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FULL PAPER

Synthesis, Controlled Release and Kinetic Studies of Polyacrylic Acid-polyethylene Oxide/β-cyclodextrin Nano-interpolymer Complex with Naproxen

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Abstract:

The aim of this work is synthesis of a nano-interpolymer complex based on polyacrylic acid-polyethylene oxide (PAA-PEO) and β-cyclodextrin as a nanocarrier biodegradable drug delivery system. Host-guest method was used to make the nano-interpolymer complex in which beta cyclodextrin (β-CD) was applied as a suitable host. The nano-interpolymer complex was characterized by Fourier transform infrared (FTIR), scanning electron microscopy (SEM), and transmission electron microscopy (TEM). Hydrogen bonding formation between two polymers was proved by infrared spectroscopy method. The particle size in range of 12 nanometer was estimated by TEM. In the next step Naproxen **(Nap)** was loaded on the PAA-PEO/β-CD three component nano-interpolymer complex Then, release of Naproxen was investigated at 37 °C (human body temperature) and pH of 2.1 (gastric pH) and 7.4 (intestine pH) with UV spectrophotometer. Optimization of the PAA/PEO/β CD were investigated and by changing the amount of β-CD. Kinetic studies were also performed by using different kinetic models to investigate the Naproxen release rate.

Keywords: nano-interpolymer complex; naproxen delivery; β-cyclodextrin; polyacrylic acid; polyethylene oxide

1. Introduction

Polymer-polymer complexes, which are resulted from noncovalent associations between groups of different polymer chains, have been studied extensively during recent years due to their potential industrial and biomedical applications [1-8]. Supramolecular polymers are defined as polymers linked by intermolecular non-covalent interactions among macromolecules. Intermolecular interactions occur through hydrogen bonds, metal-ligand interactions, donor-acceptor bonds, and host-guest interaction. Supramolecular nano-structure assembled by polymers through host-guest interaction have attracted much attention during the last decade due to their important applications [9]. Supramolecular host-guest chemistry describes the formation of molecular complexes composed of small molecules (guests) noncovalently bound to larger molecules (hosts) in a unique structural relationship [10]. Host-guest complexes are of great technological importance and have been extensively studied [11].Cyclodextrins (CD) are naturally occurring water-soluble toroidally shaped polysaccharides with a highly hydrophobic central cavity that have the ability to form inclusion complexes with a variety of organic and inorganic substrates [12-18]. The three major natural cyclodextrins are α, β, and γ-CD built up from 6, 7, and 8 glucopyranose units, respectively. CDs are often found as building blocks of supramolecular systems, self-assemblies or chemical sensors [19–24]. The ability of CDs to form inclusion complexes, in which the physicochemical properties of the guest molecules change with respect to the free molecules, has led to a variety of applications [25–31]. The inclusion complexation with cyclodextrins (CDs) is an attractive and widely used technique

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for solubility/dissolution enhancement of poorly water-soluble drugs. The CD-polymers can form nanoparticles or gels in aqueous media that can be explored as drug delivery systems [32-34].

Interpolymer complexes (IPCs) between polyacids and non-ionic polymers stabilized by hydrogen bonds have been studied for several decades [35-39]. It has been shown that the stability of such complexes essentially depends on environmental conditions (solution pH, presence of low-molecular-weight components, etc.) [37-39]. The relationships are also of interest because of their usefulness to model some biochemical processes i.e., formation and destruction of tertiary fiber structure, intercellular interactions, etc. [39]. Since PEO can form the inclusion complex with CD and interpolymer complex (IPC) with PAA, respectively, it would be interesting to know what happens after mixing CD, PEO, and PAA together. In this work various novel supramolecular polymer systems consisting of β-CD, PEO and PAA ternary components are constructed based on the hydrogen bonding interaction between PEO and PAA and host-guest interaction between CD and PEO. Then, controlled-release properties of the Naproxen from interpolymer complexe of PAA-PEO/β-CD were explored in buffer solution. In vitro release studies in buffer (pH 1.2 and 7.4) at 37 °C showed an initial burst effect followed by slow release. The nano-interpolymer complex was characterized by Fourier transform infrared (FTIR), scanning electron microscopy (SEM), and transmission electron microscopy (TEM). To investigate the Naproxen release rate, kinetic studies were also performed by using different kinetic models

2. Results and Discussion

Nano-interpolymer complex was synthesized based on polyacrylic acid-polyethylene oxide (PAA-PEO) and β-cyclodextrin as a biodegradable drug delivery system. Host-guest method was used to make the nano-interpolymer complex in which beta cyclodextrin (β-CD) was applied as a suitable host. Polyacrylic acid and polyethylene oxide can form a complex in the water and some organic solvents such as ethanol. After the formation of interpolymer complex, their solubility remarkably decreased and the complex precipitated in solvent after a short period of time.

The complexation between polyacrylic acid and polyethylene oxide through a hydrogen bond is confirmed by the shift of carbonyl absorption bond of polyacrylic acid to higher frequencies in the FT-IR spectrum. Whereas PAA has an absorption band at 1715.59 cm^{-1} (Fig. 1), which is related to the carbonyl group, it is shifted to 1730.60 cm^{-1} after formation a complex between PAA and PEO.

The FT-IR spectrum of PAA-PEO/βCD complex in Fig. 3 indicates that absorption wavelength of carbonyl group of polyacrylic acid has been shifted to higher wavelength that equals to 1730.6 cm^{-1} .This shift in the absorption bond of carbonyl demonstrates the formation of a hydrogen bond in PAA-PEO/βCD complex. The peak of nonbonding hydroxyl in pure polyacrylic acid is observed at 344.31 cm^{-1} which is shifted to 3394.89 cm^{-1} in PAA-PEO/βCD complex with the same peak intensity. This shows that nonbonding hydroxyl in PAA is changed to bonding hydroxyl by bonding a hydrogen bond with PEO and its frequency has been shifted to lower levels. The peak of the ether group of PEO in Fig. 2 is observed at 1104.65 cm^{-1} that is shifted to the 1109.09 cm^{-1} after formation of polymer complex between PAA and PEO. The peak of carbonyl group of Naproxen drug is shown at 1723.85 cm^{-1} in Fig. 4 and 1729.35 cm^{-1} in Fig. 5. It reveals that PAA-PEO/βCD ternary complex has an appropriate interaction with Naproxen drug and the absorption frequency of carbonyl group of Naproxen has been shifted to higher levels.

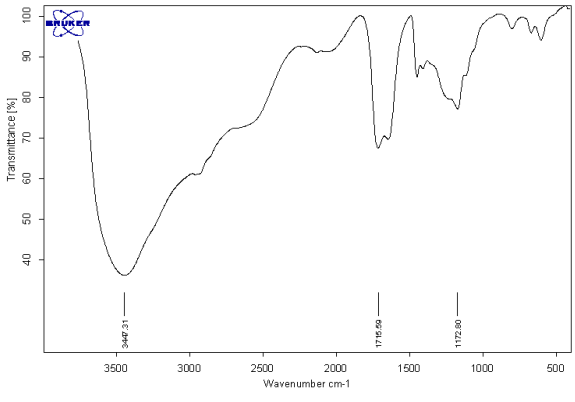


Figure1. FT-IR spectra of pure polyacrylic acid.

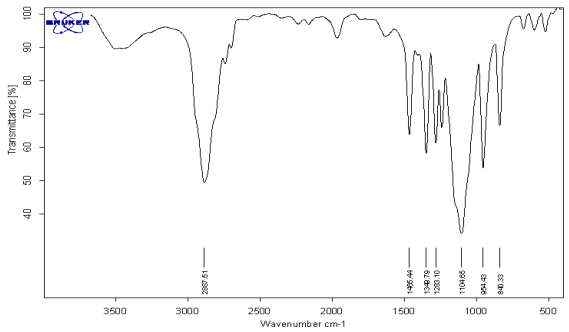


Figure 2. FT-IR spectra of pure polyethylene oxide.

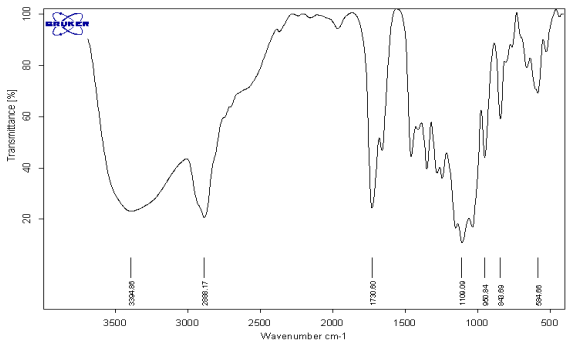


Figure 3. FT-IR spectra of ternary complexes of PAA/PEO/βCD

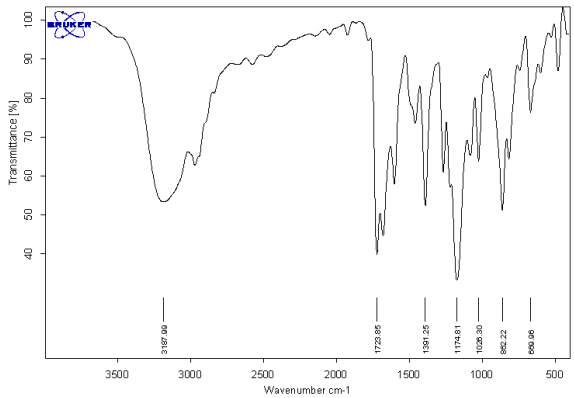


Figure 4. FT-IR spectrum of Naproxen.

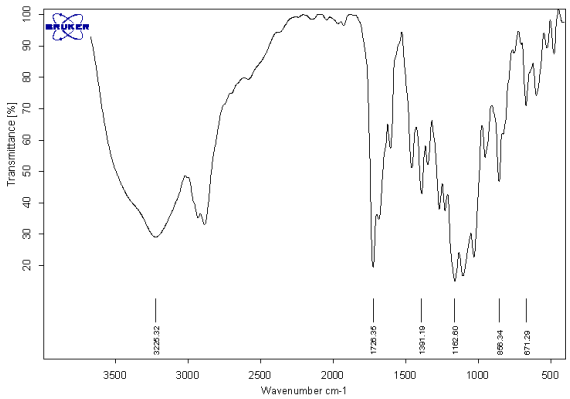


Figure 5. FT-IR spectrum of PAA-PEO/βCD containing Naproxen.

SEM images show the surface morphology very well. Considering the fact that PAA (Fig. 6) and PEO are both long chain polymers which have interaction via cross-linking hydrogen bonds, Figure 7 demonstrate their filiform structure in this complex.

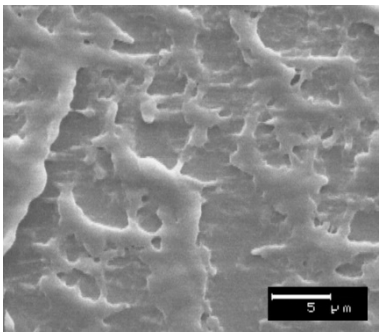
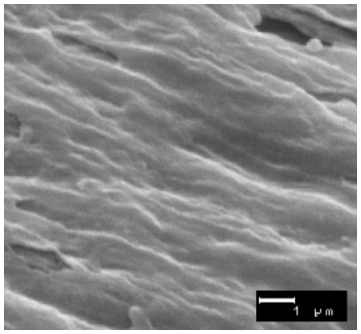
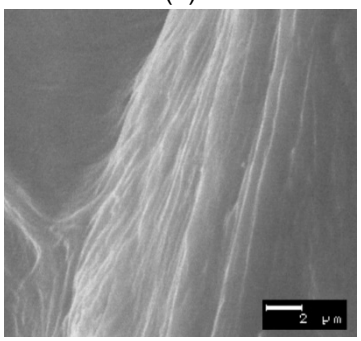


Figure 6. SEM images of pure poly-acrylic acid.



(a)

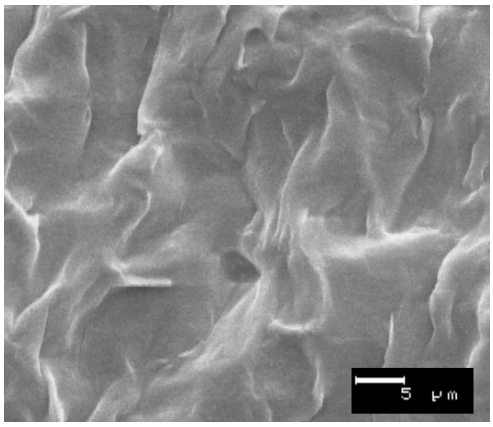


(b)

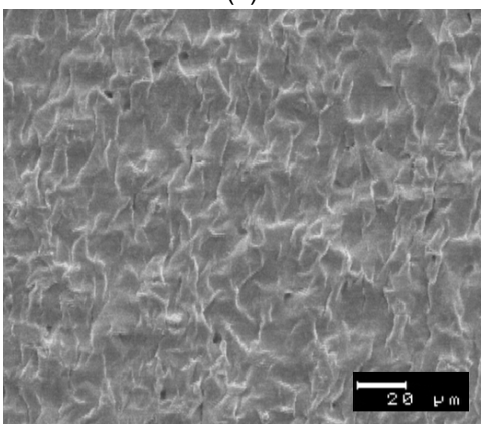
Figure 7. SEM images (a and b) of interpolymer complex of PAA/PEO.

Figure 8 show a regular porous structure that was already predicted due to the hole structure of cyclodextrin. Using TEM images, we found that the average size of the particles was in the range of about 300 nm in the absence of β-CD (Figure 9). On the other hand, it is reduced to about 10-20 nm at the presence of only 10% of β-CD (Figure 10). β-CD minimizes the size of PAA/PEO complex twenty times as much through a host-

guest system. Owing to the host-guest interaction between cyclodextrin and the linear polymers, hydrogen bonds interactions between the polymers of the complex have been weakened and the hydrophilic features of the colloidal particles have been improved extensively.



(a)



(b)

Figure 8. SEM images (a and b) of Ternary complexes of PAA / PEO / βcd.

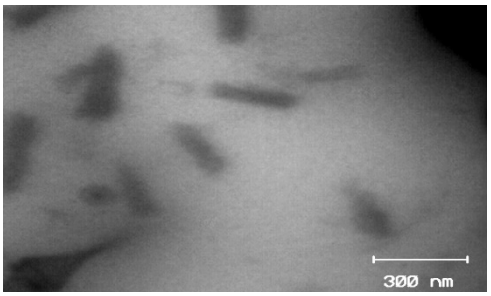


Figure 9. TEM image of complex PAA / PEO without β CD.

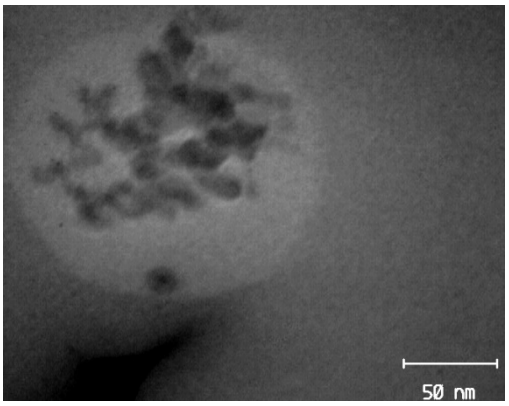


Figure 10. TEM image of complex PAA / PEO in the presence of 10% β CD.

According to the results of table 1 obtained by UV-vis spectroscopy, we found that transparency and brightness of the samples increases with increasing the amount of β-CD.

Table 1. The relationship between the concentration of β –CD and transmittance percent.

Sample	β –CD (mol)	Transmittance%
1	0	13
2	0.01	42
3	0.05	45
4	0.1	67

In order to specify the amount of drug loading, strong bases such as potassium hydroxide and sodium hydroxide were added to the nano-interpolymer complex containing Naproxen and the solution was stirred by a magnetic stirrer for 24 hours. The concentration of the loaded drug and the drug loading efficiency were calculated using the calibration curve of the Naproxen. The release percentage of Naproxen at pH 7.4 and pH 1.2 were equal to 92% and15%, respectively (Figure 11).

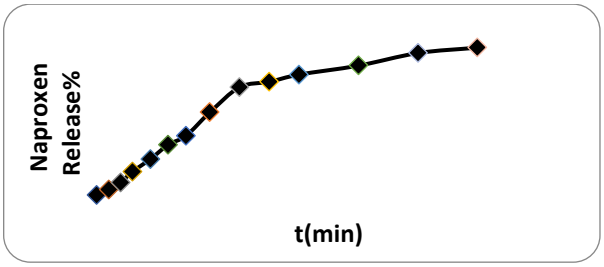


Figure 11. Drug delivery of Naproxen with nanoparticle carrier in the buffer 7.4

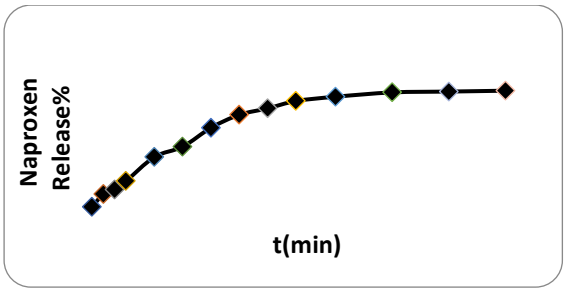


Figure 12. Drug delivery of Naproxen with nanoparticle carrier in the buffer 2.1.

Kinetic studies were also performed by using five different kinetic models to investigate the Naproxen release rate. The related diagrams were drawn according to data obtained from a spectrometer. Our criterion to choose the best kinetic model for release of Naproxen is conditions that would lead to the highest correlation coefficient. The results show that compared to other models, the Krosmeyer-Pepas model has the highest correlation coefficient, i.e. 0.965 (Table 2). Therefore it is considered as the proper kinetic model for Naproxen release at pH 7.4.Then it is known as the proper kinetic model for Naproxen release at pH 2.1.

Table 2. Parameters of some Models for mechanism of Naproxen release.

	Korsmeyer - Peppas model			Hixson-Crowell model		Higuchi model		First order model		Zero-order model	
pH	$K_{HP}(h^{-n})$	r^2	n	r^2	K_{HC}	r^2	K_H	r^2	K_1	r^2	K_0
7.4	7.775	0.965	0.620	0.802	0.003	0.948	13.71	0.738	0.014	0.889	1.387
2.1	1.510	0.966	0.5936	0.705	0.0001	0.934	2.084	0.656	0.01	0.813	0.191

3. Material and Methods

Naproxen was purchased from Abidy drug Company in Iran. PEO (with M_n=100000) and PAA (with M_n=100000) were acquired from Aldrich Chemical Company. β-CD provided from Aldrich Chemical Company and purified once by recrystallization from deionized water before use.

Preparation of PEO-PAA/β-CD: To prepare the PEO-PAA/β-CD interpolymer complex, 1.1 g of PAA was dissolved in 100 mL distilled water, followed by stirring until 24 hours. Also, 1.8 g of PEO was dissolved in 100 mL of distilled water and the solution stirred for 24 h. Different amounts of β-CD (0.1, 0.05, 0.01, 0.005 mole) were dissolved in 50 ml distilled water, followed by stirring until 24 hours. Then 50 mL vials were remarked with the numbers. After that, each vial was filed with the same volume of β-CD and with different amounts of the PAA and PEO solutions, respectively. A sample was also prepared without β-CD. The prepared suspension was magnetically stirred for 24 h. The reaction mixture was then centrifuged, followed by elution of the products by deionized water three times and dried at 40 °C in a vacuum oven for 24 h.

Drug loading: In order to drug loading, naproxen and nano-interpolymer complex solutions with 2: 1 ratio of polymer:drug was stirred with a magnetic stirrer in distilled water for 24h. The reaction mixture was centrifuged, washed three times with decarbonated water and dried in a vacuum at 40 °C.

Drug release studies: The release of Naproxen from nano-interpolymer complex was performed into a medium of phosphate buffered saline (PBS) at pH 7.4 and 2.1 while the temperature was kept at 37 °C. The solutions were stirred at 100 rpm on a magnetic stirrer for 24 h. In vitro drug release studies were performed using a dialysis membrane so that 0.01g of the drug loaded complex was poured in a porous dialysis membrane. Every 10 minutes, 3 ml of the solution was removed and immediately replaced by an equal volume of fresh buffer solution. The amount of drug released was monitored by a UV–Vis spectrophotometer at 229 nm. The percent of the drug release was evaluated by using the following equation:

$$Drug\ Release(\%)\ \frac{Amount\ of\ drug\ release(mg)}{Total\ weight\ of\ drug\ sample(mg)} \times 100 \quad (1)$$

Release kinetic modeling

There are a number of kinetic models that describe the overall release of drugs from drug loaded polymeric matrix and nanomaterials. Because qualitative and quantitative changes in a formulation may alter drug release and in vivo performance, developing tools that facilitate the study of drug release by reducing the necessity for bio-studies is always desirable. From the point of view of both economic and mechanistic interest, the use of in vitro drug kinetic models to predict in vivo bio-performance can be considered as a rational development of controlled release formulations [40-43]. These Models are based on different mathematical functions, which describe the dissolution profile. Once a suitable function has been selected, the dissolution profiles are evaluated depending on the derived model parameters. In order to determine the suitable drug release kinetic model describing the dissolution profile, the nonlinear regression module of Statistica 5.0 was used. In non-linear regression analysis the Quasi-Newton and Simplex methods minimized the least squares [44-45]. The model dependent approaches included zero order, first order, Higuchi, Hixson-Crowell, Korsmeyer-Peppas, Baker-Lonsdale, Weibull, Hopfenberg, Gompertz and regression models [46-47].

Zero-order model: Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the following equation:

$$Q_t = Q_0 + K_0 t \qquad (2)$$

where Q_t is the amount of drug dissolved in time t, Q_0 is the initial amount of drug in the solution (most times, $Q_0 = 0$) and K_0 is the zero order release constant expressed in units of concentration/time. To study the release kinetics, data obtained from in vitro drug release studies were plotted as cumulative amount of drug released versus time [48-49]. This relationship can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems, as well as matrix tablets with low soluble drugs in coated forms, osmotic systems, etc[50-51].

First order model: This model has also been used to describe absorption and/or elimination of some drugs, although it is difficult to conceptualize this mechanism on a theoretical basis. The release of the drug which followed first order kinetics can be expressed by the following equation:

$$\frac{dC}{dt} = -kc \qquad (3)$$

where K is first order rate constant expressed in units of time^{-1}. Equation (3) can be expressed as:

$$LogC = LogC_0 - \frac{kt}{2.303} \qquad (4)$$

where C_0 is the initial concentration of drug, k is the first order rate constant, and t is the time of drug release. [52]. The data obtained are plotted as log of cumulative percentage of drug remaining as a function of time which would yield a straight line with a slope of nK/2.303. This relationship can be used to describe the drug dissolution in pharmaceutical dosage forms such as those containing water-soluble drugs in porous matrix [53-54].

Higuchi model: The first example of a mathematical model aimed to describe drug release from a matrix system was proposed by Huguchi in 1961[55]. Initially, it was developed for planar systems, and the method has been extended to different geometrics and porous systems [56]. In a general way it is possible to simplify the Higuchi model [55] as follows which is generally known as the simplified Higuchi model:

$$F_t = Q = K_H \times t^{1/2} \qquad (5)$$

where, K_H is the Higuchi dissolution constant [46]. The data obtained were plotted as cumulative percentage drug release versus square root of time [54]. This relationship can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems and matrix tablets with water soluble drugs [55-56].

Hixson-Crowell model: Hixson and Crowell (1931) recognized that the particles regular area is proportional to the cube root of its volume. They derived the following equation:

$$W_0^{1/3} - W_t^{1/3} = \kappa.t..... \qquad (6)$$

where W_0 is the initial amount of drug in the

pharmaceutical dosage form, W_t is the remaining amount of drug in the pharmaceutical dosage form at time t and κ (kappa) is a constant incorporating the surface-volume relation. The equation describes the release of drug from systems where there is a change in surface area and diameter of particles or tablets [57]. To study the release kinetics, data obtained from in vitro drug release studies were plotted as cube root of drug percentage remaining in matrix versus time. This expression applies to pharmaceutical dosage form such as tablets, where the dissolution occurs in planes that are parallel to the drug surface if the tablet dimensions diminish proportionally in such a manner that the initial geometrical form is considered to be constant for all the time [58].

Korsmeyer-Peppas model: Korsmeyer *et al*. (1983) derived a simple relationship which described drug release from a polymeric system equation [59]. To find out the mechanism of drug release, first 60% drug release data are fitted in Korsmeyer-Peppas model [60].

$$M_t / M_\infty = k.t^n \qquad (7)$$

where M_t / M_∞ is a fraction of drug released at time t, k is the release rate constant and n is the release exponent. The n value is used to characterize different type of release for cylindrical shaped matrix. In other words, the value of n characterizes the release mechanism of drug as described in Table 1. For the case of cylindrical tablets, $0.45 \leq n$ corresponds to a Fickian diffusion mechanism, $0.45 < n < 0.89$ is related to non-Fickian transport, $n = 0.89$ corresponds to Case II (relaxational) transport, and $n > 0.89$ is related to super case II transport [61-62]. To find out the exponent of n, the portion of the release curve, where $Mt / M\infty < 0.6$ should only be used. To study the release kinetics, data obtained from in vitro drug release studies were plotted as log of cumulative percentage drug release versus log of time [62].

Instrumental Characterization: Infrared spectra were recorded with a Bruker Tensor 27 Fourier transform infrared spectrophotometer (FT-IR), using KBr pellets. Absorption spectra were recorded on a Shimadzu model 1601 PC UV-Visible spectrophotometer at λ_{max} of 229 nm. Scanning electron micrographs (SEM) were taken on a KYKY-EM 3200 and VEGA-TESCAN. TEM experiments were performed using a JEM-200CX microscope with an accelerating voltage of 120 kV

4. Conclusions

A nano-interpolymer complex was synthesized based on polyacrylic acid-poly ethylene oxide (PAA-PEO) and β-cyclodextrin as a nanocarrier biodegradable drug delivery system. Then, naproxen was successfully loaded onto the nano-interpolymer complex and its release behavior was investigated by using different kinetic models. The result was confirmed by FT-IR, UV-Vis, SEM, and TEM techniques. The average size of the particles was in the range of about 300 nm in the absence of β-CD, while, it is reduced to about 10-20 nm at the presence of only 10% of β-CD.

The release of Naproxen were obtaind 15.5% and 92%, in buffer 2.1 (gastric pH) and in buffer 7.4 (intestine pH) ,respectively. The formation of complex between PAA and PEO polymers can postpone the drug release rate, especially in the acidic medium, so it can be used as proper drug delivery system. The Krosmeyer-Pepas was found to be the best kinetic model both in acidic and in basic media for release of Naproxen from the system. All of these results suggest that Naproxen – PAA-PEO/β-CD are suitable for release of drug and bioactive agents.

Acknowledgments

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