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ORIGINAL ARTICLE

Synthesis and evaluation of chitosan-*graft*-poly (2-hydroxyethyl methacrylate-*co*-itaconic acid) as a drug carrier for controlled release of tramadol hydrochloride

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Abstract Chitosan-*graft*-poly (2-hydroxyethyl methacrylate-*co*-itaconic acid) has been synthesized for different feed ratios of 2-hydroxyethyl methacrylate and itaconic acid and characterized by FT-IR, thermogravimetry and swelling in simulated biological fluids (SBF) and evaluated as a drug carrier with model drug, tramadol hydrochloride (TRM). Grafting decreased the thermal stability of chitosan. FT-IR spectra of tablet did not reveal any molecular level (i.e. at <10 nm scale) drug–polymer interaction. But differential scanning calorimetric studies indicated a probable drug–polymer interaction at a scale >100 nm level. The observed Korsmeyer–Peppas's power law exponents (0.19–1.21) for the *in vitro* release profiles of TRM in SBF and other drugs such as 5-fluorouracil (FU), paracetamol (PCM) and vanlafaxine hydrochloride (VNF) with the copolymer carriers revealed an anomalous drug release mechanism. The decreased release rates for the grafted chitosan and the enhanced release rate for the grafts with increasing itaconic acid content in the feed were more likely attributed to the enhanced drug–matrix interaction and polymer–SBF interactions,

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respectively. The different release profiles of FU, PCM, TRM and VNF with the copolymer matrix are attributed to the different chemical structures of drugs. The above features suggest the graft copolymer's candidature for use as a promising oral drug delivery system.

1. Introduction

Chitosan a biopolymer derived from chitin, the most abundant natural biopolymer next to the cellulose, is inherently biocompatible (Koide, 1998), biodegradable (Ravi Kumar, 2000; Ravi Kumar et al., 2004) and antimicrobial (Koide, 1998). Hence, it is a widely opted candidate for investigating its medical applications such as drug delivery, wound dressing, etc., after suitable modifications (Zohuriaan-Mehr, 2005; Yang et al., 2008; Bhattarai et al., 2010). But its poor physical properties such as high brittleness and poor solubility require improvement to widen its medical applications particularly in drug delivery, as a carrier matrix. Many chemical and biochemical routes have been reported to modify chitosan to improve the aforesaid properties (Mino and Kaizerman, 1958; Berlin and Kislenko, 1992; Jenkins and Hudson, 2001; Jayakumar et al., 2005; Hou et al., 2010; Chen et al., 2011). Among these grafting of chitosan by graft copolymerization using biocompatible and other synthetic vinyl monomers is one of the most effective methods widely employed to incorporate desirable properties into chitosan without sacrificing its biodegradable nature. Chitosan grafting using single vinyl monomers for drug delivery and other applications has been well studied (Singh and Ray, 1994; Kweon and Kang, 1999; Kumbar et al., 2003; Kumbar and Aminabhavi, 2003; El-Sherbiny et al., 2006; Guo et al., 2008; Patel et al., 2010). But only limited studies have been made on chitosan grafting with two monomers for drug delivery applications. The hydrophobicity and hydrophilicity of the carrier contribute a lot in controlling the drug release characteristics apart from its flexibility. Hence, the present investigation is focused on the chitosan grafting using the hydrophilic itaconic acid (IA) and the comparatively more hydrophobic 2-hydroxyethyl methacrylate (HEMA) as comonomers and evaluation of the resulted chitosan grafts as a tunable drug carrier with tramadol hydrochloride (TRM), an opioid analgesic as a model drug. HEMA and IA were the preferred comonomers for grafting on the ground that they do not display any cell toxicity and hemolytic activity and possess good resistance toward penetration of microbes (Tomic et al., 2010). In addition to this introduction of itaconic acid through grafting on the surface of chitosan may impart pH sensitive swelling behavior because when the acid groups are ionized, the coiled chains extend dramatically responding to the electrostatic repulsions of the generated charges with increased uptake of solvent in the network. Moreover, the polymer–polymer and the polymer–solvent interactions show an abrupt re-adjustment in small ranges of pH and this is translated to a chain transition between extended and compacted coil states (Peppas et al., 2000). By introducing hydrophilic IA and comparatively more hydrophobic HEMA as comonomers in the graft, the hydrophobic–hydrophilic balance in the graft copolymer structure and their interactions between the polymeric chains and the aqueous media can be altered to control and achieve the desirable drug release characteristics.

2. Experimental

2.1. Materials

Chitosan (CTS, low density, 80–85% deacetylated), inherent viscosity 12.2 dL/g in 0.1 M HOAc at 30 °C) was purchased from Kerala State Co-operative Federation for Fisheries Development Ltd. and used after purification by reprecipitation. 2-Hydroxyethyl methacrylate (HEMA, Sigma–aldrich) was purified by column chromatography on activated silica gel just before use. Itaconic acid (IA, Himedia) was recrystallized from dry methanol and dried under vacuum at 50 ° for 4 h and used. Potassium persulfate (KPS, Nice Chemicals) was recrystallized with distilled water and dried. Sodium chloride, hydrochloric acid (Rankem), pepsin (Loba), anhydrous disodium hydrogen orthophosphate and sodium dihydrogen orthophosphate (Qualigens), potassium bromide (KBr, Merck), methanol and acetone (SRL, India) were used as received. Paracetamol (PCM, analgesic and antipyretic), tramadol hydrochloride (TRM, opioid analgesic) and venlafaxine hydrochloride (VNF, antidepressant), were kindly gifted by SPIC Pharma, Chennai. 5-Fluorouracil (FU, anticancer, >99% Himedia) was used as purchased. The structures of the drugs and monomers are given in Fig. 1. Simulated gastric fluid (SGF, pH 1.2) and phosphate buffer solution (simulated intestinal fluid, SIF, pH 7.2) were prepared as per United States pharmacopeia.

2.2. Synthesis of chitosan-graft-poly (2-hydroxyethyl methacrylate-co-itaconic acid) [CTS-graft-poly (HEMA-co-IA)]

Graft copolymerization was performed using 50 ml of polymerization recipes containing constant amounts of CTS (1 g), HEMA (0.5 g), KPS (0.025 g) and varying amounts of IA viz., 0.1 g (CHI-1), 0.2 g (CHI-2), 0.3 g (CHI-3), 0.5 g (CHI-5) and 1.0 g (CHI-10). In a typical grafting experiment, 1 g of CTS was dissolved in 50 ml of distilled water containing 0.5 g of IA by continuous stirring at room temperature in a four necked round bottom flask equipped with mechanical stirrer, reflux condenser, thermometer and nitrogen gas inlet. After complete dissolution, the temperature was raised to 70 °C, and 0.5 g of inhibitor freed HEMA was added immediately with the simultaneous addition of 25 mg of KPS initiator as a solution in 10 ml of distilled water. The reaction mixture was stirred continuously for another 8 h at 70 °C under nitrogen. This resulted in a grafted copolymer as a reaction mixture with a highly swollen viscous solution form. Hence, poly (2-hydroxylethyl methacrylate) which is insoluble and non-swellable in aqueous acetic acid may not be formed through homopolymerization of HEMA. After precipitation of the copolymer from the grafted reaction mixture using ice cold acetone, the graft copolymer separated becomes insoluble in aqueous acetic acid but swellable. Hence, repeated washing

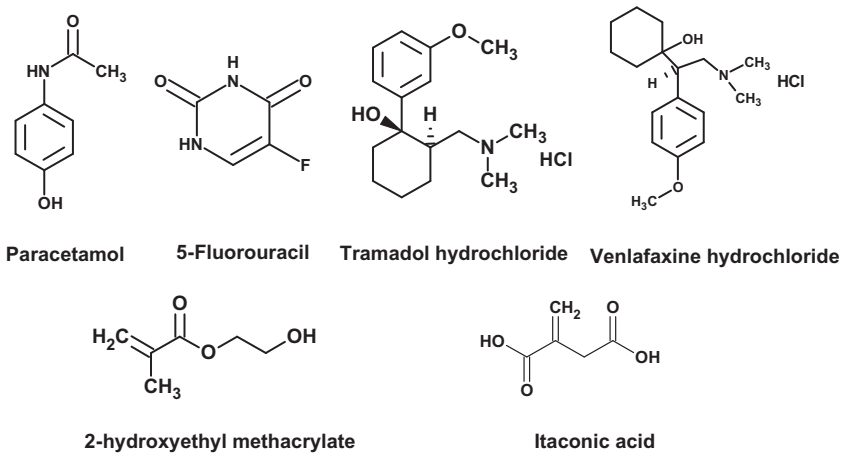

Figure 1 Chemical structure of drugs and monomers.

with 1% aqueous acetic acid was done to remove the unreacted chitosan and the homopolymer poly(itaconic acid). The graft copolymer obtained was also soxhlet extracted with methanol–water (1:2) to remove unreacted monomers and other soluble impurities if any. The purified polymer was dried under vacuum at 60 °C for 24 h. The grafting percentage (GP) for the graft copolymerization was calculated using the equation

$$GP = [(W_g - W_0)/W_0] \times 100$$

where, W_g and W_0 denote the weights of graft copolymer obtained and CTS taken for the grafting experiment, respectively.

A blank experiment was also conducted for grafting on chitosan without the monomers under the same experimental conditions of grafting and >99% of the chitosan was recovered after the blank reaction. Hence, degradation of chitosan during the grafting may not be significant and may be neglected.

3. Characterization

3.1. Fourier transform-infrared (FT-IR) spectroscopy

FT-IR spectra of CTS and CTS-*graft*-poly(HEMA-*co*- IA) were recorded on KBr pellet for the spectral range 400–4000 cm^{-1} using Shimadzu FT-IR-8400S at a resolution of 2 cm^{-1} with number of scans 48.

3.2. Thermogravimetry & derivative thermo gravimetry (TG & DTG)

TG/DTG studies were performed on TGA Q500 V20.10 Build 36 with a sample size of 1.5–3.5 mg under nitrogen atmosphere at a heating rate of 10 °C/min for the temperature range from ambient to 800 °C.

3.3. Tablet preparation

The dried graft copolymer and CTS were finely powdered using a mortar and pestle and sieved through No. 10XXX mesh (mesh size: 150). In a typical tablet (2.5 mm thickness and 13 mm diameter) formulation exactly 200 mg of graft copolymer was loaded with 35 mg of TRM by mixing and grinding in a mortar and pestle to ensure homogeneity and then compressed using a KBr press (Techno Search M15) at 5 ton pressure. The prepared tablets were also weighed using a five decimal electronic balance (Mettler Toledo AB265-S). A pure copolymer pellet of the above dimensions was also fabricated similarly without drugs for swelling studies.

3.4. Swelling studies

Swelling studies were performed in both SGF and SIF (PBS) at 37 °C on copolymer pellets (100 mg, 2.55 mm thickness and 13 mm diameter). The pellet was kept in a stainless-steel (SS) cylindrical mesh (30 mm diameter; 50 mm height) immersed in 20 ml of SGF or SIF taken in a 25 ml beaker and allowed to swell. The weights of the swelled copolymers at predetermined time intervals were calculated after wiping the mesh containing the swelled polymer with a tissue paper. Then a graph was drawn between the degree of swelling ($=(W_t - W_0)/W_0$) and time, where W_t and W_0 are the weights of the polymer after and before swelling, respectively.

3.5. Differential scanning calorimetry (DSC)

DSC thermograms of FU and TRM drugs and their tablets were recorded on Perkin Elmer Pyris 6DSC model in nitrogen atmosphere at a heating rate of 10 °C per minute. The samples (4–5 mg) were subjected to repeated heating and cooling cycles between room temperature and 175 °to remove the previous thermal history of the sample if any before recording the final thermogram up to 300 °C.

3.6. UV–Visible spectrophotometer

UV spectra of the pure drug solution and the drug released from the tablet in drug dissolution studies were recorded on Perkin Elmer Lamda 35 UV–VIS spectrophotometer (UVWINLAB software). The drugs PCM, FU, VNF and TRM were estimated in drug release studies by measuring their absorbances at their λ_{max} values of 243 nm (Kwakye and Fell, 2003), 266 nm (Huang et al., 2010), 274 nm (Obaidat and Obaidat, 2001) and 271 nm (Shan et al., 2009), respectively.

3.7. In vitro drug dissolution study

In vitro drug dissolution studies were performed in an USP apparatus Type II (Veego Model VDA-6DR) in SGF and SIF (Shantha et al., 1995) at 37 °C by embarking the compressed tablet inside the rotating (50 RPM) SS basket immersed in a thermostated biological fluid. The tablets maintain their integrity and shape during swelling for a period of time >2 h. The amount of drug released was estimated UV-spectrophotometrically by withdrawing aliquots of sample from the drug release vessel at different known time intervals and measuring their absorbance values at 271 nm (Tiwari et al., 2003; Shan et al., 2009). An average of three identical experiments was taken to determine the amount of drug released for a given set of experimental conditions. To maintain constant volume of the experimental solution a volume equivalent of aliquot sample as incubated fresh fluids was added to the solution after each withdrawal.

4. Results and discussion

4.1. Mechanism of graft copolymerization on chitosan

The proposed mechanism for the radical graft copolymerization of HEMA and IA at the reported grafting site (Lv et al., 2009) on CTS is shown in Fig. 2. Since for the increased concentration of HEMA at fixed concentrations of CTS and IA in the monomer feed, the copolymer formed are brittle and the tablet fabrication was difficult as it breaks, in the present study graft copolymers were synthesized with fixed CTS and HEMA concentrations with varying concentrations of IA. The percentages of grafting obtained for varying IA content in the feed depicted in Fig. 3 indicates that graft copolymer yield increases only marginally with increasing IA concentration due to lower reactivity ratio of IA compared to HEMA (Cowie et al., 2000). The disproportionate yield of the graft copolymer with increasing concentration IA may also be attributed to the decreased adsorption of IA monomer on the copolymer with increasing IA concentration as reported in the copolymerization of HEMA and IA (Cowie et al.,

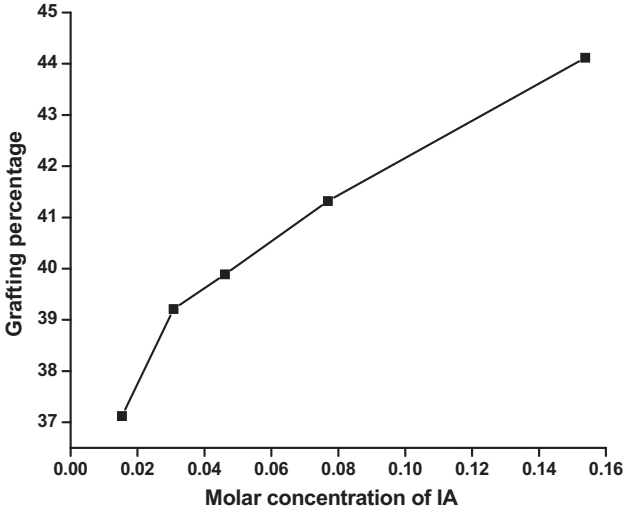

Figure 3 Variation of graft copolymer yield (%) with IA concentration in the feed.

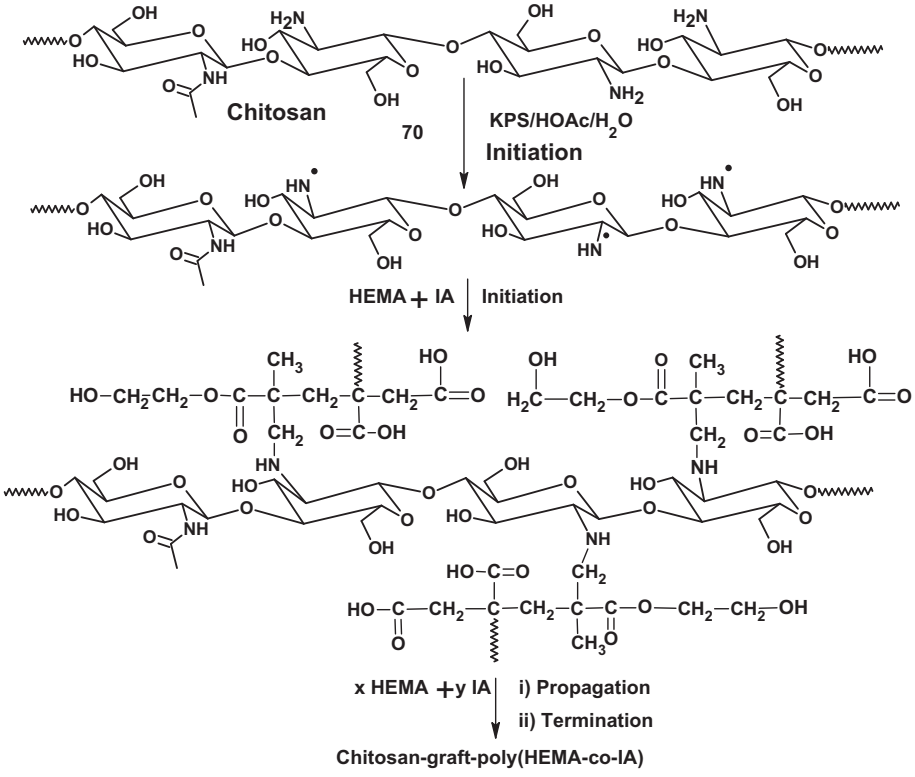

Figure 2 Mechanism for radical graft copolymerization on chitosan.

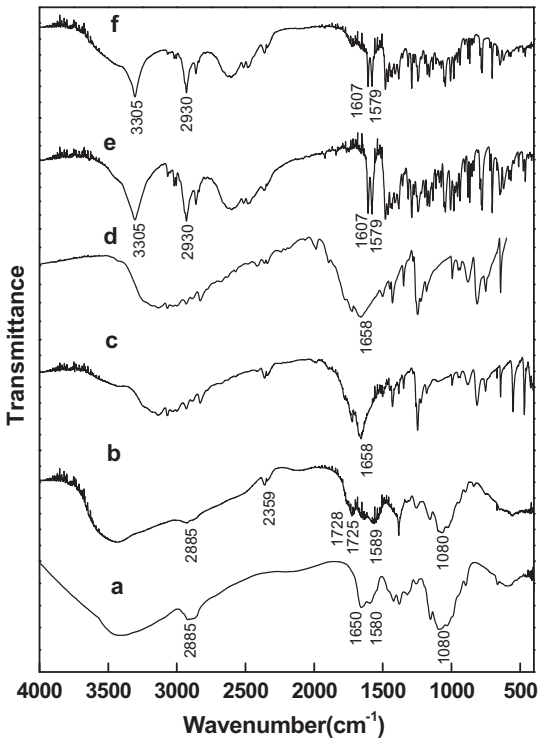

Figure 4 FT-IR Spectra of (a) CTS, (b) CTS-graft-poly (HEMA-co-IA), (c) FU, (d) FU, tablet, (e) TRM and (f) TRM tablet.

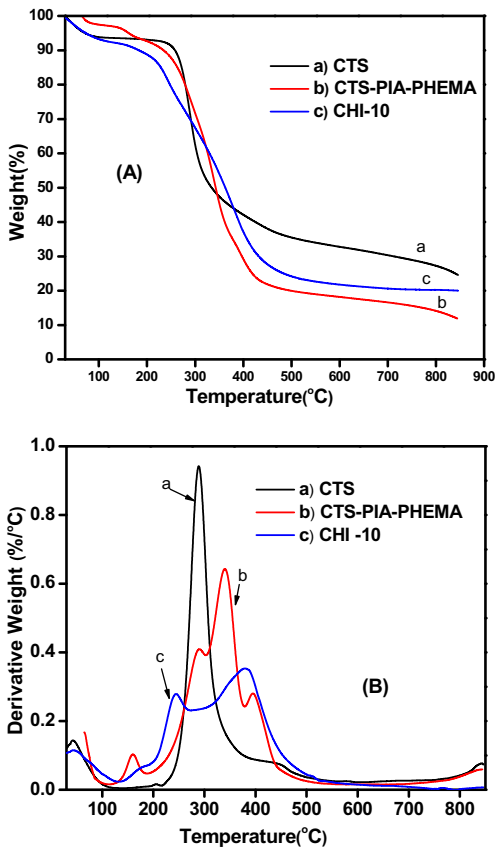

Figure 5 TG (A) and DTG (B) traces for (a) CTS, (b) CTS-graft-poly (HEMA-co-IA), and (c) CTS–PHEMA–PIA blend.

2000). The % graft yields were calculated by taking the average of three grafting yields obtained under identical conditions for each composition and were in the range 60–80% depending on the % composition of monomers and chitosan. Since the graft copolymer is insoluble in most of the common organic solvents, its molecular weight or inherent viscosity and its NMR spectra could not be studied in the present study. But the graft copolymer swells in aqueous acetic acid.

4.2. Characterization

4.2.1. FT-IR spectroscopy

The FT-IR spectra of CTS and its graft copolymer showed (Fig. 4) a broad absorption band in the range 3000–3500 cm^{-1} attributed to O–H stretching vibrations. The peaks around 2885, 1650, 1589, 1326 and 1080 cm^{-1} in the FT-IR spectrum of CTS shown in Fig. 4a are due to the stretching vibrations of aliphatic C–H, Amide I (–NH deformation of $–NHCOCH_3$), Amide II, Amide III (Miya et al., 1980; Sugama and Cook, 2000) and C–O–C, bonds, respectively. These are characteristics of the CTS polysaccharide (Radhakumary et al., 2003). Similarly the peaks observed around 2885, 1558 and 1080 cm^{-1}, in the FT-IR spectrum of the CTS-*graft*-poly (HEMA-*co*-IA) (Fig. 4b) are attributed to the stretching vibrations of aliphatic C–H, Amide I (C = O stretch of amide group), and C–O–C, respectively. The peak around 1725 cm^{-1} was assigned to the carbonyl groups of HEMA and IA. This peak together with the broadening of the –OH stretching peak around 3430 cm^{-1} confirmed the grafting of these monomers on CTS. Since the carbonyl groups in PHEMA and PIA absorb very closely around 1725 and 1728 cm^{-1}, respectively (Ferreira et al., 2000; Sugama and Cook, 2000) in CTS-*graft*-poly (IA-*co*-HEMA), these peaks overlapped and appeared as a single peak (Fig. 4b) due to overlapping. Analysis of FT-IR spectra of FU and TRM tablets (Fig. 4d and f) do not reveal any significant polymer–drug interaction at molecular level i.e., at < 20 nm scale in the solid state.

4.2.2. TG and DTG

TG and DTG thermograms of CTS and CTS-*graft*-poly (HEMA-*co*-IA) recorded in nitrogen atmosphere are displayed in Fig. 5A and B, respectively. The weight losses around 100 °C in CTS and CTS-*graft*-poly (HEMA-*co*-IA) are attributed to loss of moisture and other volatile impurities. The TG/DTG of graft copolymer displayed three step degradation in the temperature range 150–600 °. The weight loss in the temperature range 250–400 °C with maximum weight loss around 289 °C (51.34%) is attributed to chitosan back bone degradation, a complex process including dehydration of the saccharide rings, depolymerization with the formation of water, CO_2 and CH_4 (Isiklan et al., 2010). The weight loss around 170 °C is more likely attributed to degradation of poly (IA-*co*-HEMA) fragment on the CTS back bone with terminal double bonds. The weight losses observed around 280 and 380 °C are due to onset degradations of CTS moiety, and poly (IA-*co*-HEMA) residue with saturated terminal ends and CTS moiety, respectively. A degradation step noticed around 430 °C in CTS not seen in the copolymer and the observed residual weights of 8.1% and 1.6% at 830 °C in the TG traces of CTS and CTS-*graft*-poly (HEMA-*co*-IA), respectively, col-

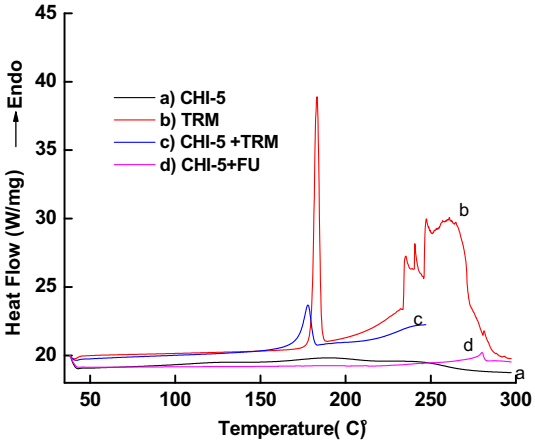

Figure 6 DSC thermograms for (a) CTS-graft-poly (HEMA-co-IA, (b) TRM, (c) TRM, tablet and (d) FU tablet.

lectively reveals that the graft copolymer with a decreased thermal stability degrades faster (Naguib,2002; Isiklan et al., 2010) compared to CTS. This was also corroborated by the residual mass of 7.1% at 830 °C in the TG traces of the polymer blend of PIA, PHEMA and CTS (Fig. 5A and B(b)). The degradation behavior of the blend, CTS and the graft copolymer are quite different indicating that the TG traces of graft copolymer displayed is not a physical mixture of CTS and the homopolymers. Different thermal degradation behavior of the graft copolymer compared to that of the blend also revealed that the grafting had occurred.

4.2.3. DSC

Typical DSC traces for TRM and FU tablets are displayed in Fig. 6. It is reported (Argin-Soysal et al., 2009) that the glass transition temperature (T_g) for CTS was in the range 146–150 °C. T_g of CTS-*graft*-poly (HEMA-*co*-IA) was not visible in the DSC. But the melting endothermic peaks of the drugs in the matrix are quite visible. The melting points of pure drugs TRM and FU determined by DSC were 183.25 and 288.77 °C (Singh et al., 2009), respectively. But in the tablets they were reduced to 177.77 and 280.14 °C, respectively. Moreover, the narrow melting endothermic peaks of the pure drugs become broadened at the base of the peak with a reduction in the onset of melting temperature (Fig. 6b and c). This tend to imply the existence of weak interaction of the drug with the matrix at a scale > 100 nm (Cheung et al., 2000; Manley, 1998).

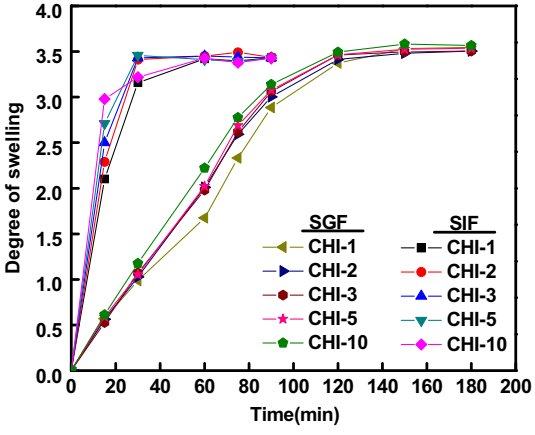

Figure 7 Degree of swelling of graft copolymer in SGF and SIF at 37 °C.

4.2.4. In vitro swelling studies

The ability of a drug carrier to preserve water is an important aspect to be investigated for drug delivery applications. To evaluate this effect, swelling studies were carried out with CTS and CTS-*graft*-poly (HEMA-*co*-IA) in SGF and SIF at 37 °C. The degree of swelling in SGF and SIF for CTS-*graft*-poly (HEMA-*co*-IA) polymers (CHI-1, CHI-2, CHI-3, CHI-5 and CHI-10) prepared with increasing concentrations of IA for fixed concentrations of CTS and HEMA are given in Fig. 7. The degree of swelling was significantly different in SGF and SIF for a matrix of typical composition. In SIF, the rate of swelling is more than that in SGF, and it attains the equilibrium value within 45 min. But in SGF the equilibrium swelling rate was attained only after 160 min. The greater extent of swelling in SIF compared to that in SGF may be more likely due to enhanced hydrogen bonding between CTS-*graft*-poly (HEMA-*co*-IA) and SIF through the formation of carboxylate anion (–COO^-). This may also be due to

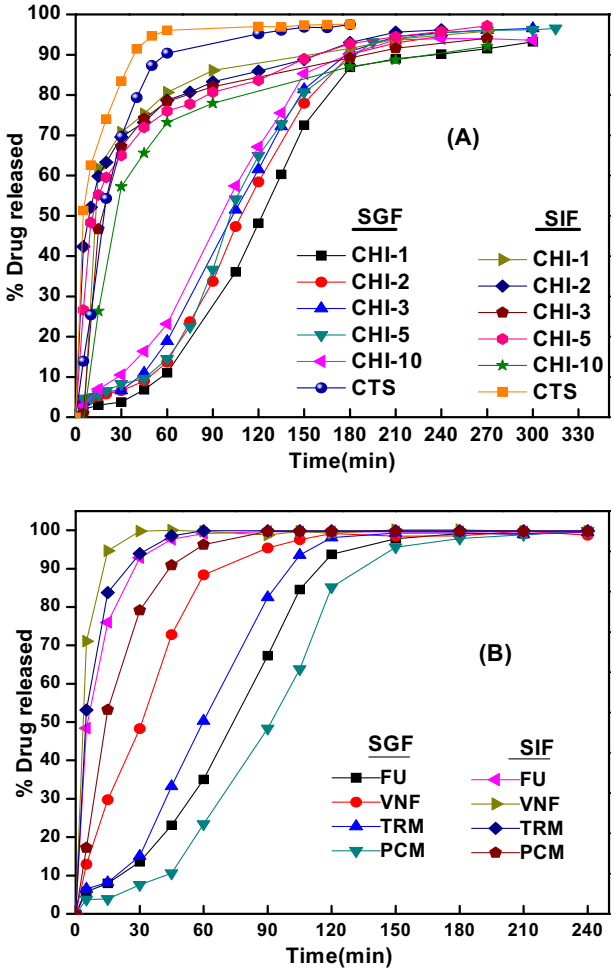

Figure 8 Release profiles of model drug TRM (A) and of FU, PCM, TRM and VNF, drugs (B) in SGF and SIF at 37 °C, with graft copolymer carriers.

lesser amount of free water molecules in SGF because of the localization of water on pepsin by secondary bond forces. At acidic pH < 2 the majority of the base and acid groups exist in $-NH_3^+$ and $-COO^-$ or $-NH_2$ and –COOH forms, and therefore ionic interaction of $-NH_3^+$ and $-COO^-$ species and hydrogen bonding between amine and carboxylic acid lead to decreased swelling for samples with lower IA content. For pH values > 7 swelling of the gels may increase again due to the dissociation of ionic cross linking and the repulsive interaction between negatively charged carboxylic groups (Milosavljevic et al., 2011). But the initial fluid uptake was rapid in both the fluids due to H-bonding interaction via the carboxylic acid. This was also supported by the marginal increase in the degree of swelling in both the fluids with increased concentration of IA in the copolymer.

4.2.5. In vitro drug dissolution study

The drug tablets were fabricated as discussed earlier (Section 3.3) and placed in the baskets of tablet dissolution test apparatus vessels containing biological medium and the amount of drug released was estimated as discussed earlier and the typical *in vitro* drug release profiles observed for TRM tablets are displayed in Fig. 8A for CTS-*graft*-poly (HEMA-*co*-IA) matrices synthesized with various concentrations of IA in the feed. Both in SIF and SGF the drug release rate was greater for pure CTS than that observed for grafted CTS. This was attributed to the burst release of the drugs due to tablet breaking after immersing in biofluids. For the same drug, the release rate is more in SIF than in SGF (Fig. 8A). This is more likely attributed to the greater degree of swelling of the matrix in SIF than in SGF. But grafting decreased the drug release in both the fluids. This is more likely attributed to the enhanced drug–polymer interaction through H-bonding between –COOH and –OH groups of CTS-*graft*-poly (HEMA-*co*-IA) and –OH group of the drug as supported by DSC (Fig. 6). With CTS as carrier, 80–85% of drug was released in SIF for the initial 30 min and this decreased to 60% with CTS-*graft*-poly (IA-*co*-HEMA matrix. But in SGF these figures were 70% and 10%, respectively. It took roughly 120 min for 60% release of drug in SGF. As in the case of swelling studies, increased concentration of IA in the feed increased the drug release rate with the corresponding copolymer matrix as carrier perhaps due to enhanced swelling and hence increased diffusion of dissolved drug TRM which is highly water soluble. Increasing the IA content in polymer will facilitate enhanced fluid-polymer interaction through H-bonding during swelling. In SIF, the carboxylic groups of the side chains will be in the ionized state and it opens up the structure. On the contrary, the CTS could be in the precipitated condition. These opposing factors will have a net effect on the release of the incorporated drug from the tablets.

Comparison of the typical release profiles of FU, PCM, TRM and VNF in the copolymer carrier of a typical composition demonstrated (Fig. 8B) the influence of chemical structures of drugs on their release kinetics. The release rates for these drugs in SGF and SIF were in the order, VNF > TRM > FU > PCM both in SIF and SGF. The higher release rates for the drugs VNF and TRM which are bulkier than FU and PCM may be attributed to their higher solubilities in aqueous medium. The lowest release rate for PCM is more likely attributed to the drug–matrix interaction through H-bonding in the swollen tablet involving phenolic –OH of PCM and its lower water solubility.

4.2.6. Drug release mechanism

To understand and analyze the *in vitro drug* release profile and mechanism from a matrix tablet the Korsmeyer–Peppas's equation (Korsmeyer et al., 1986; Ritger and Peppas, 1987) viz.,

$$M_t/M_\infty = kt^n$$

where M_t/M_∞ is the fractional release of drug at time 't' or fractional uptake of fluid in swelling in the absence of drug (M_t and M_∞, amounts of drugs released or fluid absorbed at time 't' and at equilibrium, respectively) was used. According to Peppas the above equation could adequately describe the release of solutes from slabs, spheres, cylinders and disks, regardless of the release mechanism. The slope of the linear plot $\log M_t/M_\infty$ versus $\log t$, for drug release < 50% gives the power law exponent (n) value. The equation is physically realistic for $n = 0.5$ (pure diffusion-Fickian controlled drug release) and $n = 1$ (swelling-controlled drug release or Case II transport: non-Fickian). For other values of 'n' anomalous transport kinetics, i.e. a combined mechanism of pure diffusion and Case II transport will be operating. The observed 'n' values for typical release profiles of FU, TRM, PCM and VNF were < 0.5, > 0.5 and > 1.0. These ranges of 'n' values indicate a combined mechanism of pure diffusion and non-Fickian (Case II transport) for the drug release with the grafted chitosan matrix both in SGF and SIF. This tend to imply that the driving force for the fluid penetration and drug release is a combination of concentration gradient(Fickian) and polymer relaxation (non-Fickian) as a result of thermodynamic interaction of the solvent with the polymer. The same drug release mechanism was implicated with virgin CTS as a carrier also. This mechanism may also be partly due to the weak physical interaction of the polymer matrix with drug at scales > 100 nm as indicated by the DSC studies on the tablet and the drug.

5. Conclusions

CTS-*graft*-poly (HEMA-*co*-IA) hitherto unreported has been synthesized and characterized for using it as a carrier for oral drug delivery using TRM as a model drug. Grafting decreased the thermal stability of CTS. The drug release rate was greater in SIF than in SGF due to enhanced matrix swelling in SIF, and lower with CTS-*graft*-poly (HEMA-*co*-IA) carrier compared to CTS. In SGF the initial drug release rate was sluggish but started increasing rapidly after 40 min due to increased segmental mobility. Increasing the concentration of IA in the monomer feed enhanced the drug release rate with the corresponding grafted chitosan as carriers due to enhanced polymer–biofluid interaction. For a graft copolymer of specific composition the release rates of VNF, TRM, FU and PCM follows the order VNF > TRM > FU > PCM both in SIF and SGF implying the influence of chemical structures of drugs on their release rate. The higher release rates for VNF and TRM may be attributed to their higher solubilities in SBF. The lowest release rate for PCM is more likely attributed to the drug–matrix interaction through H-bonding and its lower water solubility. The observed values (0.5–2.2) of power law exponents indicated a mixed pure diffusion and non-Fickian mechanisms for drug release in simulated biological fluids. The above features suggest that the graft copolymer can be used as a promising matrix candidate for oral drug delivery system by fine tuning its composition and pH of the simulated biological fluids.

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