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Some Variables Affecting the Formulation of Ketoprofen Sustained Release Oral Tablet using Polyelectrolyte Complex as a Matrix Former

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ABSTRACT

Ketoprofen is a non-steroidal anti-inflammatory drug used in the treatment of many diseases including rheumatoid arthritis. This investigation concerned with preparation of ketoprofen as a sustained release oral tablet using Polyelectrolyte Complex (PEC) that Composed of Chitosan (CS) as Cationic Polymer and carbopol (CP) as anionic polymer. Polyelectrolyte complex were formed by electrostatic interaction between the carboxyl group of CP and amine group of CS at pH5. (FT-IR) spectra of the complex were analyzed. Different factors affecting the swelling index and release rate were studied. The results showed that CS: CP prepared in the ratio of (1:4) had highest swelling index and release rate. Also changing the molecular weight of CS from medium (CS_m) to high molecular weight (CS_h), no significant difference observed in the dissolution profile. In addition it was seen that retardation in the release would occur as the solution of CS acetic acid was cooled to 8EC and with increasing the amount of PEC powder in formula. In conclusion the study showed retardation in the release rate with increase in the strength of PEC. Moreover, the increase in the amount of CP showed PH dependant release.

Key words: Ketoprofen, polyelectrolyte complex, sustained release, swelling index, chitosan, carbopol

INTRODUCTION

Recently there are continued efforts to design efficient carriers for the controlled release of drugs; several approaches have been investigated, including the use of PEC (Konar and Kim, 1999). These complexes have been defined as attractive polymeric drug carriers that can be used for the development of innovatory oral drug delivery systems (Lu *et al*., 2008a). These PECs are formed as precipitates when cationic polyelectrolyte bind or associate to form complex with oppositely charged polymers in an aqueous solution (Lu *et al*., 2008a; Ahmad *et al*., 2003). Several factors control the formation and the properties of PECs including proportion of opposite charges, molecular weight of the macromolecules, charge density and concentration, nature and position of the ionic groups and physicochemical environment (Etrych *et al*., 2005). A strong PEC is formed if the polyions reach to their full ionized forms or if the anions and cations in the polymers contain strong acids and bases, while a weak PEC is obtained in both weak acids and bases

(Kim *et al.*, 2004). Different methods have been used to investigate the interactions among polymers including measurements of viscosity, ratio of polymer in the media, turbidity, pH, ionic strength as a function of weight, thermal analysis, nuclear magnetic resonance, infrared-spectroscopy and powder X-ray diffraction (Tan *et al.*, 2001). The properties of PEC are usually different from those of its individual components (Surinia *et al.*, 2003). Chitosan is a copolymer of 2-glucosamine and N-acetyl-2-glucosamine; it is produced by the deacetylation of chitin (Phromsopha and Baimark, 2010). The amino groups of CS allow it to chemically react with anionic systems resulting in changing of physicochemical characteristics of such combinations (Dreve *et al.*, 2009), CS is insoluble in basic solutions at pH >6.5 and in most organic solvents but soluble in acidic solutions. It has gel forming properties in low pH range. It has a high charge density, adheres to negatively charged surfaces and chelates metal ions (Kas, 1997). Due to the cationicity of CS, its capacity to form polyelectrolyte complexes and the presence of nitrogen in its molecular structure, this polymer is considered to be is distinct from other available polysaccharides (Bhattarai *et al.*, 2010). Polyacrylic acid (Carbopol®) is anionic pH-sensitive polymers (Masteikova *et al.*, 2003), it forms a low viscosity gel at alkaline pH but remain in solution form at acidic pH (Madan *et al.*, 2009). When the pH of carbopol is increased above its pKa of about 5.5, a sol to gel transition in aqueous solution will occur (Wu *et al.*, 2007). Although carbopol has many advantages as a good candidate for an extended-release tablet matrix like a good gel-forming ability and mucoadhesive property, there are few studies on its application to the extended release dosage forms (Park *et al.*, 2008) since it has high sensitivity to the ionic environment, so its use in an ion-rich environment may interfere with adhesive and release properties of the polymer (Singla *et al.*, 2000). Carbopol is highly soluble in water so that its use as a mucoadhesive drug carrier is critically limited because it may dissolve before the desired time for delivery of the drug across the membrane, the water solubility of CP will decreased when it form PEC with CS (Cho and Choi, 2005), also PEC might solve the problem of the pH dependency of CP since its carboxyl groups are complexed with amine groups of CS, which are the main factors affecting the pH-dependant drug release (Park *et al.*, 2008). Ketoprofen is [2-(3-benzoylphenyl)propionic acid] (So *et al.*, 2009), it is a non-steroidal anti-inflammatory drug (NSAID) that have analgesic, anti-inflammatory and antipyretic effects (Ahmed *et al.*, 2006). Ketoprofen have short elimination half-life 2-3 h (Palmieri *et al.*, 2002) so that it requires multiple dosing to achieve and maintain therapeutic concentration (Philip and Pathak, 2008), also high levels of ketoprofen in the stomach can cause ulceration or bleeding, so that sustained release or enteric-coating dosage forms have been developed to improve these disadvantages, resulting in less frequent dosing and less gastrointestinal disturbance (Yamada *et al.*, 2001). The objective of this study was to formulate ketoprofen as oral sustained release tablet using (CS/CP) PEC as matrix former, through studying some variables affecting the formulation.

MATERIALS AND METHODS

Materials: Ketoprofen powder supplied by (Oubari and CO., Syria), Medium and High molecular weight Chitosan from (SigmaBAldrich, USA), Carbopol (grade 940) from (J. Baker, USA), Polyvinylpyrrolidone and Lactose from (Riedel-De-Haen AG seelze, Germany), Sodium hydroxide from (Applichem GmbH Olloweg. Germany) and Ethanol from (GCC Analytical Reagent; UK).

Equipment: United State Pharmacopoeia USP dissolution apparatus I (Copley dissolution 8000, copley scientific, U.K.), Oven (Memmert, Germany), UV-Visible Spectrophotometer (Carry UV,

Varian, Australia), Sartorius balance (Werk-GmbH, Germany), Hardness tester (Stokes, Monsanto Co. Ltd.USA), FTIR Spectroscopy (Shimadzu FTIR 8000. Japan), pH meter; pH221 Microprocessor (Hanaa, Italy), Tablet machine (Chemi Pharm, New York), Sieve (0.03 mm) (England), Electrical miller (Philips, Germany) and Electrical hand mixer (Shinon, China).

Methods

Preparation of (chitosan/carbopol) polyelectrolyte complex: According to Sung-Hyun (Park *et al.*, 2008) method carbopol aqueous solution (1 mg mL^{-1}) was prepared by gradual dissolving of CP powder in distilled water at room temperature with continuous stirring. Chitosan acetic acid solution (5 mg mL^{-1}) was prepared by gradual dissolving of CS powder in acetic acid solution (1% v/v) at room temperature with continuous stirring. The carbopol aqueous solution and chitosan acetic acid solution were mixed (Park *et al.*, 2008). The mixture was neutralized with sodium hydroxide 3 M to reach a pH of 5.0 (De La Torre *et al.*, 2003) the resulting precipitate (CS/CP PEC) was washed with distilled water and dried in oven over a 24 h period. The dried complex was ground with electrical miller. The powder passed through a 200-µm sieve and used for further study (Park *et al.*, 2008).

Fourier transforms infrared study (FT-IR): The FT-IR spectra of CS, CP and (CS/CP) PEC were obtained after making potassium bromide disks in the range of 4000-400 cm^{-1} to confirm the formation of a complex between the two polymers.

Preparation of sustained release ketoprofen tablet: Different formulas (F1-F10) as shown in Table 1 were prepared using direct compression method for the preparation of 200 mg ketoprofen sustained release tablets (wt. of each tab. is 700 mg).

Formulas (F1-F8) were prepared by mixing (CS/CP) PEC powder (using different ratios, different molecular weights of CS (high and medium molecular weight) and different amounts of powder) with ketoprofen, PVP(5%) and lactose. Formulas F9 and F10 were prepared by mixing (CS_h/CP) PEC powder (using 1:3 and 1:4 ratios but during the preparation of PEC the CS acetic acid solution was cooled to 81C) with ketoprofen, PVP (5%) and lactose. The components of the formulas was mixed for 15 min, then magnesium stearate (0.5%) was added and mixed genteelly with the other formula constituents for 1 min and compressed into tablets.

Table 1: Different formulas of ketoprofen as sustained release tablets

Formula No. Substance (mg)	F 1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Ketoprofen	200	200	200	200	200	200	200	200	200	200
Csm/CP PECamount and ratio						400	400			
						(1:1)	(1:2)			
CS_h/PCPEC amount and ratio	400	400	400	400	400			400	400	200
	(2:1)	(1:1)	(1:2)	(1:3)	(1:4)			(1:3)	(1:4)	(1:3)
PVP	35	35	35	35	35	35	35	35	35	35
Magnesium stearate	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Lactose	61.5	61.5	61.5	61.5	61.5	61.5	61.5	61.5	61.5	261.5
Temp. of CS acetic acid solution (°C)	25	25	25	25	25	25	25	8	8	25
Total weight (mg)	700	700	700	700	700	700	700	700	700	70

Evaluation of the prepared mixtures flow properties

Angle of repose: Angle of repose was determined by the fixed funnel method. A funnel with the end of the stem cut perpendicular to the axis of symmetry was secured with its tip at a given height (H) above a graph paper placed on a flat horizontal surface. The material was carefully poured through the funnel until the apex of the conical pile so formed just touches the tip of the funnel. The mean diameter (2R) of the base of the powder cone was determined and the tangent of the angle of repose is given by Krishnaiah *et al.* (2002) and Atram *et al.* (2009).

Carr's index: Carr's index values for the powder was determined by measuring the initial volume (Vp) and final volume (V_t) of a known weight (W) of material after subjecting to 100 tappings in a graduated measuring cylinder. From these volumes, the poured density (W/Vp) and the tapped density (W/V_t) values were calculated and were substituted in equation to determine Carr's index (Krishnaiah *et al.*, 2002; Atram *et al.*, 2009).

Swelling study: The degree of swelling was investigated in conditions which simulated the gastrointestinal tract (Moustafine *et al.*, 2005). Using USP dissolution apparatus I (basket method), with a basket rotation speed of 100 rpm. The dissolution medium was maintained at 37°C throughout the test. The tablet was running out in dissolution jar containing HCl solution (pH 1.2) for 2 h and the next hours in phosphate buffer solution (pH 6.8) (Yang *et al.*, 2008). The volume of swelling medium is 40 mL. After every 1 h the basket was removed from the medium, accurately dried by filter paper and weighed (Moustafine *et al.*, 2005). The swelling index was calculated as:

$$\text{Swelling index} = \left(\frac{W_t - W_0}{W_0} \right) \quad (1)$$

where, W_0 is the weight of dried tablet and W_t is the weight of tablet at time t (Trivedi *et al.*, 2011). This study was done to investigate the effect of polymers ratios on the swelling index of PEC.

Dissolution test: The drug release properties of ketoprofen sustained release tablets were determined using USP dissolution apparatus I (basket method) with a basket rotation speed of 100 rpm. The dissolution medium was maintained at 37°C throughout the test.

One tablet of each prepared formula was running out in a dissolution jar containing 750 mL of HCl solution (pH 1.2) for two hours, then in 1000 mL of phosphate buffer (pH 6.8) for the rest of the experiment. Samples of 5 mL were withdrawn at specific time intervals (0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 h), the volume of samples was replaced with 5 mL of the same buffered solution. Samples were filtered through 0.45 μm millipore filter and analyzed spectrophotometrically at 258 and 260 nm for the drug content in HCl solution (pH 1.2) and phosphate buffer (pH 6.8), respectively. The procedure was triplicated for each run test (Yang *et al.*, 2008).

Kinetics of drug release profile: The kinetics of ketoprofen release from sustained release tablet was determined by finding the best fit of the dissolution data (drug-released fraction versus time) to distinct models: zero-order, first-order, Higuchi model and Korsmeyer-Peppas model to characterize mechanism of drug release (Vueba *et al.*, 2004).

Zero order kinetic: The pharmaceutical dosage forms following this profile release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a pharmacological prolonged action (Costa and Lobo, 2001; Sinko, 2006).

First order kinetic: The pharmaceutical dosage forms following this dissolution profile, release the drug in a way that is proportional to the amount of drug remaining in its interior (Costa and Lobo, 2001; Sinko, 2006).

Higuchi model: It describes drug release as a diffusion process based in the Fick's law, square root time dependent (Costa and Lobo, 2001; Sharif Shaheen and Kazuo, 2006).

Korsmeyer-peppas model: It is used for better characterization of the drug release behavior for the polymeric systems and to understand the corresponding mechanism.

For the determination of the exponent n the portion of the release curve where Only the points within the interval ($0.1 < Q_t / Q_\infty < 0.7$) were used. When $n = 0.45$ corresponds to a Fickian diffusion release (case I diffusional), $0.45 < n = 0.89$ to an anomalous (non-Fickian) transport, $n = 0.89$ to a zero-order (case II) release kinetics, and $n > 0.89$ to a super Case II transport (Vueba *et al.*, 2004).

Ketoprofen assay: Five randomly chosen tablets of the optimum formula were thinly minced in a mortar and 17.5 mg of the resulting powder was solubilised in phosphate buffer (pH 6.8), up to a final volume of 100 mL. Several aliquots were then filtered and assayed spectrophotometrically at 260 nm, each measurement was carried out in triplicate and the results averaged (Vueba *et al.*, 2004).

Statistical analysis: The results of the experiments were expressed as a mean of triplicate samples±standard deviation and were analyzed by using Ssps package version 10; one-way analysis of variance (ANOVA) used to determine if the differences are statistically significant where ($p<0.05$) set to be significant.

RESULTS

Fourier transforms infrared study (FT-IR): The interaction between CS and CP has been studied by several investigators. The results indicated that PEC complex could be formed by the electrostatic interaction between the (-COO-) group of CP and (-NH^{3+}) group of CS when pH of the solution was about (5). To make p rotonated CS and dissociated CP solutions, CS and CP were dissolved in the acetic acid solution and water, respectively. Subsequently, the CS and CP PEC complexes were prepared with those solutions (Park *et al.*, 2008; Krishnaiah *et al.*, 2002).

In order to confirm the (CS/CP) interactions, sample was analysed by FT-IR spectroscopy. Figure 1, 2 and 3 show the FT-IR spectra of CS, CP and (CS/CP) PEC, respectively. The IR spectrum of CS shows that there are peaks at 1427.37 and 1654.98 cm^{-1}, these bands are shifted with less intensity to 1490 and 1633.76 cm^{-1}, respectively in the spectrum of (CS/CP) PEC. The IR spectrum of CP shows that the peaks at 1174.69, 1730.21 and 1435 cm^{-1} are shifted with lower intensity to 1240,1700 and 1440 cm^{-1}, respectively in the spectrum of (CS/CP) PEC.

Several peaks are observed in the regions of 3300-3425.69 and 2495.97-3578 cm^{-1} in IR spectrum of CS and CP, respectively.

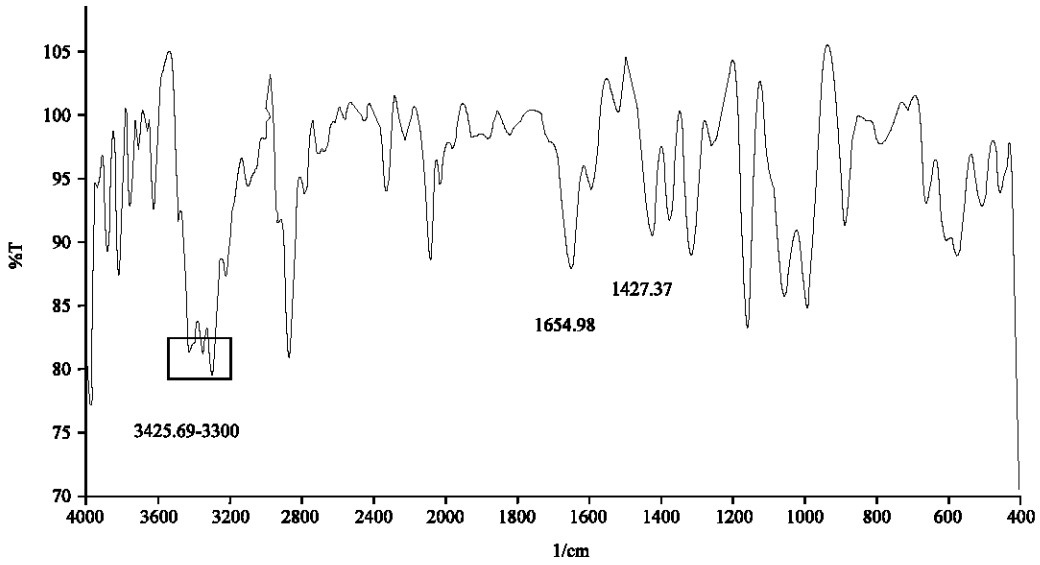

Fig. 1: FT-IR spectrum of CS

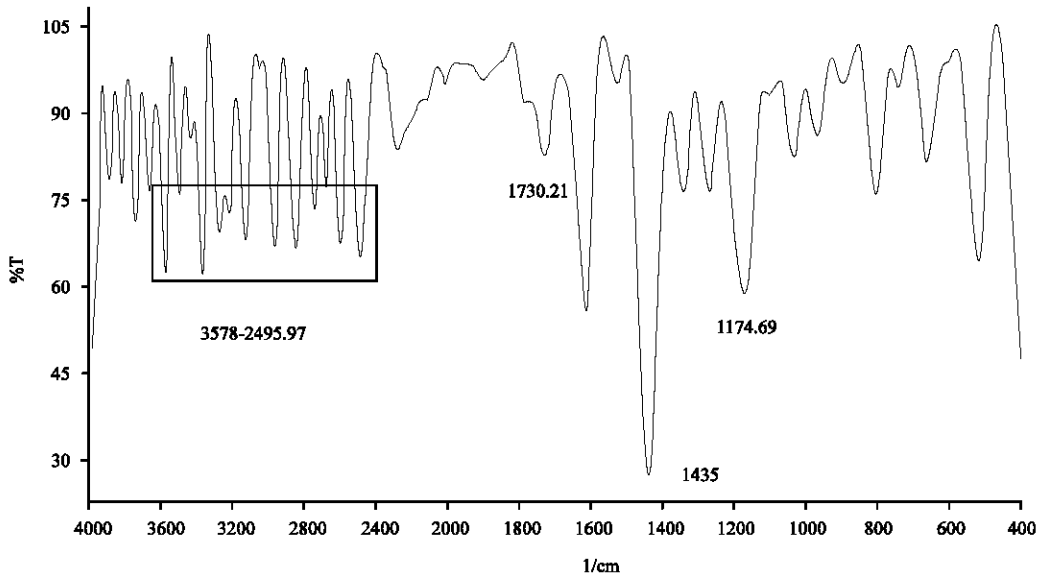

Fig. 2: FT-IR spectrum of CP

$Evaluation of the flow properties: The resulted values of angle of repose and Carr's index for the prepared powders mixture of each formula before compression them into tablets are illustrated in Table 2.

Swelling study

Effect of polymer-polymer ratios: Figure 4 shows the effect of (CS/CP) ratios on the swelling property of PEC. It was seen that as the amount of CP increased in (CS/CP) complex the swelling index also increased non significantly ($p>0.05$).

Table 2: Carr's index and angle of repose of the prepared powders mixture of each formula before compression them into tablets

Formula No.	Carr's index %)	Angle of repose	Type of flow
F1	13.3	18	Excellent
F2	3.3	20	Excellent
F3	10.0	17	Excellent
F4	6.7	18	Excellent
F5	10.0	18	Excellent
F6	10.0	16	Excellent
F7	6.6	17	Excellent
F8	3.3	18	Excellent
F9	6.6	20	Excellent
F10	10.0	21	Excellent

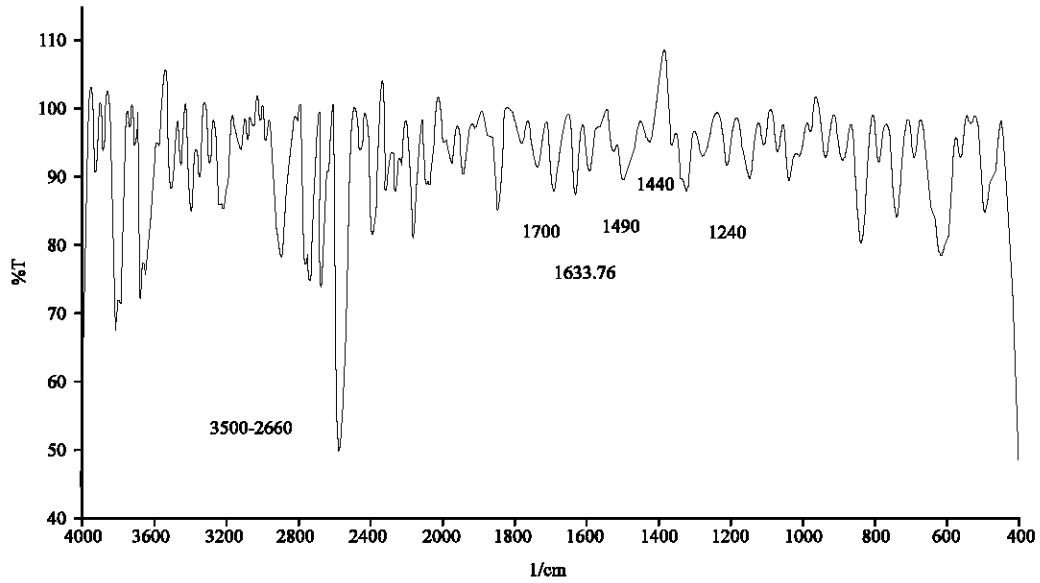

Fig. 3: FT-IR spectrum of (CS/CP) PEC

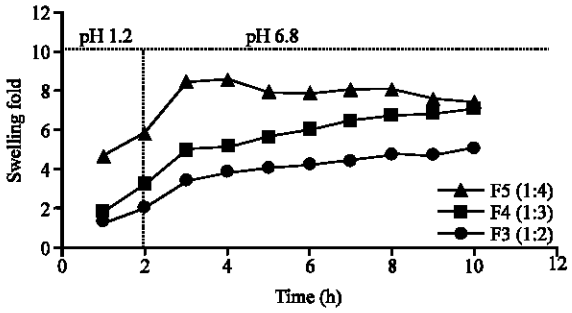

Fig. 4: The effect of (CS/CP) ratios on the swelling behavior of PEC

Variables affecting the dissolution profile of ketoprofen sustained release tablet

Effect of polymer-polymer ratios: Formulas F1, F2, F3, F4 and F5 were used to study the effect of polymer-polymer ratios. It was seen that the release was very slow in the first two hours in HCl

solution (pH1.2) while at pH 6.8 the release was faster. It was found that there was a significant ($p<0.05$) increase in the release of ketoprofen as the amount of CP increased in the complex as shown in Fig. 5.

Effect of molecular weight of CS: The effect of the molecular weight of CS was studied by using F2, F3, F6 and F7, the result is shown in Fig. 6 and 7. Formulas F2, F3 and F6, F7 were prepared utilizing high and medium molecular weight CS, respectively, it was seen that there is no significant difference ($p>0.05$) observed in the dissolution profile of ketoprofen sustained release tablet when changing from high to medium molecular weight CS.

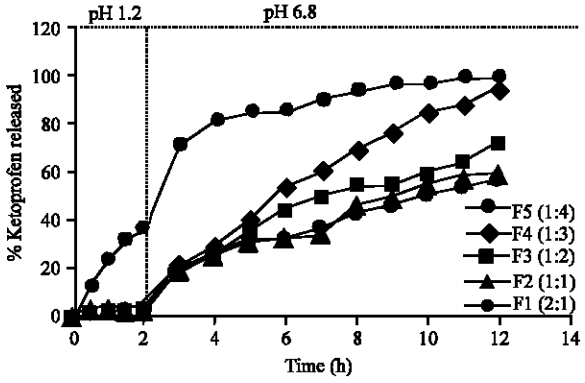

Fig. 5: The effect of (CS:CP) ratio on the cumulative release of ketoprofen

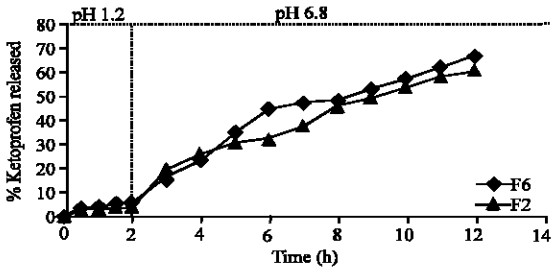

Fig. 6: The effect of molecular weight of CS on the cumulative release of ketoprofen from F2 and F6

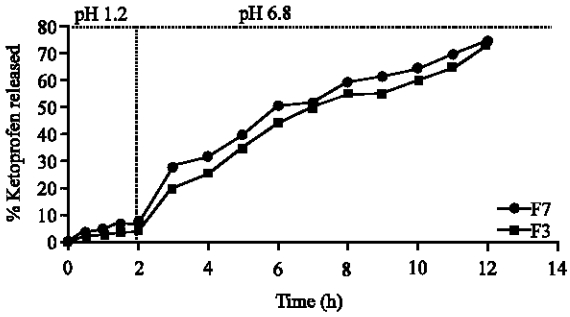

Fig. 7: The effect of molecular weight of CS on the cumulative release of ketoprofen from F3 and F7

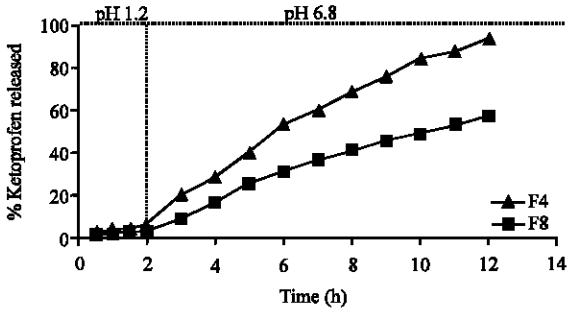

Fig. 8: The effect temperature of CS acetic acid solution on the cumulative release of ketoprofen from F4 and F8 at 25 and 8°C, respectively

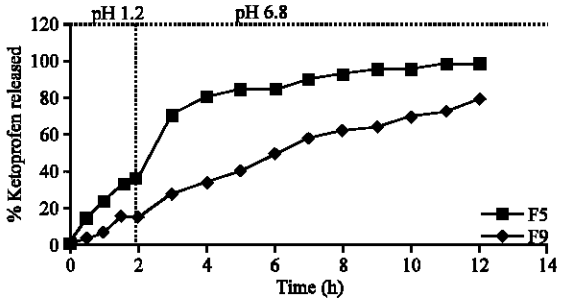

Fig. 9: The effect of temperature of CS acetic acid solution on the cumulative release of ketoprofen from F5 and F9 at 25 and 8°C, respectively

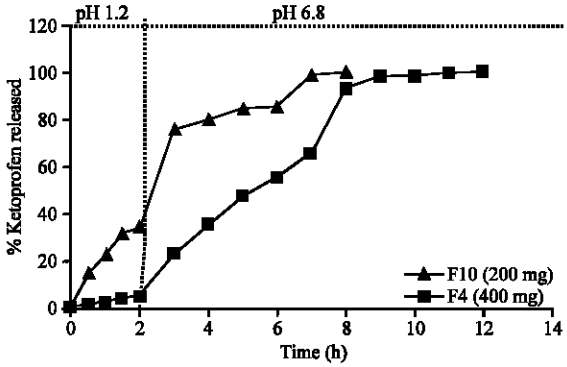

Fig. 10: The effect of the amount of PEC on the cumulative release of ketoprofen from F4 and F10

Effect of temperature of cs acetic acid solution: Figure 8 and 9 show the effect of cooling of CS acetic acid solution to 8°C on the release from F8, F9, respectively. It was seen that there is a significant retardation ($p<0.05$) in the release when the solution of CS acetic acid was cooled to 8°C.

Effect of amount of PEC used: The effect of the amount of PEC was studied by using F4 and F10. The release of ketoprofen from F10 was significantly ($p<0.05$) higher than that from F4 as seen in Fig. 10.

Determination of the release kinetics: The release kinetics of ketoprofen from all the prepared tablets was determined by finding the best fitting of the dissolution data to the mathematical models (1, 2 and 3). In addition, analysis of the experimental data according to model (4) as well as interpretation of the corresponding release exponent values n leads to better understanding of the release mechanism from tablets. Table 3 shows that n values of F1, F2, F3, F4, F6, F7, F8 and F9 are more than 0.89, while F5 and F10 have n value between 0.45 to 0.89.

DISCUSSION

Fourier transform infrared study (FT-IR): Figure 1, 2 and 3 show the FT-IR spectra of CS, CP and (CS/CP) PEC, respectively. The IR spectrum of CS shows that the peaks of 1427.37 and 1654.98 cm^{-1} assigned to the stretching of (C-N) and (C = O) groups of amide, respectively, these bands are shifted with less intensity to 1490 cm^{-1} for (C-N) group and 1633.76 cm^{-1} for (C = O) group in the spectrum of (CS/CP) PEC. The IR spectrum of CP shows that the peaks at 1174.69 and 1730.21 cm^{-1} assigned to the stretching of (C-O) and (C = O) of carboxyl group, respectively, while the peak at 1435 cm^{-1} represented the bending of (O-H) of carboxyl group. These bands are shifted with lower intensity to 1240,1440 and 1700 cm^{-1} for (C-O), (O-H) and (C = O) groups, respectively.

The region of 3300-3425.69 cm^{-1} in IR spectrum of CS assigned to the stretching for (N-H) of amide or amine group, while the regions of 2495.97-3578 cm^{-1} in IR spectrum of CP assigned to the stretching for (O-H) of carboxyl group in CP, it is seen that there is overlapping between the absorption bands of (N-H) of CS and that of (O-H) of carboxyl group of CP in the IR spectra of (CS/CP). These results suggested that (CS/CP) PEC was formed by an electrostatic interaction between the (-COO-) group of CP and ($-NH^{3+}$) group of CS.

Evaluation of the flow properties: According to the standard values of angle of repose and Carr's index (Wells, 2008) It was found that the flow of the prepared powders mixture of all formulas as shown in figure was excellent, this improvement in the flow property of the powder may be due to the reduction of electrostatic charges of the polymers by the formation PEC also may be due to the alteration of the shape and texture of PEC powder particles by crystallization (Staniforth, 2008) that result from the cross-linking of CS and CP (Livshin and Silverstein, 2007). The result was consistent with that observed in the preparation of spray-dried lactose composite particles containing an ion complex of alginate-chitosan for designing a dry-coated tablet having a time-controlled releasing function when the lactose-sodium alginate-chitosan composite particles having good compaction and flow properties (Takeuchi *et al.*, 2000).

Swelling study

Effect of polymer-polymer ratios: Figure 4 shows the effect of (CS/CP) ratios on the swelling property of PEC. (CS/CP) complex presented ionic interactions between positively charged CS and negatively charged CP, these complexes exhibited pH-sensitive swelling in acid and basic conditions. As swelling medium pH change the charge balance inside the gelling network and therefore the degree of interaction between chitosan and CP is modified and swelling occurs because of the dissociation of the complex. In acidic medium, CP was neutralized and free positive charges ($-NH^{3+}$) of CS appear inside the gel providing swelling while in basic medium CS was neutralized (Krishnaiah *et al.*, 2002).

In basic medium it was seen that as the amount of CP increased in (CS/CP) complex the swelling index also increased non significantly ($p>0.05$) due to the hydrophilic nature of CP so that

the percentage of water uptake increased on increasing the concentration of it (Zate *et al.*, 2010; Khan and Zhu, 2001). The ability of CP to absorb water is due to the presence of hydrophilic groups (-COOH) (Peppas and Khare, 1993), as the pH of the swelling medium was above 5, the ionization of the carboxylic acid groups of CP in the complex occurred and led to ionic repulsion that resulted in a more hydrophilic polymer network and contributed to higher water absorption (Bartil *et al.*, 2007). The result was similar with that observed in studying mucoadhesive bilayer buccal tablets of Atorvastatin calcium using the bioadhesive polymers Carbopol 934P, Sodium CMC, Hydroxy ethyl cellulose and Sodium alginate along with ethyl cellulose as an impermeable backing layer (John *et al.*, 2010).

Variables affecting the dissolution profile of ketoprofen sustained release tablets

Effect of polymer-polymer ratios: It was seen that the *in vitro* release of ketoprofen depended on swelling behaviour of the tablets. The release was very slow in the first two hours in HCl solution (pH1.2) because the charge density of chitosan was sufficiently high and the ionic interactions were increased resulting in the formation of much stronger network. While at pH 6.8 the release was faster because the ionic interaction between CS and negatively charged polymers CP was greatly reduced forming a loose network with increase porous surface which allows greater part of dissolution media along with counterions (Saleem *et al.*, 2010). It was found that there was a significant ($p<0.05$) increase in the release of ketoprofen as the amount of CP increased in the complex as shown in Fig. 5. It was seen that the slowest release occur from F1 at (2:1 ratio of CS/CP) because of larger amount of CS in comparison with other formulas since as the concentration of CS increased the interaction between the two polymers should have been increased forming a closer network which showed decrease in the diffusion of drug outwards of the tablets. The same result was obtained on studying different CS PEC hydrogels for modified release of diltiazem hydrochloride, when the release of diltiazem hydrochloride decreased with increasing the ratio of (CSh/CP) from (0.5:1, 1:1, 1.5:1) (Saleem *et al.*, 2010). When the amount of CP increased in the complex the release rate and the swelling index increased due to the hydrophilic nature of CP so that the percentage of water uptake increased on increasing the concentration of it (Takeuchi *et al.*, 2000) and as the pH of the medium was above 5, the ionization of the carboxylic acid groups of CP in the complex occurred and led to ionic repulsion that resulted in a more hydrophilic polymer network and contributed to higher water absorption (Bartil *et al.*, 2007).

Effect of molecular weight of CS: Formulas F2, F3 and F6, F7 were prepared utilizing high and medium molecular weight CS, respectively, it was seen that there is no significant difference ($p>0.05$) observed in the dissolution profile of ketoprofen sustained release tablet when changing from high to medium molecular weight CS, this might be due to the fact that a similar portion of CP interacted with chitosan regardless of the molecular weight of chitosan. The result was similar with that observed in the release of theophylline from extended-release matrix tablet using CS/CP interpolymer complex when CS was changed from medium to high molecular weight (Park *et al.*, 2008).

Effect of temperature of CS acetic acid solution: It was seen that there was a significant retardation ($p<0.05$) in the release when the solution of CS acetic acid was cooled to 8°C, since the viscosity of CS solution increased with decreasing the temperature (Shaji *et al.*, 2010) and the viscosity of CS in solution exhibit typical polyelectrolytic behaviors, the specific viscosity increases

with protonation of amine group in the pH range (1-6) due to the increased effective volume of the molecule by the charge repulsion (Park *et al.*, 1983) so that the protonation of amine groups increased leading to increase the electrostatic interaction with carboxyl groups of CP and stronger PEC was formed so that a retardation in the release was observed.

Effect of amount of PEC used: The release of ketoprofen from F10 was significantly ($p<0.05$) higher than that from F4 as seen in Fig. 10. This difference was due to the less amount of PEC in F10 that result in less amount of ketoprofen incorporated in the complex so rapid release occur in comparison with F4. regardless of the excepients type used, the same effect was seen in the release of ranitidine HCl or Sinomenine HCl from matrix tablets containing (CS/ polycarbophil) PEC when different amounts of PEC was utilized (Lu *et al.*, 2008b).

On the other hand the higher amount of lactose in F10 than in F4 resulted in the formation of more micro-cavities in polymer matrices because of water-soluble and hydrophilic nature of lactose so it acts as a channeling agent by rapidly dissolving and easily diffusing outward, therefore, decreasing tortuosity and/or increasing the matrix porosity (John *et al.*, 2010). Therefore, the release of ketoprofen from F10 was faster than that in F4.

Determination of the release kinetics: Table 3 shows that n values of F1, F2, F3, F4, F6, F7 and F9 are more than 0.89 indicating super case II transport (Vueba *et al.*, 2004), where the drug release involves polymer relaxation and chain disentanglement (El-Samaligy *et al.*, 2004) which suggest that the availability of free drug molecules able to diffuse remains constant over time producing the zero order observed (Jimenez-Kairuz *et al.*, 2005). While F5 and F10 have n value between 0.45 to 0.89 indicating anomalous (non-Fickian) transport which refers to a combination of both diffusion and erosion controlled-drug release (Islam *et al.*, 2008).

In F5 the n value decreased in comparison with F1-F4 indicating that the release of drug was shifted from swelling controlled in F1-F4 to a combination of both diffusion and erosion controlled-drug release in F5.

Cooling of CS acetic acid solution to 8°C during the preparation of PEC that used in F9 lead to increasing n value to 1.0726 in comparison with F5 (n = 0.7205) when the temperature of CS acetic acid solution was 25°C pointing that the release of drug was shifted from a combination of both diffusion and erosion controlled to swelling controlled -drug release.

It was seen that n value decreased as the amount of PEC powder decreased in the formula (Lu *et al.*, 2008b). As in F4 when n=1.3643 while in F10 n = 0.6261 indicating that the release of drug was shifted from swelling controlled to a combination of both diffusion and erosion controlled-drug release.

Formulas F1, F2, F3, F4, F6, F7, F8 and F9 exhibit a good fitness to zero-order model. While F5 and F10 show a better fitness to Korsmeyer-Peppas model.

CONCLUSION

Ketoprofen can be formulated as an oral sustained release tablet using PEC as a matrix former resulting in less frequent dosing and less gastrointestinal disturbance. The release rate retarded with increasing the strength of PEC till reaching the strongest one, beyond that the increasing in the amount of CP showed pH dependant release resulted in faster release rate. The release mechanism was described mainly by super case II transport (swelling controlled) that shifted to anomalous (non-Fickian) transport on decreasing the amount of PEC powder in the formula or increasing the temperature of CS acetic acid solution during preparation of PEC or using 1:4 ratio of (CS:CP).

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