. While in the case, β-CD-PIA/IBU (**Figure 5(b)**), the bulky particles of the β-CD-PIA copolymer with small needles of the IBU adhered to its surface were observed. On the other hand, the β-CD particles typically exhibited a porous morphology (rock-like particles) (**Figure 5(d)**). It can also be noticed that after grafting with IA, the particle size was increased and exhibited small uneven cavities on its surface. This may be due to the grafting copolymerization process of β-CD with PIA. In general, the presence of PIA in the copolymer induced high crystalline nature. Also, the change in the particle surface morphology confirmed the presence of a new solid phase due to the reduction in the amorphous nature of those binary systems. These observations were consistent with the aforementioned results.

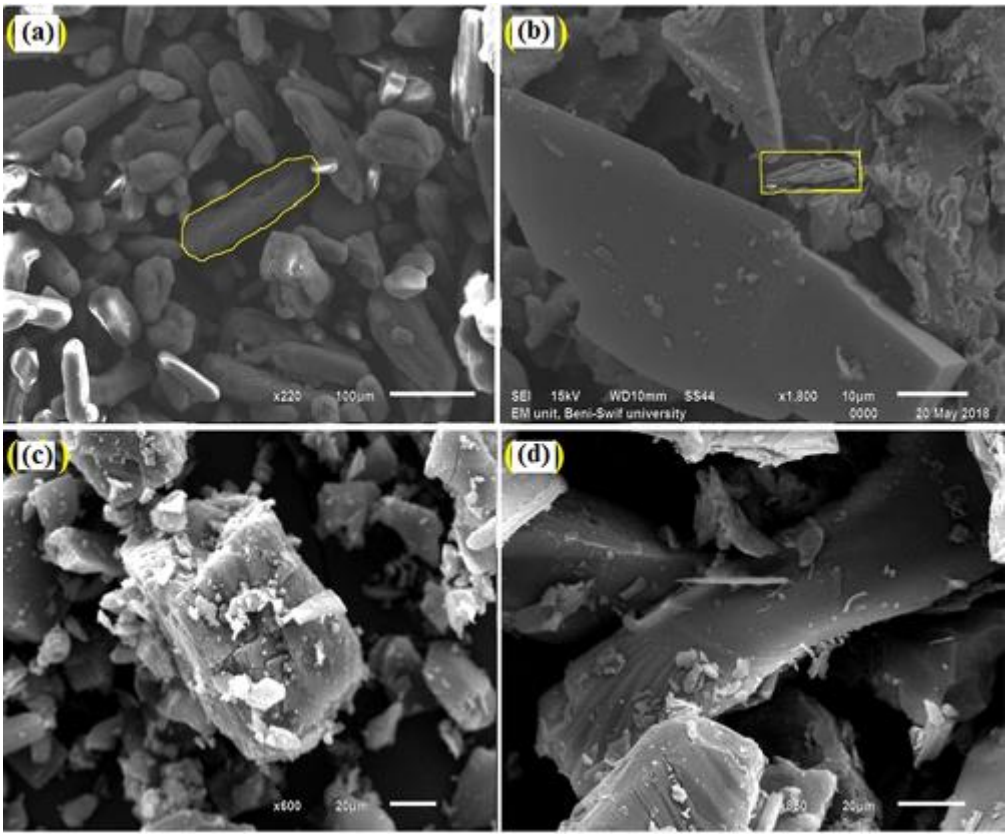


Figure 5 SEM micrographs of (a) pure IBU, (b) CD-PIA copolymer after IBU loading, (c) CD-PIA copolymer before IBU loading, (d) pure β-CD at different magnifications X100, 220 and 1800 with 10, 20 and 100 μm scale, respectively).

Effect of the different reaction parameters on the grafting process

Influence of ammonium persulphate (initiator) concentration

The influence of APS concentration on the graft copolymerization of β-CD under constant reaction conditions is shown in **Figure 6(a)**. It can be noticed that when APS concentration was increased, the percentages of the grafting yield (GY %) and the grafting efficiency (GE %) were gradually increased, as well as the percentage of the homopolymer was decreased. The optimum grafting yield was achieved at (0.2 g) 9 mM of APS at 70 °. This may be due to the APS was divided into 2 parts, the first one was used to induce the copolymerization of the monomer and the other one was consumed away with cage effect resulting in decomposition. When the concentration exceeded 9 mM, the excessive radicals could trigger multiple coupling that made the homopolymerization of IA dominant in the reaction medium, resulting in the reduction in the active site of β-CD and consequently the rate of the reaction rate was retarded [50].

Influence of itaconic acid (monomer) concentration

The influence of IA concentration on the graft copolymerization of β-CD is shown in **Figure 6(b)**. It can be noticed that when IA monomer concentration was increased, the percentages of the grafting yield (GY %) and the grafting efficiency (GE %) were gradually increased as well as the percentage of the homopolymer was decreased. The optimum grafting yield was found at 0.5 g of IA. The increase of the grafting percentage may be due to the increase of the macroradicals generated by the attack of more initiator (APS) on the saccharide units of β-CD. Consequently, the more active sites of β-CD were available to react with the monomer. Moreover, further increase of IA concentration resulted in a slow constant of the grafting yield.

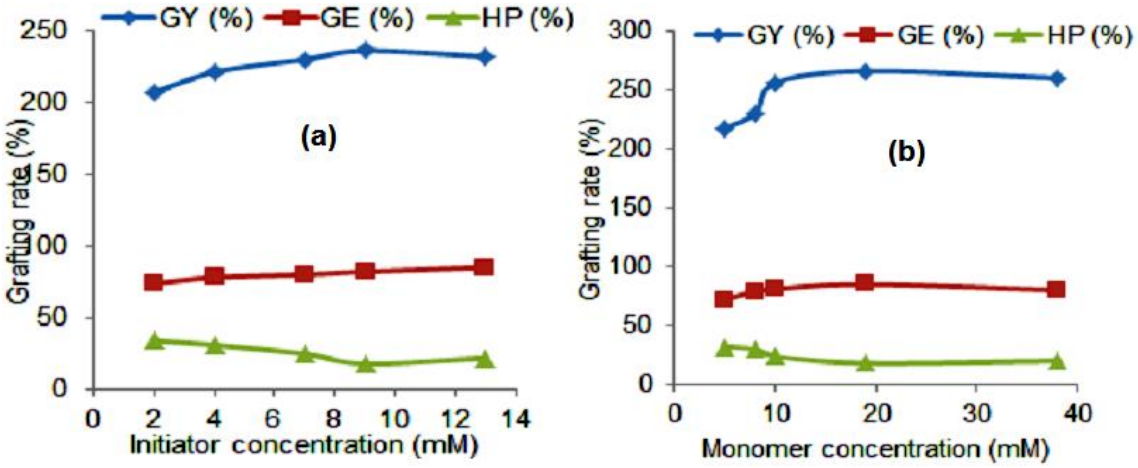


Figure 6 Effect of (a) initiator concentration and (b) monomer concentration on the copolymerization parameters under constant reaction conditions.

***In vitro* IBU release profiles and kinetic of released evaluation**

The *in vitro* IBU release profiles from the different CD-PIA formulations using SGF and SIF at 37 ℃ over 24 h were collected and analyzed as shown in **Figure 8**. During the first 4 h, a burst IBU release from all formulations was observed especially in the case of that including high IA content with respect to β-CD in the matrix (CD-PIA3 > CD-PIA2 > CD-PIA1) this may be due to the increase in the carboxylic groups at the side chains of the copolymer could be enhanced the swellability and consequently, the IBU diffusion was increased [51-53]. In the case of SGF dissolution (pH 1.2) (**Figure 7(b)**), the highest IBU cumulative release percent from CD-PIA3 was about 93.8 % relative to that in the case of the other formulations CD-PIA1 and CD-PIA2 (70.7 and 85.2 %, respectively). On the other hand, in the case of SIF (pH 7.4) (**Figure 7(a)**), the highest IBU release percent from CD-PIA3 was about 76.7 % relative to that in the case of the others (58.8 and 72.9 %, respectively). As reported previously [54,55], the drug adsorption ability of the copolymer was improved with an increase in the IA content in the copolymer structure. This has been clarified by the inclusion of more particular acidic groups into the network with high swelling ability. In other words, the carboxylic groups at the side chains were ionized and opened up the structure. Moreover, the hydrophilicity of β-CD with a small contact angle led to the enhancement of the copolymer and the aqueous medium. Consequently, the IBU diffusion was also increased [56]. After 4 h, the IBU profile was sustained released with a stable plateau. This behavior could be ascribed to the existence of an equilibrium between the free IBU and the β-CD/IBU complexed molecules in the copolymer network aqueous phase. The presence of some empty β-CD molecules might be entrapped by the free IBU and consequently the burst release could be retarded and regulated [57]. Different mathematical models (0-order, first-order and Higuchi) were chosen to evaluate the kinetic IBU released. The kinetic rate constants (k) of each model were calculated by linear regression analysis. Besides, the correlation coefficient (R^2) was determined to evaluate the accuracy of the fitness. To explain the IBU release profiles, the different kinetic models (0-order, first order and Higuchi) were applied. The kinetic rate constants (k) and the correlation coefficient (R^2) were recorded in **Table 3**. It was observed that the first-order model was the best fit for describing the IBU release from CD-PIA copolymer in comparison with the other ones (R^2 = 0.987).

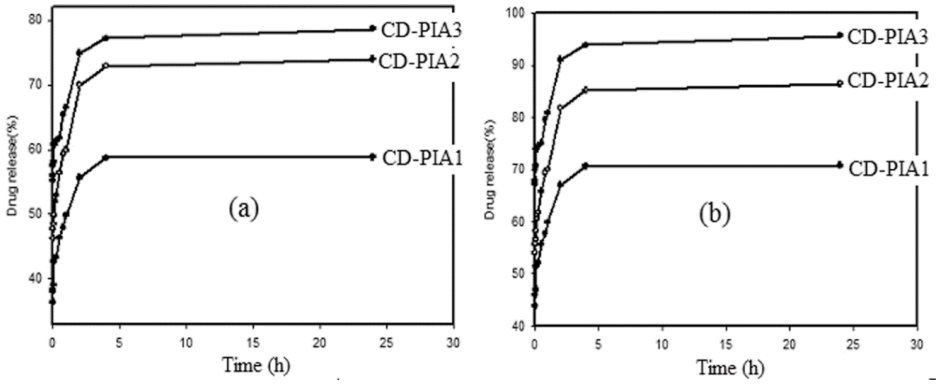


Figure 7 *In vitro* cumulative IBU release profiles at different interval times in (a) SIF at pH 7.4, (b) SGF at pH 1.2 from the different CD-PIA formulations at 37 °.

Table 3 Kinetic parameters of the *in vitro* IBU release from different CD-PIA copolymers.

Sample	Kinetic model	Rate constant (k)	R^2
CD-PIA1	zero-order	2.606	0.803
	first-order	0.37	0.959
	Higuchi	32.43	0.865
CD-PIA2	zero-order	4.687	0.916
	first-order	0.31	0.945
	Higuchi	25.11	0.927
CD-PIA3	zero-order	18.59	0.945
	first-order	0.215	0.987
	Higuchi	18.78	0.969

Conclusions

The IBU was loaded onto the synthesized β-CD/PIA copolymer using free-radical copolymerization technique. At high IA concentration, the vinyl content and interpolymer cross-linking were found to be reduced. The resulting copolymers were proved *via* FT-IR ^{1}H-NMR, TGA, XRD, TEM and SEM analyses. The kinetics of copolymerization were investigated. The optimal copolymerization process was found at the ratio of 1:2 (β-CD:IA). The kinetic of IBU released showed the best fit with first-order model. The synthesized copolymer showed a substantial response at pH level which the release rate of IBU was slightly higher at low pH. Moreover, the release of IBU using the synthesized copolymer has been a great advantage in the stomach (at low pH). If the release of IBU is delayed, it will be beneficial. It was suggested that this copolymeric device is very promising for the release and selection of IBU.

Acknowledgements

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