

CROSSLINKED CHITOSAN HYDROGEL MATRIX TABLETS FOR CONTROLLED RELEASE OF GABAPENTIN

NARASIMHA S. MANAGOLI^{1,4}, RAGHAVENDRA V. KULKARNI²,
N. RAMARAO^{3,*}, I. S. MUCHANDI¹

¹BVVS's HSK College of Pharmacy, Bagalkot-587101, Karnataka, India.

²BLDEA's College of Pharmacy, BLDE University Campus, Bijapur-586101, India.

³Chalapathi Institute of Pharmaceutical Sciences, Guntur 522034, Andhra Pradesh, India.

⁴Acharya Nagarjun University, Nagarjunanagar, Guntur 522510, Andhra Pradesh, India.

*corresponding author: pharma_75raghu@yahoo.com

Abstract

The aim of the present study was to prepare hydrogel matrix tablets for controlled release of an antiepileptic drug, gabapentin. The hydrogels were prepared by crosslinking chitosan using four different crosslinking agents namely, anhydrous dextrose (DXT), sodium tripolyphosphate (TPP), urea-formaldehyde (UF) and acetaldehyde (AL). They were characterized by differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and X-ray diffraction (XRD) analysis. The matrix tablets were prepared by conventional wet granulation method and evaluated for weight and drug contents variations, hardness and friability and were within the specified range. The matrix tablets were capable of releasing the drug for 12 h depending upon the formulation variables. The tablets prepared by plain chitosan discharged the drug quickly, while those prepared by using AL crosslinked-hydrogel released the drug more slowly in a controlled manner. In general, the order of drug release from the crosslinked-hydrogel matrix tablets on the basis of crosslinking agents, was found to be DXT > TPP > UF > AL. Drug release mechanisms from all the tablets followed non-Fickian transport.

Rezumat

Studiul prezintă etapele de preparare și analiză farmaco-tehnologică a unor tablete cu gabapentin, utilizând ca matrice, în formularea acestor tablete, a unor hidrogeluri obținute prin legarea "încrucișată" (*crosslinking*) a chitosanului cu: dextroză anhidă (DXT), tripolifosfat sodic (TPP), uree-formaldehidă (UF) și acetaldehidă (AL). Matricele tabletelor au fost preparate prin metoda convențională a granulării umede și au fost analizate prin calorimetrie diferențială, analiză termogravimetrică și difracție cu raze X. Au fost de asemenea determinați parametrii specifici, precum friabilitatea formelor farmaceutice obținute, conținutul în substanță activă precum și profilele de dizolvare. S-a concluzionat că eliberarea gabapentinului din matricile nou elaborate, depinde de asocierea chitosanului cu agenții de legare încrucișată astfel: DXT>TPP>UF>AL, iar mecanismul eliberării este de tip non-Fickian.

Keywords: Chitosan, Crosslinked chitosan, Hydrogel matrix tablets, Controlled release, Gabapentin.

Introduction

Gabapentin, 2-[1-(aminomethyl)cyclohexyl]acetic acid, is a structural analog of γ -aminobutyric acid (GABA), with an incorporated cyclohexyl ring. Gabapentin is currently marketed as an adjunctive therapy for partial seizures in adults with epilepsy and for the management of post herpetic neuralgia [1,2]. It is rapidly absorbed following oral single-dose administration to healthy volunteers [3]. Gabapentin has a relatively short half-life (5 h), requiring three doses per day in most of the patients [4]. Dosing regimens requiring three or four doses per day leads to significant noncompliance in epilepsy patients. Therefore, it is a good candidate for controlled release (CR) formulation. In addition to an increased patient compliance, CR formulation assures, prolonged and stable exposure to gabapentin, providing other clinical benefits, including greater efficacy, prolonged duration of action, and a reduced incidence of adverse effects related to peak drug levels [5,22].

Recently, the study of controlled release of drugs and other bioactive agents from polymeric devices fabricated using particularly biodegradable natural polymers such as chitosan, has interested many researchers. Different systems, ranging from coated tablets and gels to biodegradable microspheres and osmotic systems, have been explored experimentally and computationally to get pre-designed release profiles [6]. Chitosan has a glycosaminoglycan-like structure and a wide range of outstanding characteristics such as biodegradability and ready commercial availability in different grades. A considerable attention has been focused on chitosan (CH) hydrogels and their use in tissue engineering scaffolds, CR formulations and implants [7-9]. CR applications include both sustained delivery over days/weeks/months/years and targeted (e.g., to a tumor, diseased blood vessel, etc.) delivery on a one-time or sustained basis [10]. CR formulations can be used to reduce the amount of drug necessary to cause the same therapeutic effect and convenience of fewer and more effective doses leading to increased patient compliance [11].

The major limiting factor for the application of chitosan in drug delivery is its poor water solubility and rapid swelling in the acidic environment leading to burst release of loaded drug. To overcome these limitations and to enhance applications of chitosan, modifications have been effected by crosslinking and also several derivatives have been developed over the years with improved properties [12-14].

Considering the potential of chitosan, the present work aimed to prepare chitosan based hydrogels using different crosslinking agents such as anhydrous dextrose, sodium tripolyphosphate, urea- formaldehyde and acetaldehyde. Further, these hydrogels have been used for the preparation of gabapentin matrix tablets for controlled release formulations.

Materials and Methods

Materials

Gabapentin was obtained as a gift sample from Cipla Ltd. (Mumbai, India). Chitosan was purchased from Vishu Aquatech, Madras, India. Sodium alginate (SA), acetaldehyde (AL), sodium tripolyphosphate (TPP), anhydrous dextrose (DXT), urea, formaldehyde, lactose, magnesium stearate, and starch were purchased from S.D. Fine-Chem Limited (Mumbai, India). Double distilled water was used throughout the study. All other chemicals were purchased from local laboratory chemicals suppliers and used without further purification.

Crosslinking of chitosan

Crosslinking with anhydrous dextrose (CHDXT)

A 2% (w/v) solution of chitosan in 2% (v/v) aqueous solution of acetic acid was prepared by stirring to obtain a clear solution. An appropriate amount of anhydrous dextrose (DXT) (10% w/w of dry chitosan) was added under stirring at 120 °C over a period of 1 hour. Then the reaction mixture was allowed to cool to room temperature and cured for two days at 68 °C, followed by neutralization with 10% (w/v) NaOH. The cured mass was cooled to room temperature and acetone was added. Precipitated hydrogel (CHDXT) was separated by decantation and repeatedly washed with distilled water to remove any unreacted material. Further it was dried at 40 °C for 24 h, powdered and stored in a well closed container [15].

Crosslinking with sodium tripolyphosphate (CHTPP)

A 2% of chitosan was dissolved in 2% (v/v) aqueous acetic acid solution by stirring to get clear solution. To this solution, 10% (w/w of dry chitosan) of sodium tripolyphosphate (TPP) was added and kept at 4 °C for 1 hour and the pH of the solution was maintained at 5.5. Acetone was added to precipitate the hydrogel and the obtained hydrogel (CHTPP) was repeatedly washed with distilled water to remove any unreacted material.

Further it was dried at 40 °C for 24 h; powdered and stored in a well closed container.

Crosslinking with urea-formaldehyde (CHUF)

To a 2% (w/v) solution of chitosan in 2% (v/v) aqueous acetic acid solution prepared by gentle heating and stirring, the required amounts of urea-formaldehyde (UF) (10% w/w of the dry weight of chitosan) and 1.12 M H₂SO₄ were added and stirring was continued for 1 hour. Acetone was added to precipitate the hydrogel and the obtained hydrogel (CHUF) was repeatedly washed with distilled water to remove any unreacted material. Further it was dried at 40 °C for 24 h; powdered and stored in a well closed container [16].

Crosslinking with acetaldehyde (CHAL)

Chitosan solution (2% w/v) was prepared by stirring in 2% (v/v) aqueous acetic acid solution using a homogenizer until the chitosan dissolved completely. To this solution, acetaldehyde (AL) (10% w/w of the dry weight of chitosan), 0.5 mL of 0.1 N HCl were added and mixed for 1 h at 50°C. Acetone was added and the precipitated hydrogel (CHAL) was repeatedly washed with distilled water to remove any unreacted material. Further it was dried at 40 °C for 24 h; powdered and stored in a well closed container [17].

Characterization of the hydrogel

Differential scanning calorimetric (DSC) analysis

Samples of 5-6 mg were sealed in an aluminum DSC pan and an empty sealed aluminum pan was used as reference. The samples were heated from 40-300 °C at a heating rate of 10 °C/min under nitrogen atmosphere using a microcalorimeter (Perkin Elmer, Pyris 6 DSC, USA) to obtain thermograms.

Thermogravimetric analysis (TGA)

The samples were heated from 0-600°C at a heating rate of 10°C/min under argon atmosphere using a microcalorimeter (Perkin Elmer, USA) and thermograms were recorded.

X-Ray diffraction studies (XRD)

The spectra of the samples were recorded using a Philips, PW-171, X-ray diffractometer with Cu-NF filtered CuK α radiation. Quartz was used as an internal standard for calibration. The powder X-ray diffractometer was

attached to a digital graphical assembly and a computer with Cu-NF 25KV/20mA tube as a CuK α radiation source in the 2 θ range 0-80°.

Preparation of hydrogel matrix tablets

Different tablet formulations were prepared by the wet granulation method. Required quantities of gabapentin, and hydrogels CH, CHTPP, CHDXT, CHUF, CHAL, and macromolecular microsphere composite (MCC) were passed through 80 mesh sieve, mixed thoroughly and a sufficient amount of binding agent (starch paste 5 % w/v) was added slowly. After a sufficient cohesiveness was obtained, the mass was sieved through the 22/44 mesh sieve. The granules were dried at 40 °C for 12 h and thereafter kept in a desiccator for 12 h at room temperature. Once dry, the granules retained on the 44 mesh sieve were mixed with 10% of fines (granules that passed through the 44 mesh sieve), talc and magnesium stearates were added as glidant and lubricant respectively and compressed into tablets using a rotary tablet compression machine (Karnavati Minipress I, Ahmedabad, India). The total weight of tablets was 500 mg and each tablet contained 100 mg gabapentin and other pharmaceutical ingredients as listed in Table I.

Table I
Formulation details of hydrogel matrix tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
CH	150	250	--	--	--	--	--	--	--	--
CHDX	--	--	150	250	--	--	--	--	--	--
CHTPP	--	--	--	--	150	250	--	--	--	--
CHUF	--	--	--	--	--	--	150	250	--	--
CHAL	--	--	--	--	--	--	--	--	150	250
Active Drug	100	100	100	100	100	100	100	100	100	100
MCC	235	135	235	135	235	135	235	135	235	135
Talc	10	10	10	10	10	10	10	10	10	10
Magnesium stearate	5	5	5	5	5	5	5	5	5	5

Further, granules were evaluated for bulk density, tap density, packing ability and flow property. Tablets were evaluated for weight variation, drug content, hardness, friability, equilibrium swelling and *in vitro* drug release.

Evaluation of tablets

Drug content uniformity

Ten tablets were randomly selected and incubated in 100 mL United states Pharmacopeia (USP) phosphate buffer of pH 7.4 for complete

swelling at 37°C for 12 h. Then the tablets were crushed in a glass mortar with a pestle, heated gently for 3 h to extract the drug completely and centrifuged to remove the polymeric debris. The clear supernatant solution was analyzed for the drug content using an UV-visible spectrophotometer (Model Pharmaspec UV-1700, Shimadzu, Japan) at 215 nm.

Equilibrium swelling study

The equilibrium swelling of the hydrogel tablets was studied by mass measurement. Accurately weighed tablets were incubated with 100 mL phosphate buffer solutions of pH 1.2 and 7.4 at 37°C. The tablets were taken out after 8 h and blotted carefully, without pressing hard, to remove the excess surface liquid. The swollen tablets were weighed using the electronic microbalance (Shimadzu, Japan) and the swelling ratio was calculated.

In vitro drug release

In vitro drug release study was carried out using a USP-23 rotating dissolution tester. The dissolution was measured at 37.0 ± 0.5 °C and 50 rpm speed. The drug release from the tablets was studied in 900 mL acidic medium (pH 1.2) for 2 h and in alkaline medium (pH 7.4 phosphate buffer) till end of the study. At predetermined time intervals, 5 mL aliquots were withdrawn and replaced with the same volume of fresh solution. The amount of drug released was analyzed using an UV-visible spectrophotometer at 215 nm.

The obtained data were fitted to various mathematical models such as Zero order release kinetics, Higuchi model, and Korsmeyer-Peppas models to find which model is the best fit for the release profile obtained.

Results and Discussion

The chitosan based hydrogel tablets were prepared and evaluated for controlled release of gabapentin (Figure 1).



Figure 1

Image of the chitosan based hydrogel matrix tablets F1 to F10.

Chitosan hydrogels were prepared by crosslinking with different crosslinking agents namely; DXT, TPP, UF and AL (Figure 2).

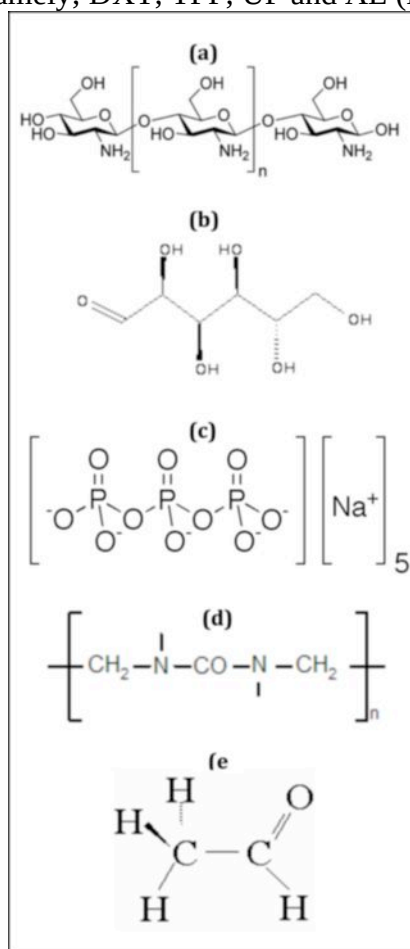


Figure 2

Chemical structures of chitosan (a), dextrose (b), sodium tripolyphosphate (c), urea-formaldehyde (d) and acetaldehyde (e)

In the case of crosslinking with DXT, the aldehyde or keto groups of DXT can react with the amino groups of chitosan leading to the formation of a Schiff base complex which then transforms to aminoglycoside complex by a tautomerization process and further reacts with another amino group of chitosan again. [18], while in the case of crosslinking with AL, the chitosan can be easily crosslinked by the Schiff base mechanism under mild conditions [19]. The amino groups of chitosan can be crosslinked with UF in the presence of sulphuric acid [16], while with TPP, chitosan forms an ionic crosslinking. [20].

Characterization of crosslinked-chitosan

The chitosan based hydrogels were characterized by DSC, TGA and X-ray diffraction studies.

DSC analysis

The DSC tracings of CH, and hydrogels CHDX, CHTPP, CHUF and CHAL are shown in Figure 3.

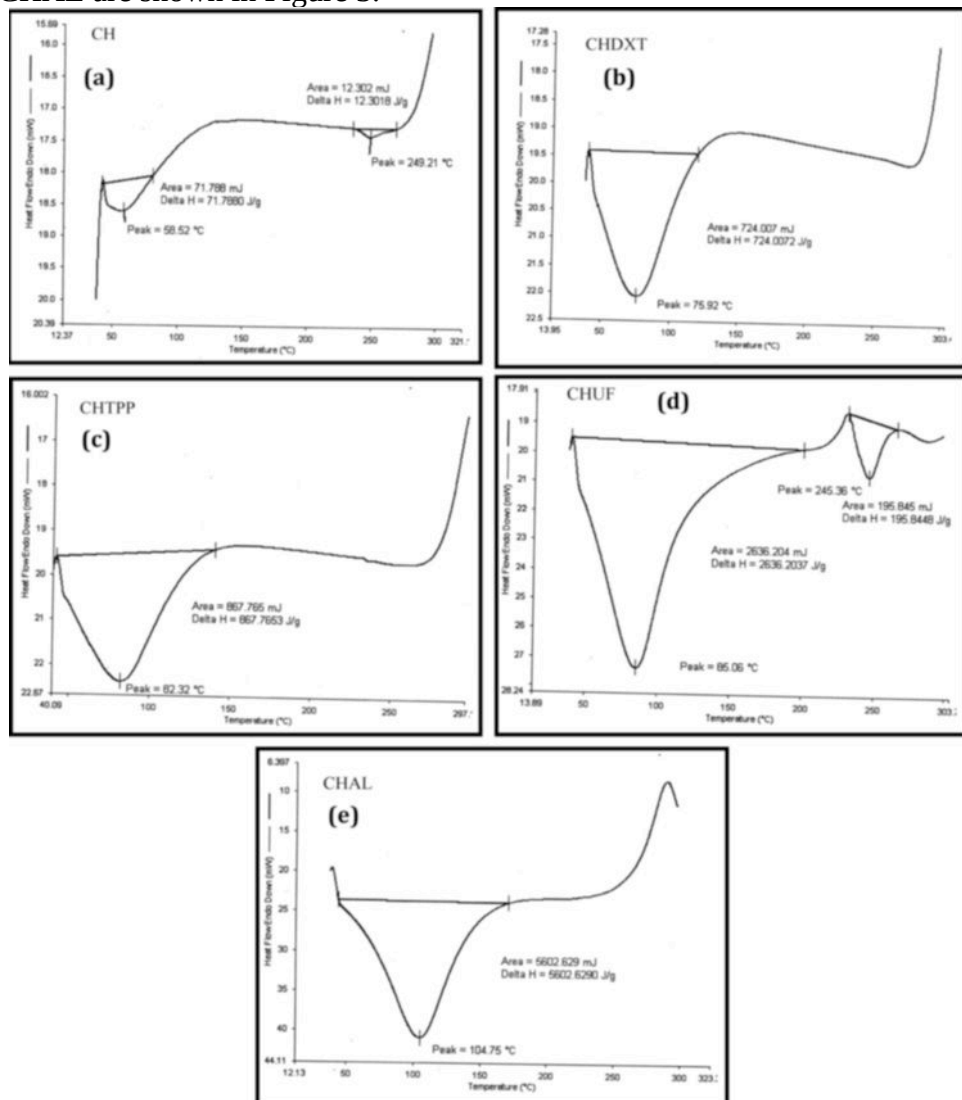


Figure 3

DSC thermograms (a) CH, (b) CHDX, (c) CHTPP, (d) CHUF and (e) CHAL.

CH exhibited the endothermic peak at 58.52 °C, while CHDX, CHTPP, CHUF and CHAL at 75.92, 82.32, 85.06, 104.75 °C respectively. In all the cases of hydrogels, a shift in endothermic peaks was observed towards higher temperatures compared to CH and the order was as follows CHAL > CHUF > CHTPP > CHDX > CH. This shift in the endothermic peak towards higher temperatures could be due to the formation of more rigid hydrogel network as a result of crosslinking.

TGA

Typical TGA thermograms of CHDX, CHTPP, CHUF and CHAL are shown in Figure 4.

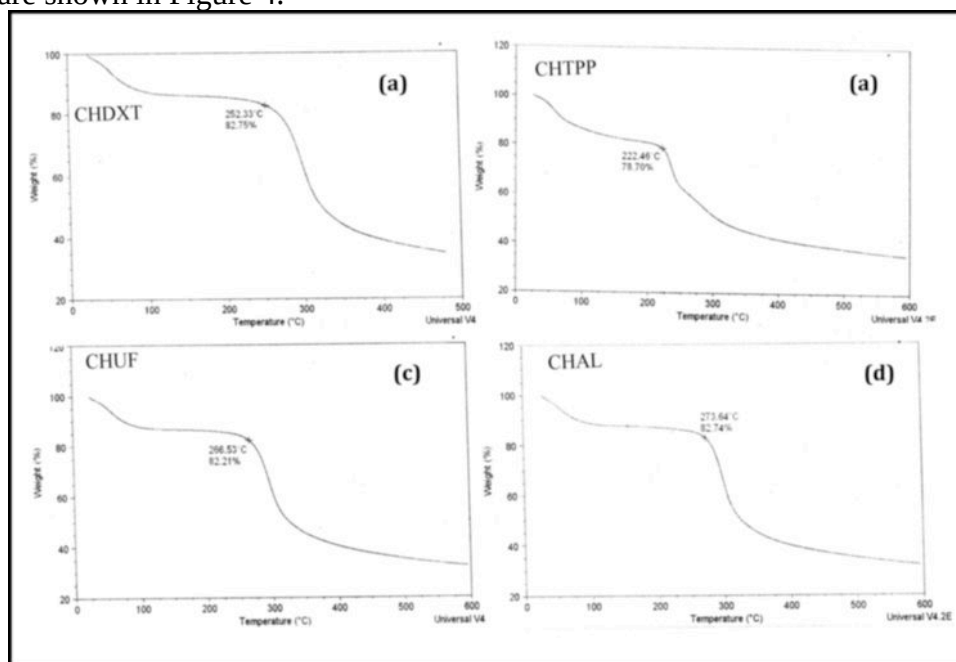


Figure 4

TGA thermograms (a) CHDX, (b) CHTPP, (c) CHUF and (d) CHAL.

In the case of CHDX (Figure 4.a), a weight loss of 17.25% up to 252°C was observed. It is due to loss of free water present in the polymer network. Above 252°C, it decomposed, due to the degradation of the polymer network. The weight loss reached a value of 62 % at 600 °C. The weight loss in case of CHTPP (Figure 4.b), was 21.3% up to 222 °C, due to the loss of water present in the polymer and further, the weight loss reached a value of 65 % at 600 °C, due to the decomposition of polymer matrix. A similar pattern was observed for CHUF (Figure 4.c), with an initial weight

loss of 17.8% at 266°C. It reached the value of 67% at 600°C. Whereas, CHAL (Figure 4.d) showed decomposition at higher temperature than 273°C with an initial weight loss of 17.26% at 273°C and finally reached a value of 68% at 600°C. From this study, it can be inferred that the thermal stability of hydrogels was in the following order CHAL > CHUF > CHTPP > CHDX. This increase in the thermal stability indicates the formation of stronger and stiffer hydrogel network as a result of crosslinking.

XRD studies

The XRD studies are useful to investigate the crystallinity of the polymer network because crystallinity increases with the stiffness of the polymer network. The X-ray diffractograms of CH, CHDX, CHTPP, CHUF and CHAL are presented in Figure 5.

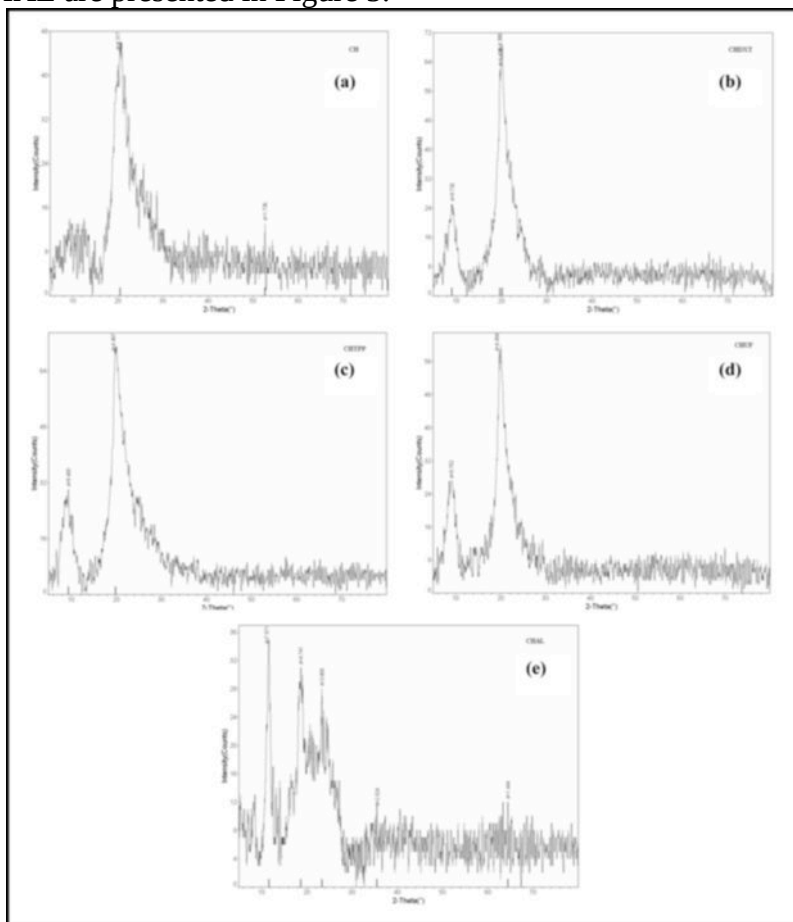


Figure 5

X-ray diffractograms (a) CH, (b) CHDX, (c) CHTPP, (d) CHUF and (e) CHAL.

All the samples have shown characteristic peaks between 2θ of 1° and 80° due to the crystallinity. The crystallinity was in the order CHAL > CHUF > CHTPP > CHDX > CH. This order of crystallinity, consistent with the order of stability by DSC and TGA, indicates that the crystallinity increases with increased crosslinking, and it may be attributed to increased stiffness of the polymer network.

Evaluation of tablets

The results of granules evaluation suggests that all the granules exhibited good flow properties with the angle of repose values less than 30° . A good packing ability of the granules was indicated by Carr's compressibility index and Hausner ratio as the values were in the range of 12.50 to 16.85 and 1.125 to 1.169 respectively (Table II).

Table II
Evaluation results of hydrogel granules

Tablets Code	Bulk density (g/mL)	Tap density (g/mL)	Carr's Index	Hausner ratio	Angle of repose
F1	0.47	0.53	12.766	1.128	25.51°
F2	0.46	0.52	13.043	1.130	27.12°
F3	0.48	0.54	12.500	1.125	26.82°
F4	0.5	0.58	16.000	1.160	26.26°
F5	0.42	0.48	14.286	1.143	25.85°
F6	0.51	0.58	13.725	1.137	29.94°
F7	0.45	0.52	15.556	1.156	27.57°
F8	0.51	0.59	15.686	1.157	26.95°
F9	0.445	0.52	16.854	1.169	26.78°
F10	0.48	0.56	16.667	1.167	26.89°

The weight and drug contents of all the tablets were within the range of 500 mg to 515 mg and 94.10 % to 97.36 % respectively and were found to be within the specified range (Table III).

Table III
Evaluation results of hydrogel tablets

Tablet Code	Weight (mg)	Hardness (kg/cm ²)	Friability (%)	Drug content (%)	Swelling ratio in pH 1.2 solution	Swelling ratio in pH 7.4 solution	Release mechanism (n)
F1	500	6	0.35	96.89	5.120	3.220	0.51
F2	505	5.7	0.25	95.03	4.257	3.089	0.56
F3	505	5.5	0.36	94.10	4.420	0.242	0.63
F4	515	5.3	0.15	95.96	3.903	0.198	0.66
F5	500	6	0.56	96.43	4.860	2.680	0.59
F6	505	6.2	0.35	97.36	4.178	2.218	0.61
F7	515	6	0.34	96.24	2.951	2.000	0.67
F8	505	5.9	0.62	96.80	2.772	1.980	0.69
F9	500	6	0.42	95.92	2.040	1.740	0.70
F10	509	5.8	0.67	95.45	1.670	1.434	0.74

The hardness and friability were in the range of 5.3 to 6.2 kg/cm² and 0.15 % to 0.67 % respectively, indicating the sufficient mechanical strength of the prepared tablets.

The release of the entrapped drug from the hydrogels depends on the swelling behavior, because the swelling opens up the pores of network and provides a gateway for drug release. The equilibrium swelling study of the hydrogel tablets was carried out in phosphate buffer of pH 7.4 and the results are shown in Table II. It was observed that the swelling of hydrogel tablets depends upon the type of crosslinking agents used. The tablets prepared with plain chitosan have shown higher swelling ratio as compared to those prepared with crosslinked-chitosan hydrogel tablets. The swelling of hydrogel tablets was in the order CHDX > CHTPP > CHUF > CHAL and this observed reverse order, compared to the stiffness order of CHAL > CHUF > CHTPP > CHDX deduced from XRD, DSA and TGA, is in agreement, because as the stiffness decreases, swelling is expected to increase. It was also noticed that the swelling of the hydrogel tablets was higher in the solution of pH 1.2 as compared to the swelling in the solution of pH 7.4. It may be due to hydration of cations, formed by the basic amino group of chitosan moiety under acidic condition.

The *in-vitro* drug release study was performed using a dissolution rate test apparatus in 0.1 N HCl (pH 1.2) for 2 h and in phosphate buffer (pH 7.4) till the end of the study. The dissolution profiles are given in Figure 6.

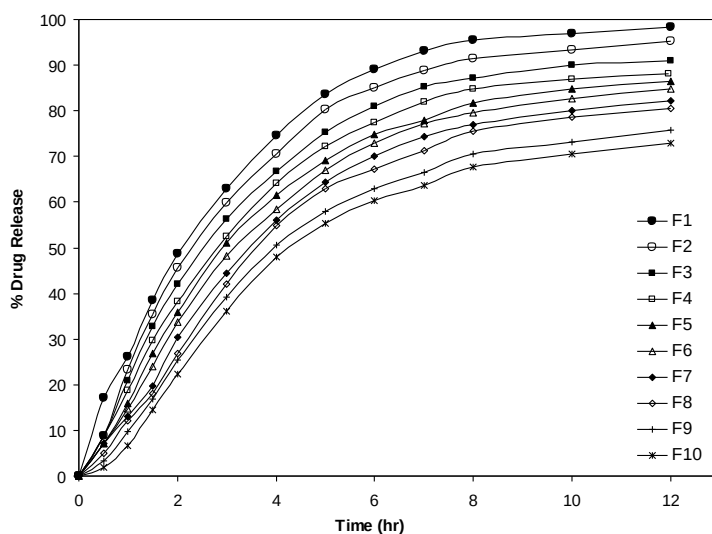


Figure 6

Drug release profiles of hydrogel matrix tablets F1 to F10

The results indicated that the F1 tablets, prepared with plain chitosan, have shown a higher drug release rate in the initial hours; 89 % of drug was released at the end of 6th hr, while the tablets prepared with crosslinked-chitosan (F3 to F10) have shown progressively slower drug release and some of them have shown premise of releasing the drug up to 12 h depending upon the formulation variables. The type of crosslinking agents affected the drug release rate, and in the case of the tablets prepared with CHUF (82%) it was slower than for the tablets prepared with TPP (86%), which in turn was slower than DXT drug release rate (90%) at the end of 12 h. CHAL tablets showed more prolonged drug release profiles (75%) as compared to DXT, TPP and CHUF at the end of 12 h. This could be due to the formation of stiffer polymer network at higher crosslink densities by decreasing the free volume of the polymer matrix, thereby reducing the movement of drug molecules through the polymer network. This could also reduce the swelling as well as the drug release from the matrix. On the other hand, an increase in polymer concentration decreased the release rate of drug from the polymer matrix.

To understand the drug release mechanism release, data was fitted to an empirical equation [21]:

$$\frac{M_t}{M_\infty} = Kt^n \quad (1)$$

where M_t is the amount of drug released at time t , M_∞ is the total amount of drug loaded, K is constant and n values are the indication of the type of release mechanism. The calculated n values have been shown in Table IV.

Table IV

Drug release mechanisms and kinetic values of drug release from matrix tablets

Tablet code	Zero order Equation		Higuchi Equation		Korsemeyer's Equation	
	n	r	n	r	n	r
F1	4.63	0.98	26.50	0.97	0.51	0.99
F2	4.81	0.80	24.18	0.98	0.56	0.99
F3	4.46	0.99	21.66	0.99	0.63	0.99
F4	4.89	0.98	19.52	0.99	0.66	0.99
F5	3.77	0.98	18.85	0.99	0.59	0.98
F6	4.57	0.97	23.59	0.99	0.61	0.98
F7	4.85	0.98	23.61	0.99	0.67	0.99
F8	5.25	0.94	24.51	0.98	0.69	0.99
F9	5.78	0.93	23.25	0.98	0.70	0.98
F10	4.89	0.94	22.54	0.98	0.74	0.98

r : correlation coefficients, n : release mechanism

The values of n showed the dependency on the crosslinking agents used for the preparation of hydrogels; the tablets prepared with un-crosslinked CH have shown higher n values as compared to the tablets prepared with CHDXT and the tablets containing CHAL have shown higher n values than the CHUF, which in turn was higher than the CHTPP. The calculated n values suggested that the mechanism of drug release followed the non-Fickian transport [21].

Conclusions

The crosslinked-chitosan based hydrogels were successfully prepared and used for the preparation of matrix tablets for the controlled release of gabapentin. The weight and drug contents of all the tablets were found to be uniform. The hardness and friability were within the specified range. The matrix tablets were capable of releasing the drug for 12 h depending upon the formulation variables. The order of drug release from the tablets (DXT > TPP > CHUF > CHAL) was consistent with the swelling ratios. The tablets prepared by plain chitosan discharged the drug quickly, while those prepared by crosslinking with AL released the drug more slowly in a controlled manner. Drug release mechanisms followed the non-Fickian transport. This study demonstrated that the drug release rate from the chitosan matrices could be controlled by crosslinking as exemplified by controlled release of gabapentin. Since there is no marketed controlled release formulation of gabapentin, the present findings will be useful in developing such formulations.

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