Controlled Release of Carbamazepine from Carboxymethyl Chitosan-Grafted- 2-Hydroxyethylmethacrylate Matrix Tablets

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ABSTRACT: The aim of the study was to prepare the controlled release dosage of carbamazepine matrix tablets using wet granulation technique. The graft copolymerization of carboxymethyl chitosan (CMCH) with 2-hydroxyethylmethacrylate (HEMA) was carried out. The product was characterized by Fourier-transform infrared, scanning electron microscopy, transmission electron micrograph, and X-ray diffraction anayses. CMCH-*g*-HEMA was used as binder to prepare the matrix tablets containing carbamazepine. The properties of tablets like hardness, friability, and dissolution influenced by binder were studied. *In vitro* release of the matrix tablets was carried out with the phosphate-buffered solution (pH 7.4) at 37°C and 100 × *g* using USP dissolution test apparatus. Release rate of carbamazepine from controlled release matrix tablets was compared with the commercially marketed tablet, Tagretol 200. Results show that after 6 hrs percentage drug release of formulated tablet CGH_5 was 20.42% and that of Tegretol 200 was 18.32%.

Key words: chitosan; carboxymethyl chitosan; controlled release; graft copolymers; FTIR

INTRODUCTION

Rate preprogrammed drug delivery plays a great role in predetermined duration of medication and has been increasing its high acceptability in advanced control release technology. So far, it has been reported that many different types of controlled-release dosage form have been developed for improved clinical efficacy of drug and patient compliance.[1,2] A number of methods and approaches have been used in their formulation and are well reviewed.[3]

Drug release from hydrophilic matrix tablet is strongly influenced by the proportion of matrix forming polymer, the dimensions, and geometry of the tablet.[4] The matrix tablets refer to a tablet in which the drug is embedded in skeleton of nondissolving material. It needs simply compression of blended drugs, retardant materials, and additives to form tablets. It is one of the least complicated and convenient approaches to manufacture sustained release dosage forms that consist of a drug dispersed in a polymer.[5–8] Alternatively, retardant drug blends can be wet granulated before compression. Microfine pores within insoluble matrix effectively regulate the passage of drug from matrix to depot fluid. The matrix tablet, which incorporates the active ingredient in an inert material matrix, has been well known to act as an effective sustained release medicament.[9] Carbamazepine was selected as model drug in this study. It is an antiepileptic drug used to reduce or suppress seizures. The medication is also commonly prescribed to relieve certain neurogenic pain such as trigeminal neuralgia. This drug decreases abnormal electrical impulses through nerve cell pathways by inhibiting the activity of sodium channels in neurons.

Chitosan is a partially deacetylated polymer of acetyl glucosamine obtained after alkaline deacetylation of the chitin. It imparts interesting properties such as biocompatibility and biodegradability,[10–13] further its degradation products are nontoxic, nonimmunogenic, and noncarcinogenic.[14,15] Therefore, chitosan finds prospective applications in many fields such as biomedicine, drug-delivery system, waste water treatment, functional membrane, and flocculation. However, chitosan finds limited application due to the fact that it is soluble only in some dilute acids. Recently, there has been a growing interest in chemical modification of chitosan to improve its water solubility and widen its

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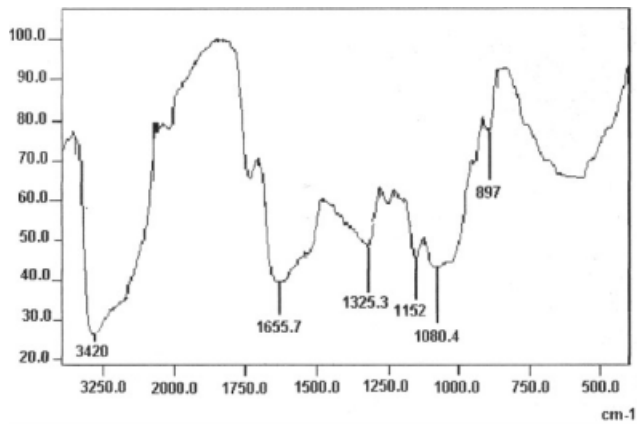

Figure 1 FTIR spectra of chitosan.

applications in particular in drug delivery.[16–24] Among various methods, graft copolymerization is most attractive, because it is a useful technique for modifying the chemical and physical properties of natural polymers. Grafting of chitosan allows the formation of functional derivatives by covalent binding of a molecule onto chitosan backbone. Properties of chitosan such as antioxidant, antibacterial along with its water solubility is reported to have improved by polymeric grafting.[25,26] Grafting of chitosan is a common way to improve its properties such as bacteriostatic effect,[27] and enhance the absorption properties.[28,29] Although, grafting of chitosan modifies its properties, it is possible to maintain some interesting characteristics such as mucoadhesivity,[30] biocompatibility,[31,32] and biodegradability.[33] The potential applications of grafted chitosan in various fields, such as controlled drug delivery, biomedical, and tissue engineering.

In the present work, we synthesized multiple-derivatives of chitosan, i.e., carboxymethyl chitosan (CMCH)-*g*-2-hydroxyethylmethacrylate (HEMA) graft copolymers. The graft copolymers used as binder for controlled release tablets of carbamazepine were prepared and its release profile was studied.

EXPERIMENTAL

Materials

Chitosan (molecular weight 8.4×10^4; degree of deacetylation 85%) provided by Central Institute of Fisheries Technologies, India, ceric ammonium nitrate (CAN), magnesium stearate, talc, and starch of analytical grade were supplied by S.D. Fine Chemical, India. HEMA was obtained from National Chemicals, India. Carbamazepine, a model drug from Novartis Pharma (India) was used for the study and Tagretol 200, a commercial product. All other reagents were of analytical grade and were used without further purification.

Preparation of *O*-Carboxymethylchitosan

Chitosan (10 g) was swolen in isopropanol (100 mL) in a three-necked flask equipped with a stirrer motor, a condenser thermometer pocket, and a heating metal. Then, sodium hydroxide (13.5 g) was added to alkalize the reaction mass. The mixture was stirred at 25°C temperature for 1 h. meanwhile, monochloroaceticacid (15 g) dispersed in isopropanol was then added into the reaction mixture dropwise within 30 min. The reaction mass was stirred for 4 h at 55°C. After completion of carboxymethylation, isopropanol was decanted off. A required quantity of ethyl alcohol (80%) was added to precipitate out the product. Solid product was filtered and washed with 80–90% ethyl alcohol. Finally, it was vacuum dried at 50°C. The degree of substitution of CMCH was determined by titration and found to be 0.31.[34–36]

Graft copolymerization

CMCH (2 g), HEMA (4 mL), and double distilled water (100 mL) were charged into a three-necked round bottom flask maintained at 40°C in water bath. Nitrogen gas was bubbled with stirring for 30 min to remove the dissolved oxygen. CAN (0.2*M*) dissolved in 10 mL of HNO_3 (0.3*M*) was slowly added which initiated the graft copolymerization and reaction continued for 3 h at 40°C. Products were neutralized with 10% NaOH and the graft copolymer was precipitated out by acetone. Product was filtered and washed first with acetone and then with methanol : H_2O (90 : 10), so that all the unreacted CMCH and ceric salt were removed. Homopolymers were extracted with alcohol for 48 h, and the product was dried at 50°C for 24 h.[24]

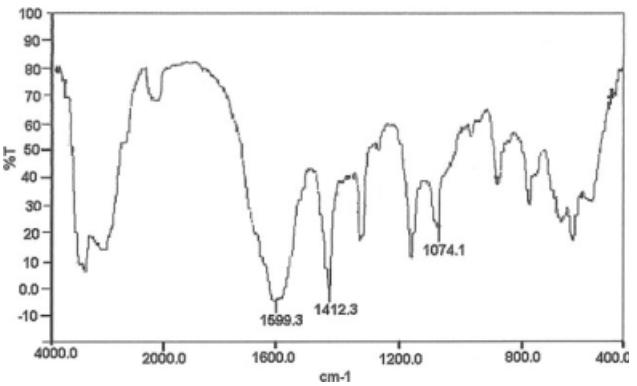

Figure 2 FTIR spectra of CMCH.

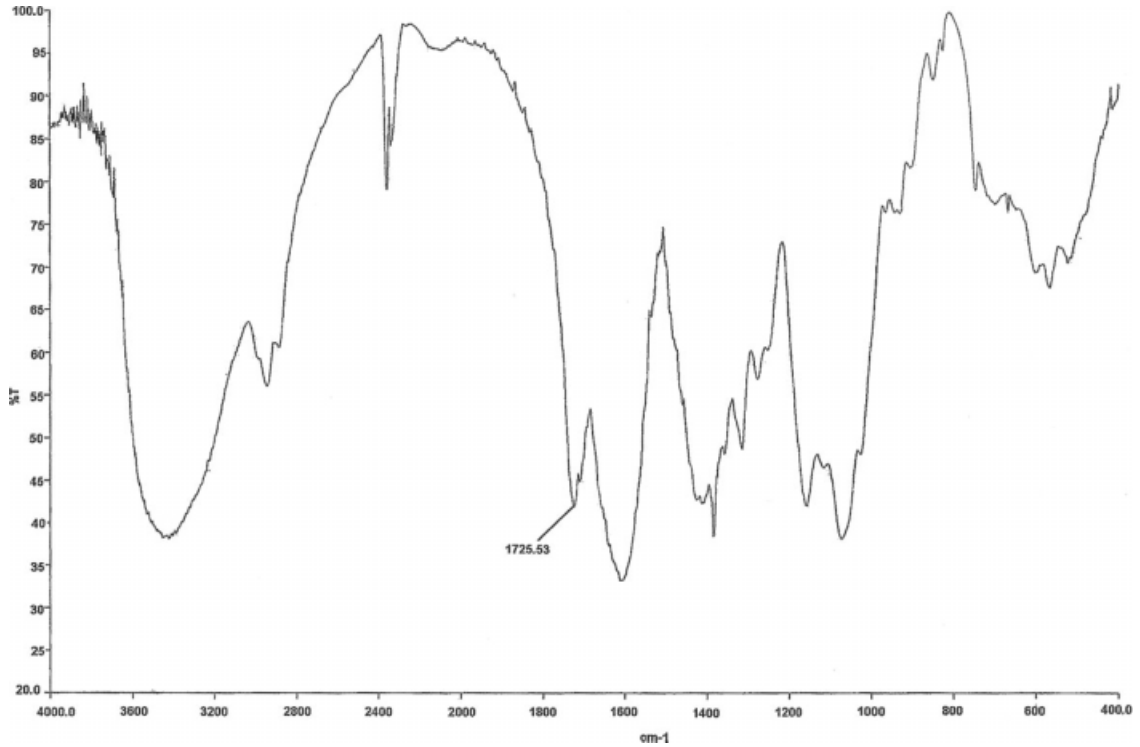

Figure 3 FTIR spectra of CMCH-*g*-HEMA.

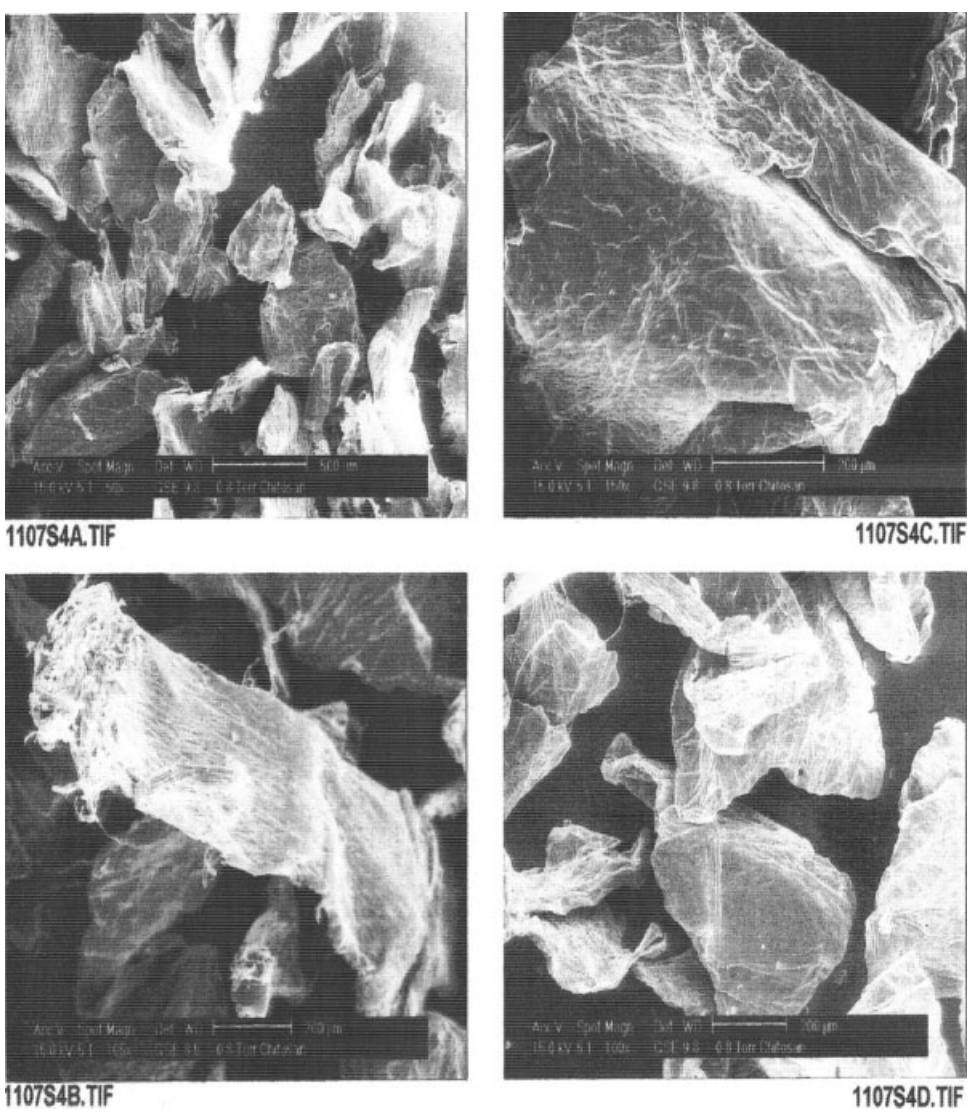

Figure 4 SEM of chitosan.

Characterization

Infrared spectra of chitosan derivatives were recorded with a PERKIN ELMER Fourier-transform infrared (FTIR) spectrometer using KBr pellets. Scanning electron microscopy (SEM) of chitosan, CMCH, and graft copolymer were carried out using SEM XL-Series from Philips, The Netherlands, operated at 15 kV. Transmission electron micrographs (TEM) of CMCH and CMCH-*g*-HEMA were obtained using transmission electron microscope (Philips, Netherlands, Model: Technal 20) having tungsten electron source and 200 kV accelerating voltage. Powder X-ray diffraction patterns of chitosan and graft copolymers were carried out by Xe-filled counteract solid state liquid nitrogen cooled detector, X'' pert-Philips instrument equipped with a θ–θ goniometer under the following operation conditions; 40 kV and 35 mA with Cu $K\alpha_1$-radiation at λ 1.54056 Å. The relative intensity was recorded in the scattering range (2θ) of 0–167°.

Preparation of matrix tablets

Tablets were prepared by wet granulation method. Briefly, carbamazepine, lactose, starch, and 1 to 5% graft copolymer as a binder were mixed in a mortar with small amount of distilled water. The pasty mass was passed through # 10 mesh and then dried at 45°C in vacuum drier. After complete drying, mass was passed through # 22/40 mesh. The oversize particles were considered as granules and the undersize was named as fines. Granules and fines were kept separately. The granules were mixed with 10% fines, 2% magnesium-stearate (lubricant), and 1% talc. Five batches of matrix tablets of different binder concentration (1–5%) were prepared for this study. In

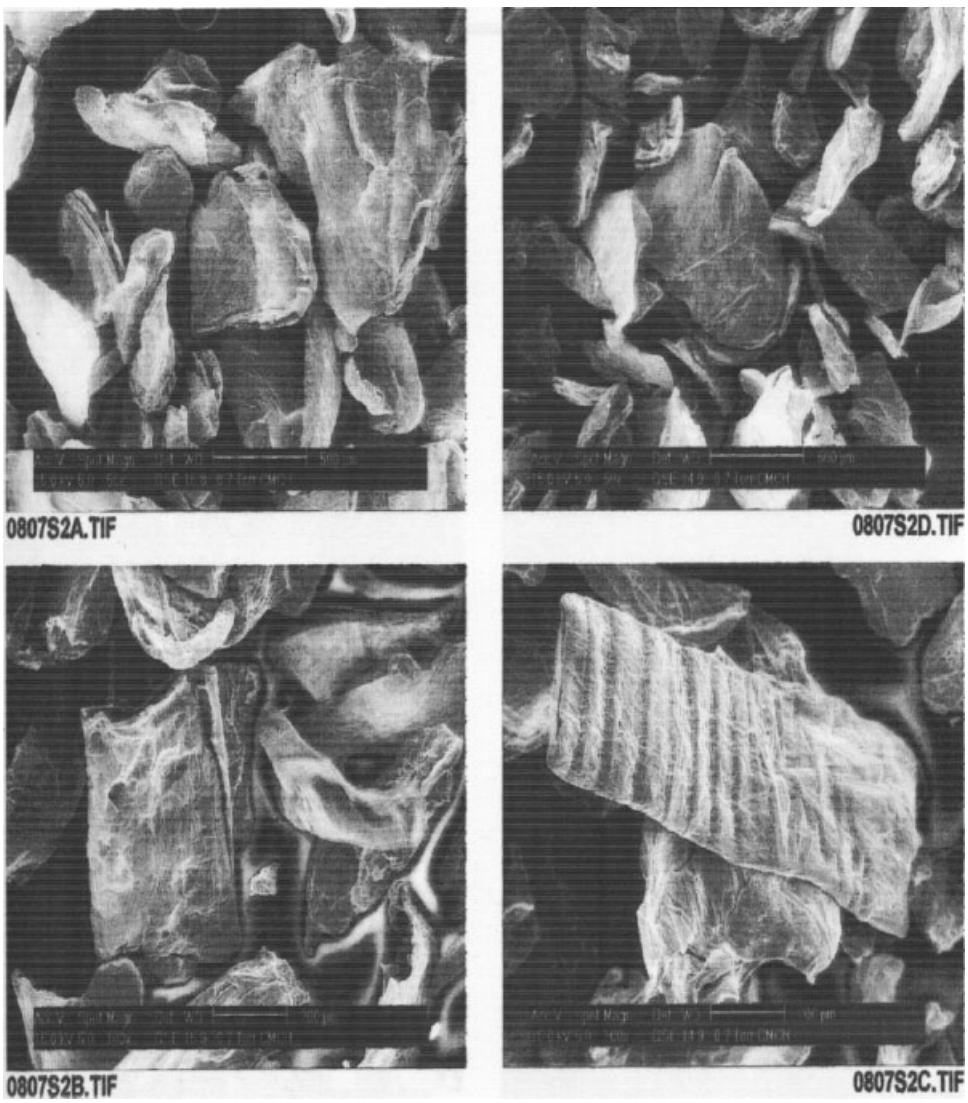

Figure 5 SEM of CMCH.

each batch, 20 matrix tablets were prepared at different binder percent ranging from 1 to 5%.

Physical properties of tablets

All the physical properties measurements are carried out as per the standard procedure described by Lachman et al.[37]

Weight

The weight (mg) of each of 20 individual tablets was determined after dusting and placing it on an electronic balance.

Friability

It was determined by weighing 15 tablets after dusting and placing them in friability tester and rotating the basket vertically at 25 × *g* for 4 min (100 drops) using VEEGO friabilator. Friability was calculated by the following equation.

$$\% \text{ Friability} = \frac{\text{original weight} - \text{final weight}}{\text{original weight}} \times 100$$

Hardness

It was determined with the help of a Monsonto hardness tester.

In vitro dissolution studies

The dissolution studies were carried out using two matrix tablets from each batch using an "Electrolab Dissolution Tester USP (XXI) TDT-06" as per the procedure described by Ansel et al.[38] Nine hundred milliliters of phosphate buffer solution of pH 7.4 was used in each vessel (total six vessels) as

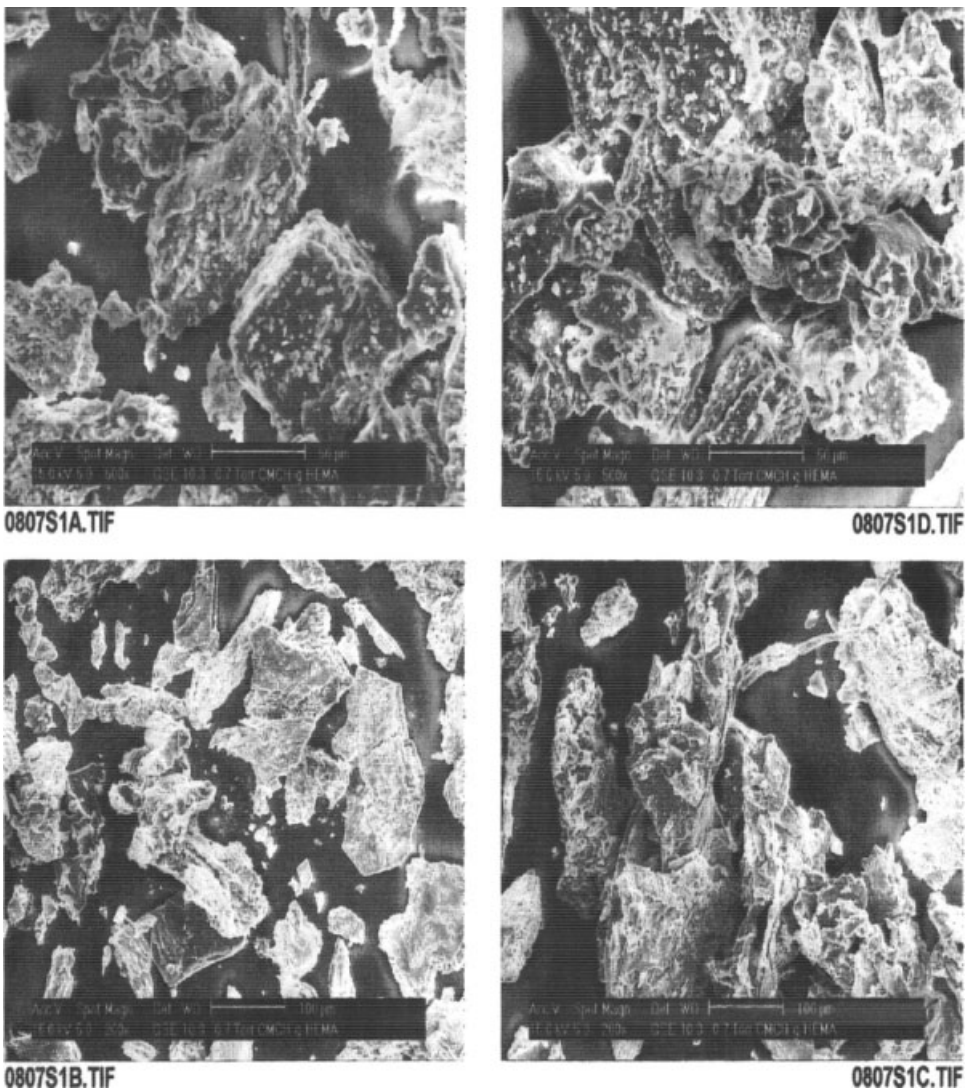

Figure 6 SEM of CMCH-*g*-HEMA.

dissolution medium. The temperature of dissolution medium was set at 37 ± 0.5°C and paddle rotation was set at 100 × *g*. Time was recorded as soon as the tablets were put into the dissolution jar. Five milliliters of samples were withdrawn from each jar at appropriate time intervals (15, 30, 60, 90, 120, 180, 240, 300, and 360 minutes) for the analysis of drug content. The same amount of fresh phosphate buffer was replaced immediately to the dissolution medium to compensate the volume. The dissolution study was carried out for 6 h. The extent of carbamazepine released from each matrix tablet was measured at 285 nm wavelength using a Schimadzu UV-1650 PC spectrophotometer. The phosphate buffer of pH 7.4 was used as blank. By using this absorbance data release profile, a graph of percentage drug release vs. time was plotted.

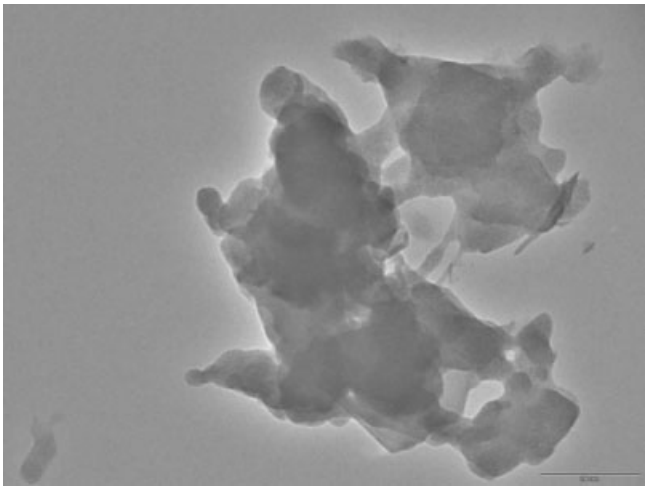

Figure 8 TEM of CMCH-*g*-HEMA.

RESULTS AND DISCUSSION

Characterization of chitosan derivatives

Structural changes of chitosan and its derivatives were confirmed by FTIR spectroscopy (Figures 1–3). The IR spectrum of chitosan (Fig. 1) shows peaks assigned to the saccharide structure at 1152, 1080, 1028, and 897 cm^{-1}, and a strong amino characteristic peak at around 3420, 1655, and 1325 cm^{-1} are assigned to amide I and II bands, respectively. In the IR spectrum of CMCH (Fig. 2), the strong peak at 1412.3 cm^{-1} could be assigned to the symmetrical stretching vibration of COO^-. The asymmetrical stretching vibration of COO^- (1900−1550 cm^{-1}) overlapped with the deforming vibration of NH_2 at 1599.3 cm^{-1} to obtain a very strong peak. And C—O absorption peak of hydroxyl group became stronger and move to 1074.1 cm^{-1}. The results indicated that the substitution occurred at C_6 position. In the IR spectrum of CMCH-*g*-HEMA (Fig. 3), characteristic peak of C=O was obtained at 1725.53 cm^{-1}. From the IR data, it is clear that the grafted copolymer CMCH-*g*-HEMA had both characteristic peaks of PHEMA and the saccharide of chitosan and its derivatives, which could be an effective evidence of grafting.

The SEM of chitosan, CMCH, and its graft copolymer are shown in Figures 4–6, respectively. Carboxymethylation and graft copolymerization modified the surface morphology and also its physical, chemical, and biodegradable characteristics of chitosan. It is clearly seen from Figures 4 and 5 that flaky nature of chitosan was little modified in carboxymethylation process. The fibrous nature of CMCH was totally modified in the graft copolymer. In Figure 6, CMCH-*g*-HEMA showed the clustered irregular structure.

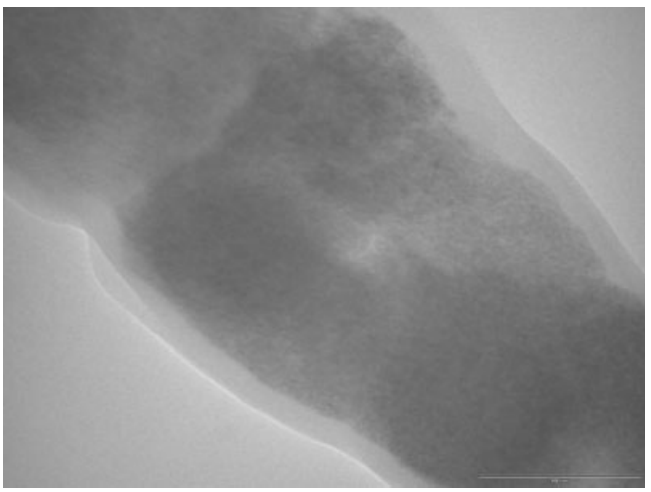

Figure 7 TEM of CMCH.

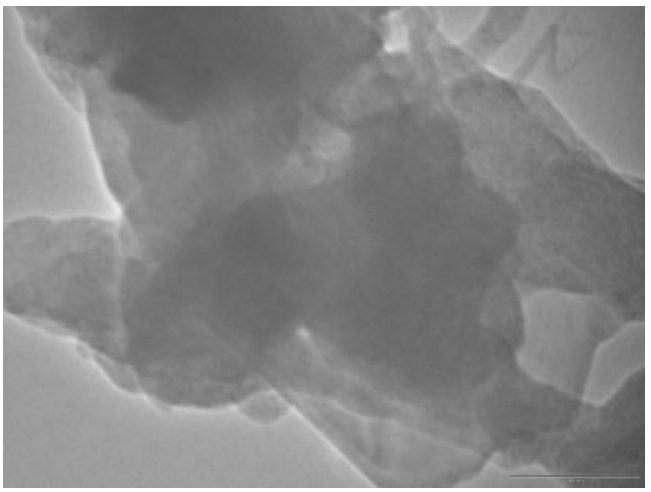

Figure 9 TEM of CMCH-*g*-HEMA.

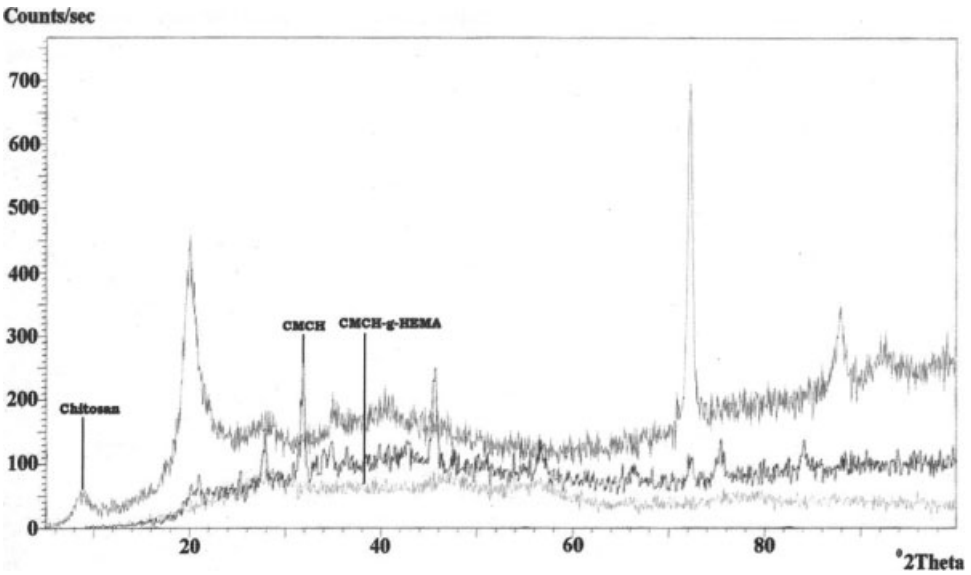

Figure 10 XRD of (a) chitosan; (b) CMCH; and (c) CMCH-*g*-HEMA.

TEM of CMCH and graft copolymer are shown in Figures 7–9. TEM of CMCH in Figure 7 shows almost cylindrical particle. Micrographs of CMCH-*g*-HEMA show cluster of aggregated particles with different dimensions having dark (CMCH) and light (HEMA) portion in Figures 8 and 9, which confirm grafting.

Figure 10 shows the powder X-ray diffractograms obtained from chitosan, CMCH, and CMCH-*g*-HEMA. Chitosan shows the maximum intensity obtained at $2\theta = 20^\circ$ and $2\theta = 72^\circ$ for two peaks, which match the values reported in the literature.[39] The crystallinity index (CrI, %) was calculated for chitosan, CMCH, and CMCH-*g*-HEMA. The formula used for calculation took into consideration I_{110} at 20° as maximum intensity and I_{amp} as the intensity of amorphous diffraction at 16°.

$$\text{CrI}\% = (I_{110} - I_{amp}) \times 100/I_{110}$$

The calculated values for chitosan, CMCH, and CMCH-*g*-HEMA were 88, 80, and 61%, respectively. After carrying out carboxymethylation, the CMCH does exhibit some crystallinity as it can be seen in the XRD. Compared with chitosan and CMCH, the grafting decreases intensity of both the peaks, i.e., almost no peak is observed which is clearly visible. The graft copolymerized samples become amorphous as compared with crystalline chitosan. The grafting of HEMA takes place randomly along the CMCH chain, giving rise to a random copolymer. This efficiently destroys regularity of packing of the original CMCH chains, which in turn results in formation of amorphous copolymer.

Physical characterization of the matrix tablets

The detailed compositions of CMCH-*g*-HEMA matrix tablet formulations are given in Tables I and II. Physical properties of tablets like friability, hardness, and weight variation of the formulated tablets are listed in Table III. The average weight of the 20 matrix tablets was acceptable due to the granule flow ability properties. The flow characteristics were improved by adding starch, as a glidant, to the granular mixture. The minimal friability obtained confirmed the suitability of the wet-granulation

TABLE I
Formulation of Granules for Tablets

Code content	CGH_1	CGH_2	CGH_3	CGH_4	CGH_5
Carbamazepine (g)	4	4	4	4	4
Lactose (g)	6	6	6	6	6
Starch[a] (mg)	250	250	250	250	250
CMCH-*g*-HEMA (mg)	100	200	300	400	500
Weight of granules obtained (g)	6.920	6.690	7.480	8.190	7.656

[a] 2.5% of total weight of drug and lactose.

TABLE II
Formulation of Tablets

Code content	CGH_1	CGH_2	CGH_3	CGH_4	CGH_5
Granules (g)	6.920	6.690	7.480	8.190	7.656
Lubricant[a] (mg)	200	200	200	200	200
Talc[b] (mg)	100	100	100	100	100
Fines[c] (mg)	690	669	748	810	765
total weight (g)	7.910	7.659	8.270	9.300	8.721

[a] 2% of total weight of drug and lactose.
[b] 1% of total weight of drug and lactose.
[c] 10% of granules.

technology for the preparation of these CMCH-*g*-HEMA matrices.

In vitro drug release profiles

Figure 11 shows the dissolution profiles of carbamazepine for the formulations prepared with different binder (1–5%) concentrations as well as marketed product. As the concentration of binder increased, release of the drug was decreased, since at higher binder concentration gelling properties of binder increases and due to this diffusion of drug from highly swelled network becomes difficult, so drug release rate was slow at higher binder concentration. By comparing the release data of formulated and marketed tablets, it was found that after 6 h the percentage drug release of formulated controlled release tablet (CGH_5) and that of the marketed one (Tagretol 200) were 20.90 and 18.33%, respectively, i.e., almost similar.

CONCLUSIONS

In the growing demands for the controlled drug delivery system, it was a need of the market to have potential binder for the system. In the endeavor CMCH-*g*-HEMA has been synthesized successfully by graft copolymerization using CAN as an initiator. This graft copolymer was used as binder for the formulation of controlled release tablets, and best results were obtained using binder concentration at 5%. It gave comparable results, with the standard drug tablet (Tagretol 200), confirming the fact that CMCH-*g*-HEMA is a potential binder.

TABLE III
Properties of Formulated Control Release Tablets

Code	Friability (%)	Hardness (kg/cm^2)	Average weight of 20 tablets (mg)
CGH_1	1.567	4.8	530.8
CGH_2	1.258	4.9	517.6
CGH_3	1.751	5.0	518.5
CGH_4	1.350	5.2	509.4
CGH_5	1.108	5.5	516.0

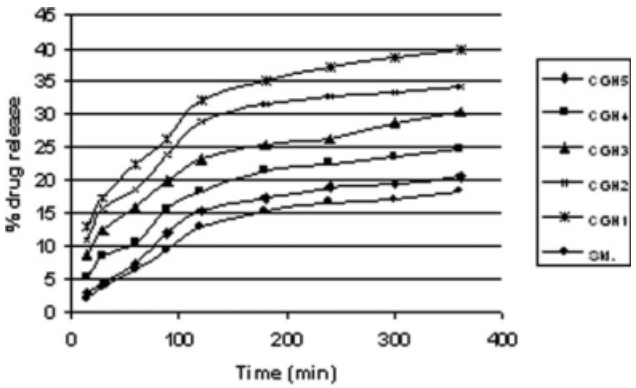

Figure 11 Drug release profile of carbamazepine and standard drug.

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