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Formulation of sustained release matrix tablet using Chitosan/Ghatti gum polyelectrolyte complex

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ABSTRACT

Chitosan/ghatti gum polyelectrolyte complexes were synthesized using different proportions of chitosan (CH) and ghatti gum (GG). The optimum CH: GG ratio was 20:80, which produced highest product yield. Polyelectrolyte (PEC) samples were characterized by differential scanning calorimetry (DSC) and FT-IR spectroscopy. Matrix tablets using PEC as matrix and Diltiazem Hcl as a model drug were formulated by wet granulation technique. The matrix tablets were evaluated for pharmacotechnical properties, in vitro release and release data analysis. FT-IR studies confirmed that PEC formed a complex through an electrostatic interaction between the NH_3^+ groups of CH and the carboxylate (COO-) group of ghatti gum. In vitro drug release results showed that, the optimum formulation showed controlled release for more than 12hrs. The drug release from this tablet showed a pH-independent release profile and the release profile of Diltiazem Hcl from the respective tablets followed first order kinetics and the mechanism follows non-fickian (anamolous) transport. The results of the present study indicated that polyelectrolyte complex of CH and GG can be used as an effective matrix former to extend the release of the Diltiazem Hcl.

Keywords: Chitosan; Ghatti gum; Polyelectrolyte complex; Dilitiazem hydrochloride; Sustained release.

INTRODUCTION

Polyelectrolyte complexes (PECs) are the association complexes formed between oppositely charged particles (e.g. polymer-polymer, polymer-drug and polymer-drug-polymer). These are formed due to electrostatic interaction between oppositely charged polyions which avoids the use

of covalent cross linkers. In general, these polymeric networks are well tolerated, biocompatible and are more sensitive to changes in environmental conditions [1, 2].

Chitosan is a deacetylated derivative of chitin, which is a naturally occurring polysaccharide comprising copolymers of glucosamine and N-acetylglucosamine. Chitosan is biocompatible and biodegradable cationic polymer which is most widely used due to its reduced toxicity and better patient compliance. The cationic amino groups on the C2 position of the repeating glucopyranose units of chitosan can interact electrostatically with the anionic groups (usually carboxylic acid groups) of other polyions to form polyelectrolyte complexes. Many different polyions from natural origin (e.g. pectin, alginate, carrageenan, xanthan gum, carboxymethyl cellulose, chondroitin sulphate, dextran sulphate, hyaluronic acid) or synthetic origin (e.g. poly (acrylic acid)), polyphosphoric acid, poly(L-lactide) have been used to form polyelectrolyte complexes with chitosan in order to provide the required physiochemical properties for the design of specific drug delivery systems [2].

Ghatti gum is a gummy exudation from the stem of Anogeissus latifolia, belonging to the family *Combretaceae*. It is a complex water soluble polysaccharide, occurs in nature as a calcium-magnesium salt. It is composed of L-arabinose, D-galactose, D-mannose , D-xylose ,and D-glucuronic acid in a molar ratio of 10:6:2:1:2 with traces of 6-deoxyhexose. The fact that the gum is naturally available, inexpensive and non-toxic has also fostered the interest in developing the gum for pharmaceutical use. Ghatti gum is approved for food use and is in the GRAS (Generally Recognized as Safe) list under the food and Drug Act (US-FDA).

Diltiazem hydrochloride (DTZ) is a calcium channel blocker that is widely prescribed for the treatment of hypertension and angina. However, its bioavailability is 30 to 40 % owing to first pass metabolism and has an elimination half-life of 3.5 h. Therefore, DTZ requires multiple daily drug dosage in order to maintain adequate plasma concentrations, is thus a suitable model candidate for sustained drug delivery [3].

Chitosan shows high solubility in acidic pH because of which it shows burst effect in stomach which is undesirable for formulating a sustained release tablet [4]. This study addresses to overcome this inherent defect of chitosan by preparation of a chitosan/ghatti gum complex and characterization of the synthesized polyelectrolyte complex. Similar works have been reported extensively in literature as method for making chitosan as release retardant polymer. The novelty of the present work is that ghatti gum is being used as an anionic polymer to prepare a PEC which has not been reported justifying in development of PEC between chitosan and ghatti gum.

MATERIALS AND METHODS

Diltiazem hydrochloride (DTZ) were obtained free of charge from Micro Lab Ltd, Bangalore, India. Ghatti gum were purchased from Sigma Aldrich, Steinheim, Germany while talc, magnesium stearate, hydrochloric acid, sodium hydroxide, and potassium dihydrogen phosphate were all obtained from Merck, Mumbai, India and aerosol is obtained from (Aerosil-200, Degussa Corp, Dusseldorf, Germany). All chemicals were either of pharmaceutical or analytical

grades. The reference diltiazem hydrochloride tablet used for the study was Dilzem SR (Torrent Pharma Ltd, India).

Preparation of PECs

CH solution was prepared in 2% v/v acetic acid. Solution of GG was separately prepared by hydrating them in distilled water. Solution of chitosan in 2% acetic acid was slowly added with stirring into GG aqueous solution to give CH/GG proportions as seen in the table. The complexes were left at room temperature for 12 h and then centrifuged. The solid complexes were washed with distilled water and resulting mixture was poured into petri plates and dried in oven at 40 °C for 24 h. The dried complex was grounded and the powder was passed through a 200-µm sieve and used for further study. The yield was calculated as a percentage of initial polysaccharide content.

Preparation of core tablets

Matrix tablets were prepared by wet granulation method. Drug and IPC complex in the ratio 1: 1.5 were mixed in a mortar and pestle, and the mixture is passed through mesh (No. 44). Granulation was done using a solution of PVP K-30 in sufficient iso-propyl alcohol. The wet mass was passed through mesh No.16. The wet granules were air dried for ~2 hours. The granules were then sized by mesh No.22 and mixed with aerosil (4 mg). Talc and magnesium stearate are added in the ratio of 2:1. Tablets with a total weight of 250±5 mg were compressed using a hydraulic press with a 9-mm diameter with a compressional force of 1.5 tons with a dwell time of 15 seconds.

***In vitro* studies**

The dissolution test were carried out using a USP type I apparatus (model TDT-08l, Electrolab, Mumbai, India) at 100 rpm and 37°C for the first 2 h in simulated gastric condition (0.1NHCl) and later in 900 mL of pH 7.4 phosphate buffer. Five ml of the dissolution samples was withdrawn at regular intervals of time and replaced with an equal volume of drug-free dissolution fluid to maintain sink conditions. The samples were suitably diluted with blank dissolution fluid and analyzed for drug release by UV-visible spectrophotometer at 237 nm [5].

Water uptake and erosion studies

Erosion and water uptake of the tableted formulations was determined under conditions identical to those described for dissolution testing using SGF as a medium. Water uptake and mass loss were determined gravimetrically according to the below mentioned equations Three tablets were used per time point. At the predetermined times, the tablets were lightly patted with tissue paper to remove excess surface water. The swollen weight of tablets was determined(Ts) and then the same tablets were dried in a vacuum oven at 40 °C for 48 h, the remaining dry weight of the tablet (Tf) was determined. The study was carried out in triplicate. Swelling (%) and erosion (%) as calculated using Eq 1 and 2, respectively [6].

Swelling (%) = (Ts – T)/T x 100 ………………………………………………………….. (1)

where Ts is the weight of the swollen tablet and T is the initial of the tablet, i.e., prior to the test.

Erosion (%) = (T – Tf)/Tf x 100 …….. (2)
where T is the initial weight of the tablet and Tf is the weight of the tablet after the erosion test.

FT-IR spectroscopy
FT-IR studies were carried out to evaluate the compatibility of the drug and the polymers used using Shimadzu FTIR 8400S. The pellets were prepared by pressing the sample with KBr.

Thermal analysis
Thermal analysis of samples were carried out with a DSC; Perkin-Elmer, Pyris-1. All thermogravimetric analysis was performed with 2-4 mg of powdered samples in a perforated aluminium pan, under nitrogen atmosphere and heating rate of 10 ^{0}C/min.

Kinetic analysis of dissolution data
To study the mechanism of drug release from the matrix tablets, the release data were fitted to zero-order, first-order, and Higuchi equations. The dissolution data were also fitted to the well-known Korsmeyer exponential equation, which is often used to describe drug release behavior from polymeric systems.

$$Log\left(M_t / M_f\right) = Logk + nLogt \quad \text{..... (3)}$$

The diffusional exponent "n", which is indicative of the mechanism of drug release, was obtained by plotting the log value of percent drug released against log time for each batch according to Eq 3. A value of n = 0.45 indicates Fickian (case I) release; > 0.45 but < 0.89 is non-Fickian (anomalous) release; and > 0.89 indicates super case II type of release. Case II generally refers to the erosion of the polymeric chain and anomalous transport (non-Fickian) refers to a combination of both diffusion and erosion controlled-drug release.

The similarities between two dissolution profiles were assessed by a pair-wise model-independent procedure such as similarity factor (f_2).

$$f_2 = 50Log\left\{\left[1+\frac{1}{n\sum_{n=1}^{n=i}\left(R_t - T_t\right)^2}\right]^{-0.5} \times 100\right\} \quad \text{..... (6)}$$

where n is the number of pull points, R_t is the reference profile at time point t, and T_t is the test profile at the same time point; the value of f_2 should be between 50 and 100. An f_2 value of 100 suggests that the test and reference profiles are identical and, as the value becomes smaller, the dissimilarity between release profiles increases [7].

Statistical analysis
Comparison among the developed formulation and the reference formulation (Dilzem- SR) was made by Student t-test at 95 % level of confidence using GraphPad.Prism.Ver.5.0.4.

RESULTS AND DISCUSSION

General characterization

Polyelectrolyte complex reaction between ghatti gum (GG) and chitosan (CH) can be represented by:

$$GG - COO^- + CH - NH_3^+ \longrightarrow GG - COO^{-+}NH_3 - CH$$

Table 1 shows the product yield of PEC samples when the chitosan-GG ratio increases. The optimum mass ratio was taking at the point where a maximal yield of solid complex was obtained. The maximal yield was obtained when the ratio of CH: GG was 20:80 (w/w). Denuziere et al. [8] shows that the best polyanion – polycation ratio obtained using conductometric and potentiometric titration also correspond to the maximum yield of precipitated PEC. Chavasit and Torres also used the maximum amount of solid complex as the optimum ratio between opposite charged polymers in PEC formation [9].

Table 1: Composition of polyelectrolyte complexes of chitosan (CH) and ghatti gum (GG)

PEC samples	CH: GG weight ratio (%)	Product yield (%)
PEC 1	10:90	27.8
PEC 2	20:80	57.6
PEC 3	30:70	49.7
PEC 4	50:50	38.5
PEC 5	60:40	26.3
PEC 6	90:10	3.4

In vitro drug release and data analysis

The *in-vitro* release studies were carried out for formulations in both acidic and basic media and the release profile is shown in the Fig. 1. The % drug release at the first hour for pure chitosan, ghatti gum and optimum PEC was 14, 33 and 25 % respectively with more than 95 % getting released by end of 8 hrs whereas around 80 % was released in case of PEC. This release pattern was anticipated and can be very well explained based on previous such similar studies. Chitosan has high solubility in pH 1.2 which is due to the free amino groups present in the molecule which become ionized resulting in rapid dissolution with burst effect [10], whereas at alkaline pH also the drug released quickly. This might be due to the poor gel forming ability and easy disintegration characteristics of chitosan as reported [11]. In case of ghatti gum the release observed at 1st hour was higher with slower release in between followed by rapid release later. This pattern of drug release is attributed to the dissolving of the drug present on the tablet surface, gradual swelling followed by rapid erosion which predominates in the later half as observed. In case of the PEC, the drug release was sustained with delay as the time prolonged. This was because it involves formation of new bonds or correction of the distortions of the polymer chains with the resulting difference in electrostatic interactions [1] between the polymer backbone altering the matrix stability and swelling profile of the blend polymer compared to the pure chitosan/ghatti gum accounting for the above release pattern.

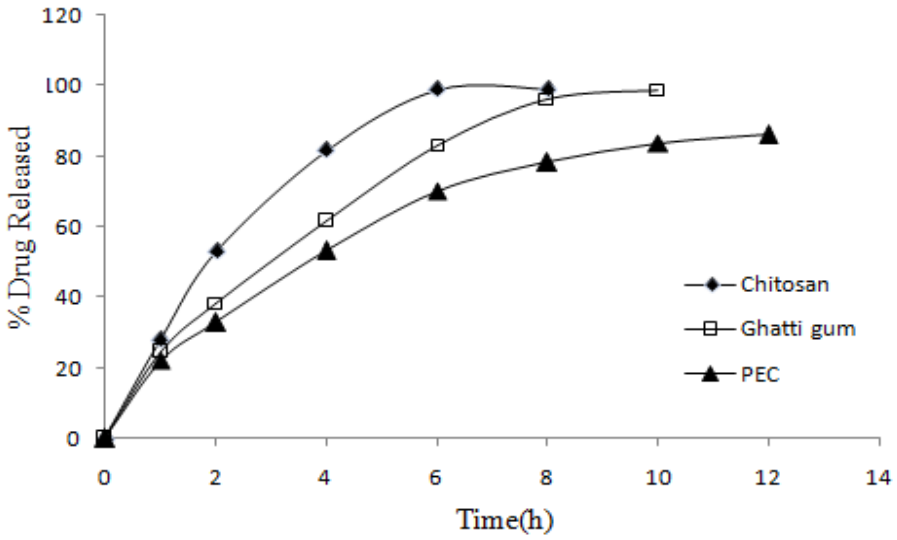

Fig 1: Dissolution profile of formulations
*(**Note**: For A, ♦ =chitosan**;** □ =ghatti gum**;** ▲=PEC**)***

The similarity factor (f_2) was 72.50, suggesting that the dissolution profiles of optimum PEC and standard product, Dilzem SR were very similar.

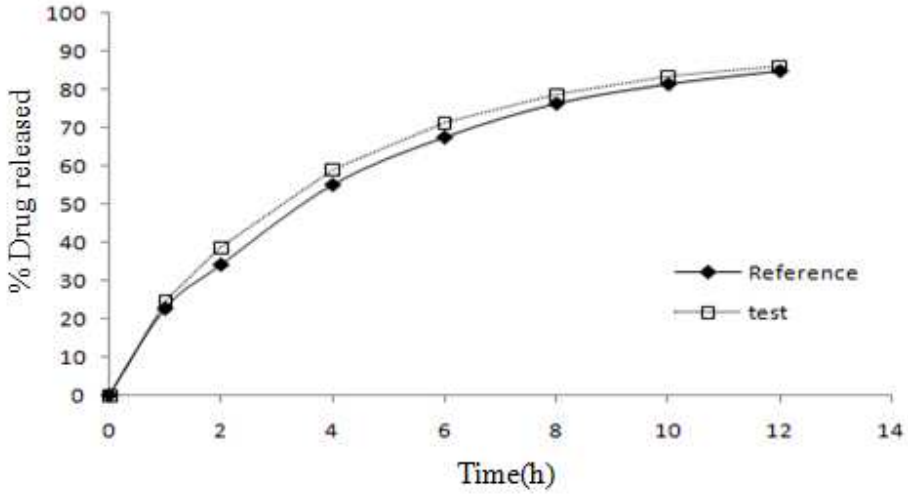

Figure 2: Comparitive in vitro diltiazem hydrochloride release profile for f_2 test: reference is Dilzem-SR tablet and test is prepared tablet.

Fig. 2, the f_2 factor confirms that the release of DTZ from the prepared tablets was similar to that of the marketed tablet.

The release data showed high linearity with the Korsmeyer equation. The values of release exponent “n” were characteristic of Anomalous (non-Fickian) diffusion and indicated a combined effect of diffusion and erosion mechanisms for controlled drug release.

Table 2: Kinetic parameters of the dissolution data for Diltiazem Hydrochloride

	Korsmeyer-Peppas Equation		Zero-Order Equation		Higuchi Equation	
Carrier	n	R^2	K_0	R^2	K_H	R^2
Ghatti gum	0.624	0.987	11.56	0.987	28.67	0.976
PEC	0.564	0.996	12.31	0.985	27.34	0.984
Chitosan	0.416	0.991	14.45	0.989	30.56	0.968

Water uptake and erosion

Fig. 3 shows the water uptake and erosion profiles for GG/CH PEC and standard preparation. The percentage swelling and erosion at the end of 12 hours was 182 and 250%, 38 and 34% respectively.

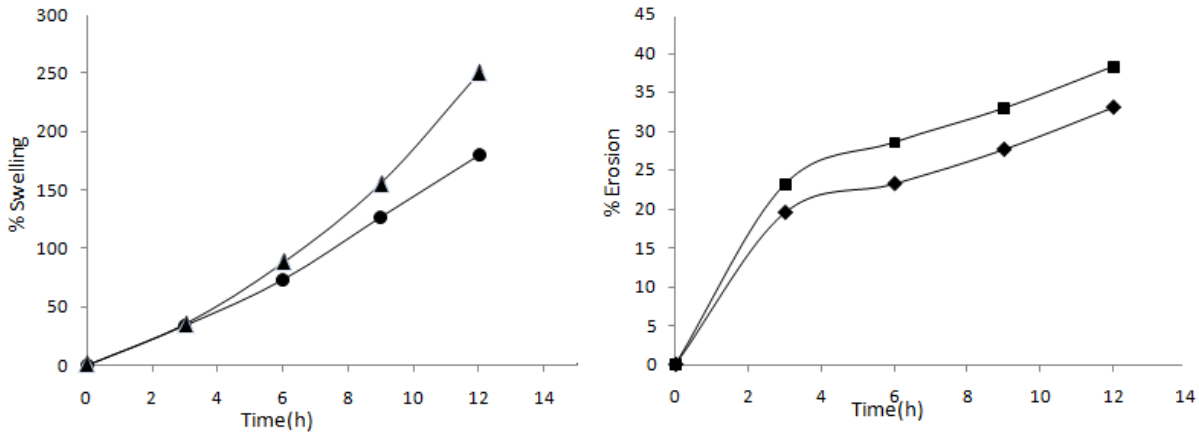

Figure 3: Swelling and eroding behaviour of Formulation F6 (■,●) and standard DTZ formulations (◆ ,▲).

Thus the matrices underwent both swelling and erosion at the same time immediately after placement in the dissolution medium and this continued over the 12 h period of the study. PEC sample and the standard DTZ had overlapping erosion profile throughout the study period but their swelling behaviour were similar only up to the 6th hour. The decrease of swelling was observed in the PEC sample which can be explained due to interaction between COO^- groups of ghatti gum and NH_3^+ groups of chitosan, which led to more compact structure and therefore less water absorption. The graphs were almost linear as observed indicating a balance between a swelling and erosion resulting in sustained drug release as observed from the in-vitro drug release profile [12].

Thermal analysis

The DSC thermograms of the ghatti gum, chitosan and Ghatti gum/Chitosan PEC is shown in the Fig. 4. In the DSC thermogram of chitosan, the chitosan showed endothermic peak at 102.5 ^oC whereas the decomposition of ghatti gum was observed at approximately 85.36 ^oC at which the ghatti gum was melted and decomposed sequentially. The broad endothermic peak near 100 ^oC was attributed to the physically bound-water. The endothermic peak of the PEC due to bound water was smaller than that of chitosan. The water absorption ability of chitosan is expected on account of its amine group being reduced by the complexation of chitosan with Ghatti gum. Similar behavior was also observed for chitosan/carbopol interpolymer complex [13]. Therefore,

the water absorption capacity of the PEC may be lower than chitosan. The reduced water absorption capacity might result in the slow disintegration of the PEC matrix and the extension of drug release from the PEC matrix.

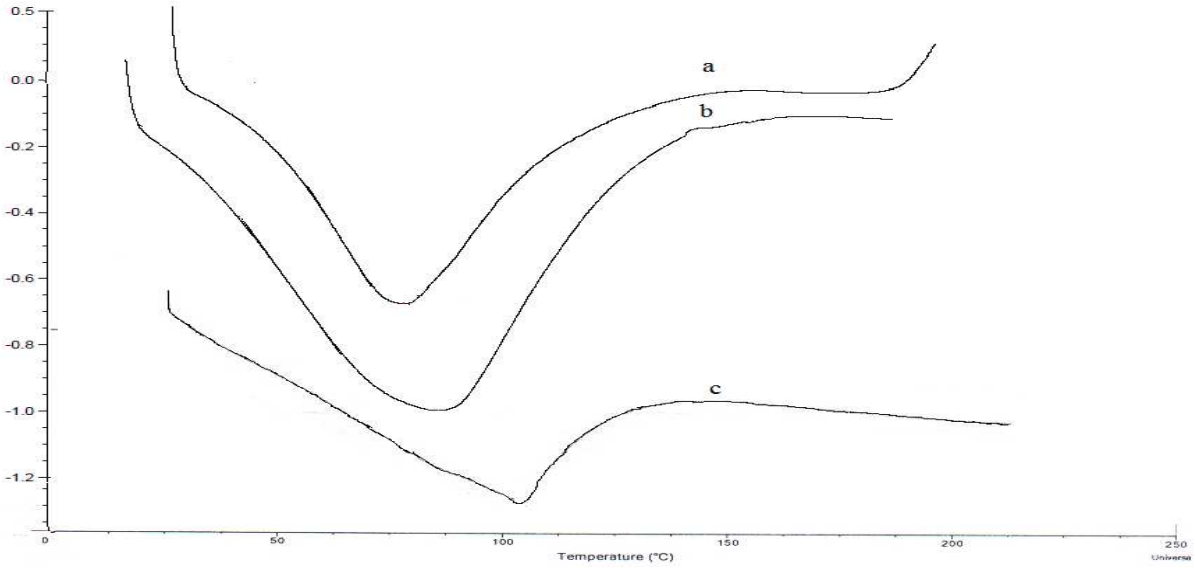

Figure 4: DSC thermograms of a) Ghatti gum, b) Ghatti gum/Chitosan PEC, c) Chitosan

FT-IR spectroscopy

The PECs, chitosan and ghatti gum samples were characterized by infrared spectroscopy (Fig. 5).

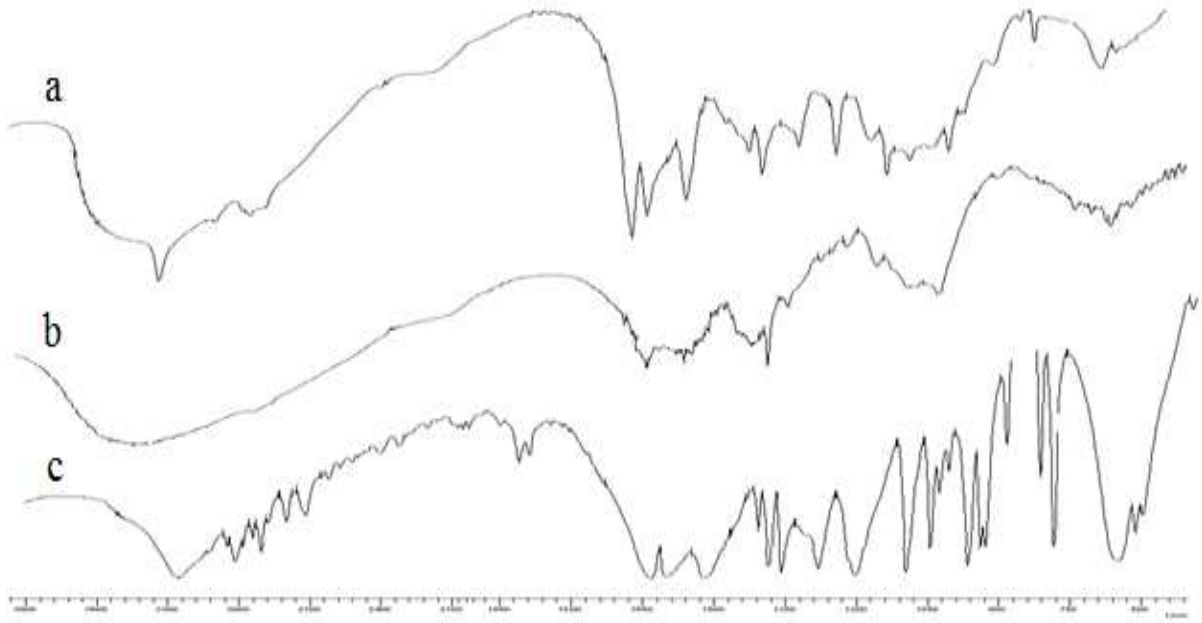

Figure 5: FT-IR spectra of a) Chitosan, b) PEC and c) Ghatti gum

Because the degree of deacetylationof chitosan is 85 %, the amine group of the 2-aminoglucose unit and the carbonyl group of the 2-acetaminoglucose unit of chitosan showed absorption bands at 1595 cm^{-1} and 1656 cm^{-1} respectively [14]. The peak at 1627 cm^{-1} in the IR spectrum of ghatti gum is attributed to COO^- groups of uronic acid residues. In addition, the NH_3^+ peak was known to appear between 1600 and 1460 cm^{-1}. Therefore, the appearance of a new broad band around 1560 cm^{-1} was believed to be overlapped peak of COO^- and NH_3^+ peak. These results suggested that the Ghatti gum/Chitosan PEC was formed by an electrostatic interaction between the COO^- group of ghatti gum and NH_3^+ group of chitosan.

Statistical analysis

GG/CH PEC did not significantly differ in terms of drug release ($p < 0.05$) from the commercial DTZ product used as standard.

CONCLUSION

Ghatti gum being more hydrophilic and less viscous compared to other gums cannot efficiently control the drug release. Chitosan with its pH dependent solubility profile cannot be used alone for formulating sustained delivery system. This study demonstrates the complexation of ghatti gum with chitosan to form a PEC in controlling diltiazem release and showed pH-independent release profile. Based on a derived dissolution parameter, f_2, the formulation with GG/CH PEC was closest to the commercial diltiazem tablet used as standard. The results of the study indicated that the release rate of Diltiazam HCl was lower for formulations containing polyelectrolyte complex as matrix forming polymer when compared with the formulations containing ghatti gum alone. Thus the polyelectrolyte complex can be used as a better alternative to the gum/chitosan as matrices for sustained release tablets.

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