Research Article

FORMULATION AND EVAUATION OF HYDROGEL BASED ORAL CONTROLLED DRUG DELIVERY SYSTEM FOR GABAPENTIN

Deepa S Angadi, Jayadev N Hiremath, Anita R Desai and NS. Managoli

Department of Pharmaceutics, H.S.K College of pharmacy Bagalkot. India.

ABSTRACT

The aim of the present work was to prepare hydrogel matrix tablet for oral controlled release of an antiepileptic drug, Gabapentin. The hydrogels were prepared by crosslinking chitosan with acetaldehyde. The samples were characterized by (DSC) differential screening calorimetry analysis.The matrix tablets were prepared by wet granulation method, and evaluated for Precompression and post compression parameters. In-vitro dissolution studies were carried out using USP type II dissolution test apparatus. Among different formulations matrix tablets containing crosslinked hydrogel and HPMC K100 (1:1) ratio gives best dissolution profile and good physical integrity, free from any drug-polymer interaction and provide a method of achieving controlled drug action through uniform drug release up to 15 hr compared with other formulations. All the formulations were subjected for kinetic studies and fitted zero order model indicating that the drug release was by anomalous transport.

Keywords: Gabapentin, controlled release, crosslinked chitosan and HPMC K100.

INTRODUCTION

The oral drug delivery system is known for decades and is most widely utilized route of administration among all routes that have been explored for systemic delivery of drug via pharmaceutical dosage forms , oral route is considered most natural uncomplicated , convenient and safe because of its ease of administration, patient acceptance ,cost effectiveness and manufacturing process [1].

Recently novel polymeric matrices have been used as controlled release device for a variety of drugs. Amongst these water insoluble swellable hydrophilic polymers which are also called as hydrogels are being used as drug device for controlled release formulations. A Hydrogel is a cross linked network formed from a macromolecular hydrophilic polymer. It is stable up on swelling in water, varying from 10% to thousands of times of its own volume. The physical properties, including swelling, permeation, mechanical strength, and surface characteristics can be modulated through structural modification[2-5]. Modified chitosan hydrogels have been proven to be a potential carriers for delivery of different drug molecules with respect to size and type[6-8]

Gabapentin, 2-[1-(aminomethyl) cyclohexyl1) acetic acid, is a structural analog of γ- amino butyric acid (GABA), with an incorporated cyclohexyl ring. Gabapentin is currently marketed as an adjunctive therapy for partial seizers in adults with epilepsy and for the management of post hepatic neuralgia[9-10]. It is rapidly absorbed following oral dose[11] and has a relatively short half-life (5h), requiring three doses per day in most of the patients[12]. Further saturable transport system for Gabapentin results in non-linear absorption , Cmax increases less than three fold when the dose is increased from 300 to 900 mg. Controlled release formulation in addition to patient compliance assures prolonged and stable exposure to Gabapentin, providing other clinical benefits, including greater efficacy, reduced incidence of adverse effects related to peak drug levels[13,14] .

Hence the present work is aimed to design, develop and characterized the hydrogel based sustain release matrix tablet using crosslinked chitosan and HPMC K100 for controlled release of Gabapentin.

MATERIALS AND METHODS

MATERIALS

Gabapentin was obtained as a gift sample from Glenmark Pharmaceuticals Ltd, Goa, chitosan was procured from Himedia laboratories Pvt Ltd Mumbai, Hydroxy propyal methyl cellouse (HPMC K100) gift sample from On top Pharmaceutical Pvt Ltd Bangalore, Microcrystalline cellulose (MCC), Talc, acetaldehyde from Sdfine Chem limited Warli Road Mumbai, and magnesium stearate was purchased from Loba Chemie Mumbai.

Preparation of cross linked chitosan (CHAL) with acetaldehyde:
Chitosan solution (2% w/v) was prepared by stirring in 2% (v/v) aqueous acetic acid using a homogenizer until the chitosan dissolves completely. To this solution, acetaldehyde (AL) 20% w/w of dry chitosan and 0.5 ml of 0.1 N HCL were added and stirred for 1 h at 50 ^{o}C. Acetone was added and precipitated hydrogel (CHAL) was repeatedly washed with distilled water to remove any un-reacted material. Further it was dried at 40 ^{o}C for 24 h; powdered and stored in a well closed container.

Preparation of CHAL and HPMC K100 blend hydrogel matrix tablet.
The CHAL – HPMC K100 matrix tablets were prepared by conventional wet granulation method. Accurately weighed quantities of GBP, crossed linked chitosan, HPMC K 100 and microcrystalline cellulose (MCC) were passed through sieve ♯ 80 and mixed to get uniform mass. To this sufficient amount of binding agent (starch paste 5% w/v) was added. After required cohesiveness was attained, the mass was sieved through 22/44 mesh. The granules were dried at 40 oC for 12 h and then kept in a desiccator for 12 hrs at room temperature. The granules retained on 44 mesh were taken and mixed with 10% of fines, talc and magnesium stearate were added and then compressed in to tablets using a compression machine. Total weight of each tablet was 500 mg which contain 100 mg of Gabapentin.

Table 1: Formulation table

Ingredients.(mg)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}
Gabapentin	100	100	100	100	100	100	100	100	100	100
Chitosan	---	150	---	---	---	---	---	---	---	---
HPMC K 100	---	---	150	---	50	100	150	50	100	150
CHAL	---	---	---	150	100	100	100	150	150	150
Magnesium stearate.	5	5	5	5	5	5	5	5	5	5
Talc.	10	10	10	10	10	10	10	10	10	10
Microcrystalline cellulose.	385	235	235	235	235	185	135	185	135	85

PREFORMULATION STUDIES
FTIR study
Potassium bromide (KBr) was dried in hot air oven at 60°C for 1hr. The samples were prepared by mixing it thoroughly with potassium bromide. This mixture was then placed in a scanning slot of Fourier Transform Infra-Red (FTIR) spectrophotometer and scanned at range from 400 to 4000 cm^{-1} to obtain FTIR of API. The spectrum was then compared with the spectrum of reference standard.

Differential scanning calorimetry (DSC)
The accurately weighed samples (5- 6mg) of selected formulations were sealed in an aluminium DSC pan and an empty sealed aluminium pan was used as reference. The samples were heated from 40 – 300 ^{o}C at a heating rate of 10^{o} C/ min under nitrogen atmosphere using a microcarimeter (Perkin Elmer, pyris 6 DSC, USA) to obtain thermograms.

Scanning electron microscopy (SEM) The SEM analysis was carried out by mounting the samples on the tube using double sided adhesive tape and sputter coated with platinum using a sputter coater (Edward S 150, UK). The coated tablets were observed under SEM at room temperature. The acceleration voltage used was 10 KV with the secondary electron image as a detector.

Pre-compression parameters
Angle of Repose (Ɵ)
The angle of repose of powder blends was determined by the funnel method. Accurately weighed powder blends were taken in funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of heap of the powder blends (2cm). The powder blends were allowed to flow through the funnel freely on to its surface. The diameter of powder cone was measured and angle of repose was calculated.

$$\text{Ɵ} = \tan^{-1}(h/r)$$

Where,
Ɵ = Angle of repose, h = Height of the pile, r = Radius of the base pile.

Bulk-density

The powder sample was accurately weighed and transferred to a measuring cylinder. Then bulk volume was noted. Bulk density was calculated by using the formula.

Bulk-density = Mass of the powder/Bulk volume

Tapped-density

The powder sample was accurately weighed, transferred to measuring cylinder and subjected to 100 tapping's. Then volume was noted as tapped volume. Tapped density was measured by using the following formula.

Tapped-density= Mass of the powder/Tapped volume.

Carr's Index

Carr's index is an indication of the compressibility of powder. This is obtained from bulck density and tapped density.

Carr's Index was calculated by using the following formula.

Carr's Index = (Tapped density - Bulk density/Tapped density) x 100

Hausner's Ratio

Hausner ratio is an index of ease of powder flow, it is calculated by following formula.

Hausner's ratio= Tapped density/ Bulk density

Post Compression Parameters

Thickness

Control of physical dimension of the tablet such as thickness and diameter is essential for consumer acceptance and tablet uniformity. The thickness and diameter of the tablet was measured using Vernier calipers. It is measured in mm.

Hardness

The Monsanto hardness tester was used to determine the tablet hardness. The tablet was held between a fixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of hardness of the tablet. Hardness was expressed in kg/cm2.

Friability (F)

Tablet strength was tested by Roche friabilator. Pre weighed tablets were subjected to 100 revolutions (4min), taken out and were dedusted. The percentage weight loss was calculated by rewriting the tablets. The % friability was then calculated by,

F= (W initial – W final / W initial)*100

Where,

F = Percentage friability

W initial= Initial weight before friability test.

W final= Final weight after friability test.

If % Friability of tablets is less than 1% it is considered acceptable.

Weight variation

Randomly selected ten tablets were weighed individually and together in a single pan balance. The average weight was noted and standard deviation calculated. The tablet passes the test if not more than two tablets fall outside the percentage limit and none of the tablet differs by more than double the percentage limit.

PD= W avg - W initial/ W avg *100

Where, PD = Percentage deviation,

W avg = Average weight of tablet,

W initial = individual weight of tablet.

Swelling Index

The extent of swelling was measured in terms of percentage weight gain by the tablet. One tablet from each formulation at triplicate manner was taken and kept in a Petri dish containing pH 6.8

phosphate buffer. At the end of 1 hour, the tablet was withdrawn and the excess water was removed by placing the tablet on tissue paper and weighed. Then for every 1 hour, weights of the tablets were noted and the process was continued till the end of 8 hours. The swelling index was calculated using following formula:

% (S.I.) = {(Mt) – (Mo)/ (Mo)} x 100

Where, S.I. = Swelling index
Mt = weight of the swollen tablet at time t
Mo = initial weight of the tablet at time Zero (0)

Drug content

Three tablets were weighed and crushed in a mortar. The weighed powder containing to 100mg equivalent of drug was dissolved in 100ml of phosphate buffer pH 6.8. Subsequently, the solution in volumetric flask was filtered; suitable dilutions were carried out and final solutions were analysed at 212nm using UV- visible spectrophometer Shimadzu UV- 1600, Japan.

***In-vitro* drug release studies**

In vitro drug release studies were carried out using USP XXII dissolution apparatus type II (Electrolab, Mumbai, India) at 75 rpm. The dissolution medium consist of 900 ml of pH 6.8 phosphate buffer for 15 hour , maintained at 37 ± 1 ^{0}C. The drug release at different time intervals was measured using an ultraviolet visible spectrophotometer (Shimadzu) at 212 nm. The study was performed in triplicate.

RESULTS AND DISCUSSION

Preformulation study

Description

The sample of Gabapentin was found to be white powder having no odour.

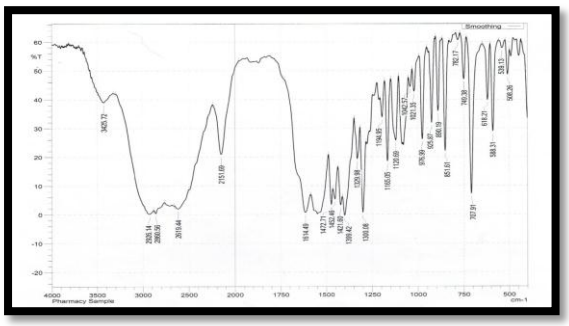
Determination of solubility

Gabapentin drug is freely soluble in water, partially soluble in glacial acetic acid, ethanol, methanol and other aqueous / organic solvents.

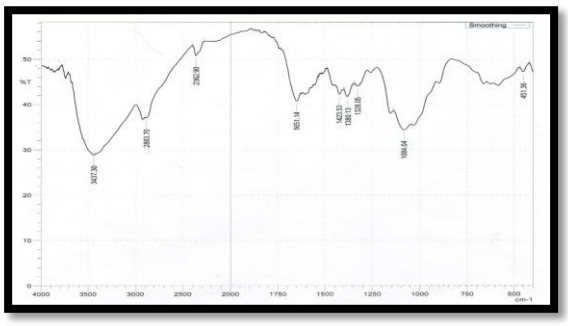
Determination of melting point

Melting point of Gabapentin drug was found to be 162°C.

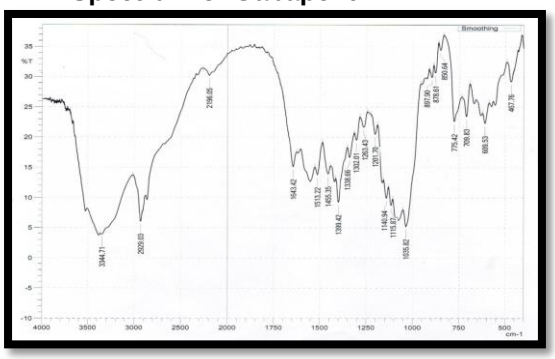
COMPATIBILITY STUDIES



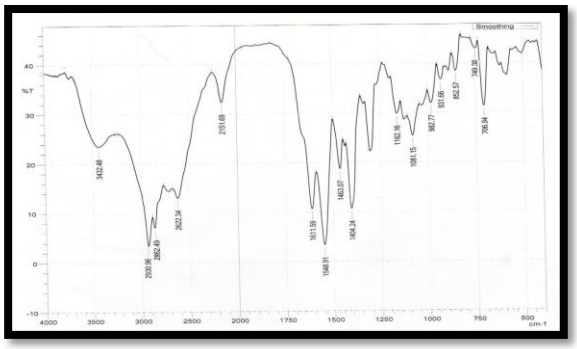
FTIR Spectrum of Gabapentin



FTIR Spectrum of Chitosa



FTIR Spectrum of F10



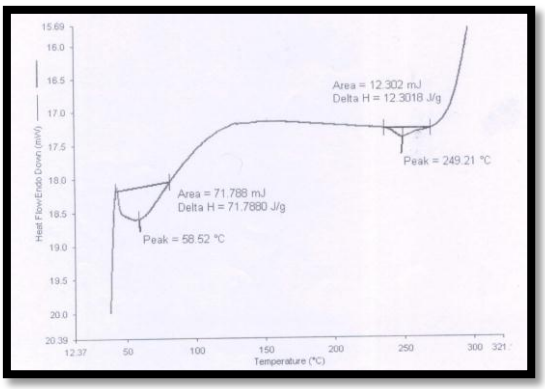
FTIR Spectrum of CHAL

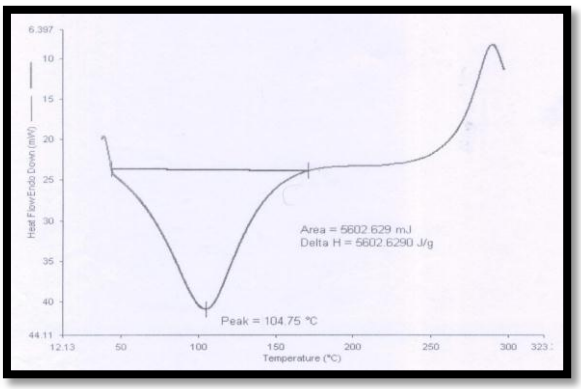
a) FTIR spectrum to establish cross linking between chitosan & acetaldehyde.

FTIR analysis: The FTIR spectra of CH and CHAL given in figure 14and 16 confirms the crosslinking of chitosan with acetaldehyde. In case of chitosan (CH) the peak at 3437 cm^{-1} is assigned for stretching vibration of hydroxyl and amino groups, the peak at 2883 cm^{-1} is due to C-H stretching. The band at 1651 cm^{-1} is due to C=O stretching and another band around 1570 cm^{-1} corresponds to N-H bending and the peak at 1084cm^{-1} is due to C-O stretching of ether group. While in case of CHAL, peak at 3424cm^{-1} is assigned for starching vibration of hydroxyl group, The peak at 2927cm^{-1} is due to stretching vibrations of –CH group, the peak at 1652cm^{-1} is attributed to carbonyl stretching vibrations of acetamide group, and imine bonds (C=N) formed by crosslinking reaction between the amino groups of chitosan and acetaldehyde. This peak confirms the formation of schiff base after crosslinking reaction.

The peaks at 2926 and 2860 cm^{-1} are due to $–NH_3^+$ stretching vibrations. The peak at 3425 cm^{-1} might be attributed to stretching vibration of –OH group. The peak at 2151cm^{-1} corresponds to the distinct side chain and/or CN stretching vibrations of Gabapentin, polymorphs. The peaks in the region of 1700-1500cm^{-1} could be assigned as the ionised asymmetric carboxyl ate and NH_3^+ deformation vibration. The peaks at 1472,1452,1421,1399 cm^{-1} corresponds to asymmetric carboxyl ate band and/or CH_2 deformation band. Where as in the spectra of physical mixture of Gabapentin and other excipients almost all the peaks related to Gabapentin were noticed with slight variations. This confirms the compatibility of Gabapentin with excipients in the formulation.

DSC Analysis



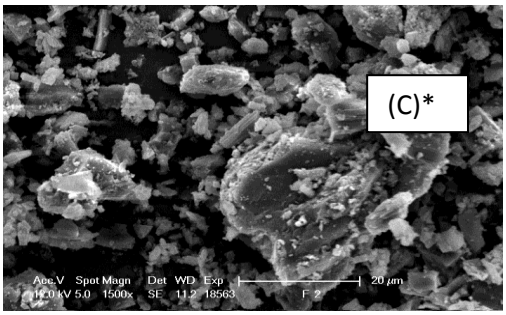


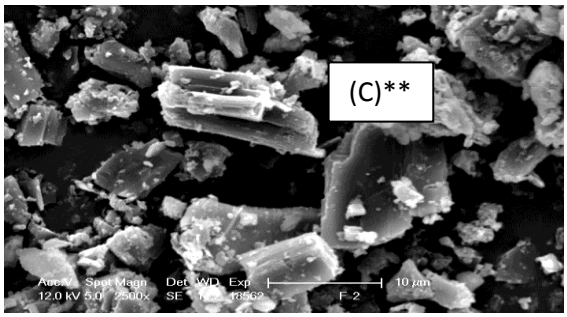
DSC Thermogram of Chitosan (CH) **DSC Thermogram of Crossed linked Chitosan (CHAL)**

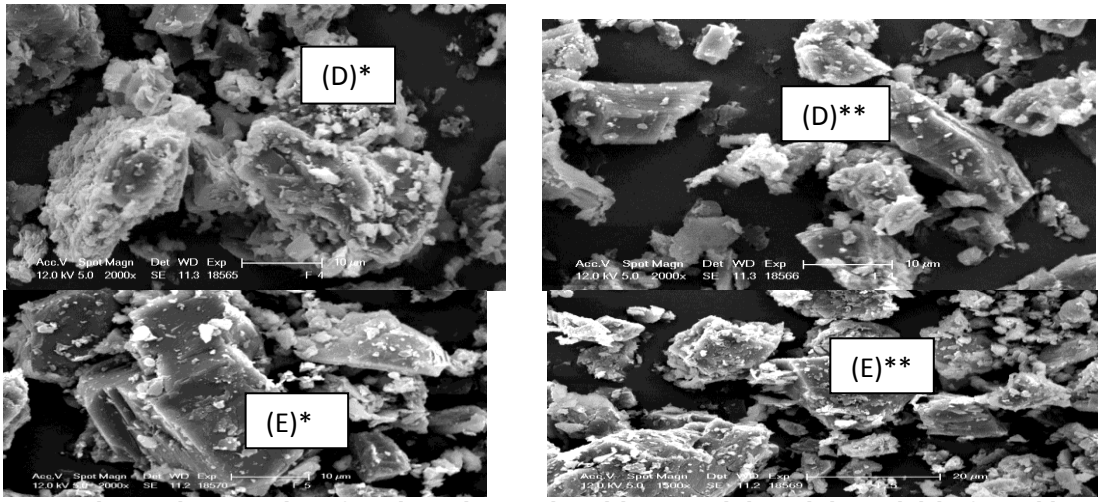
The DSC tracings of chitosan (CH) and cross linked chitosan with Aldehyde (CHAL), are shown in the fig CH exhibited the endothermic peak at 58.52 ^oC while CHAL at 104.75^oC. A shift in endothermic peak for the hydrogel towards the higher temperature compared to CH would be due to the formation of more rigid hydrogel network as a result of crosslinking.

SEM Analysis.

The surface morphology of the hydrogel tablets before and after dissolution







SEM Photomicrographs of Hydrogels matrix tablets F4 (C),F5 (D), F7 (E) before (*) and after (**) the dissolution testing

The surface morphology of hydrogel tablets before and after the dissolution testing was studied using SEM photomicrographs, which are shown in fig 22.The surface of the hydrogel tablets was smooth and uniform before drug release testing whereas after testing the surface has became porous with polymeric erosion as evident from SEM photomicrographs. This indicates that the hydrogel network has undergone swelling and drug might have diffused out through the matrix by polymer chain relaxation and erosion.

PRE-COMPRESSION STUDY

Table 6: Precompression parameters of tablets

Batch no	Bulk density (gm/ml) ±SD	Tapped Density (g/ml) ±SD	Compressibility (%)	Housner's Ratio	Angle of Repose ±SD
F_1	0.562±0.001	0.605±0.002	6.9306	1.074468	25.60±0.435
F_2	0.531±0.001	0.573±0.0030	7.01754	1.07532	27.41±0.369
F_3	0.527±0.001	0.567±0.002	6.9076	1.0789	23.32±0.225
F_4	0.516±0.005	0.583±0.003	8.7871	1.0963	27.16±0.283
F_5	0.470±0.003	0.4934±0.001	4.5832	1.04227	24.88±0.977
F_6	0.521±0.001	0.575±0.003	9.280	1.10145	29.28±0.306
F_7	0.563±0.002	0.601±0.002	6.2895	1.0671	26.19±0.245
F_8	0.531±0.004	0.564±0.003	7.695	1.083365	28.29±0.480
F_9	0.531±0.003	0.571±0.003	6.916	1.0743	27.35±0.545
F_{10}	0.509±0.002	0.559±0.003	7.8286	1.08493	28.26±0.514

For all the formulations angle of repose was found in the range of 23.32° ±0.225to 29.28°±0.306, Bulk density was found to be in range of 0.470±0.003 to 0.563±0.002 gm/ml, and tapped density was found to be in the range of 0.493±0.001 to 0.605±0.002 gm/ml, The % compressibility of all the formulations lie within the range of 4.583 to 9.28% indicating excellent flow property of prepared granules. . The values lie within the range of 1.04 to 1.1014%

POST COMPRESSION STUDY

Table 7: post compression parameters of tablets

Batch no	Weight variation(mg) ±SD	Friability% ±SD	Hardness (Kg/cm^2) ±SD	Thickness (mm)	Drug content ±SD
F_1	500.2±1.135	0.120±0.049	5.93±0.850	4.14	96.630±1.70
F_2	500.9±1.197	0.452±0.040	5.8±0.929	4.11	95.54±0.334
F_3	500.3±125	0.245±0.035	5.4±0.305	4.19	98.93±0.305
F_4	501.4±1.315	0.746±0.041	5.5±0.208	4.34	95.63±0.335
F_5	500.9±1.152	0.341±0.040	5.46±0.305	4.12	97.50±0.252
F_6	501±1.129	0.359±0.040	5.4±0.100	4.22	95.50±0.301
F_7	500±1.256	0.136±0.032	5.71±0.090	4.25	97.63±0.384
F_8	500.5±1.325	0.365±0.030	5.71±0.268	4.17	94.638±0.361`
F_9	500.6±1.856	0.236±0.025	5.36±0.251	4.11	98.36±0.238
F_{10}	500.7±1.965	0.357±0.036	5.73±0.122	4.23	97.53±0.235

The tablet thickness of all the formulations lie within the range of 4.11to 4.34mm, The tablet hardness was found to be in the range of 5.36±0.251 to 5.93±0.850 kg/cm^2 , The weight variation was found to be in the range of 500±1.256 to 501.7±1.315 mg. The % friability of all the formulations was found to be between 0.120±0.049 to 0.74±0.04 % , The drug content estimation data for all the formulations were found to be between 94.638± to 98.93±0.335%.

5.5 SWELLING INDEX

Table 8: Swelling Index of formulations F1 to F10

Time Hour	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}
1	7.446	11.82	9.795	10.40	3.488	3.454	3.082	1.92	3.08	1.96
2	22.33	23.84	12.85	17.61	7.089	8.211	6.003	22.7	4.55	4.22
3			17.92	23.04	10.91	12.21	8.743	24.9	7.02	7.07
4			21.348		13.54	16.02	12.56	28.4	8.37	9.76
5					18.49	18.73	15.93	30.1	12.21	12.3
6					20.57	21.15	17.73	32.5	14.89	15.1
7					22.55	22.97	19.58	33.6	17.54	18.5
8						23.67	22.68	35.2	19.39	19.3

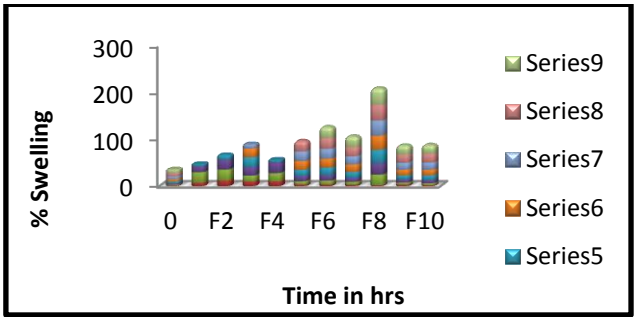


Fig. 12: Swelling index in %

Formulation F2 containing drug & plain chitosan showed higher swelling ratio as compared to the tablets prepared with cross linked chitosan hydrogel tablets. In case of F5, F6 &F7 containing crosslinked chitosan and HPMC K100 in the ratio 2:1, 1:1 & 3:2, respectively, F6 showed higher swelling index at the end of 8hrs, where as in case of F8, F9 and F10 formulations containing crosslinked chitosan to HPMC K100 in the ratio 1:3, 2:3, and 1:1 the higher swelling index was observed with F8. However a steady increase in swelling rate was observed for F10 containing equal proportion of polymers.

IN- VITRO DISSULATION STUDY

Drug release profile was studied using percentage drug release versus time(hr) plot. The results are depicted in Table No.16 & 17. Formulations F1, F2, F3, F4 and F5 showed 98.63±0.51%, 97.060±0.41%, 95.23±0.27%, 95.61±0.24%, 96.911±0.27%. Release of drug respectively at 15 hrs. Formulations F6, F7, F8, F9 & F10 showed 94.01±0.32%, 96.26±0.46%, 95.87±46, 95.99±0.24%, 90.56±0.56 and 96.86±0.63Respectively. Among all formulations F10 has shown controlled release of drug.

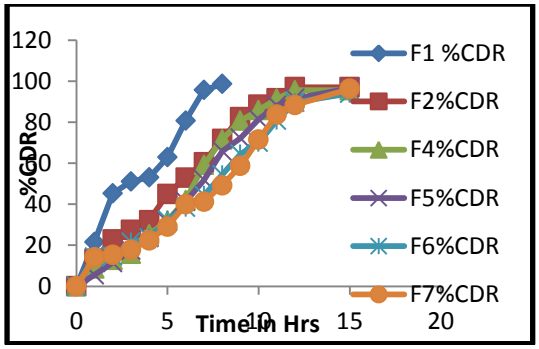


Fig. 13: Cumulative % of drug release F2, F4, F8, F9, and F10

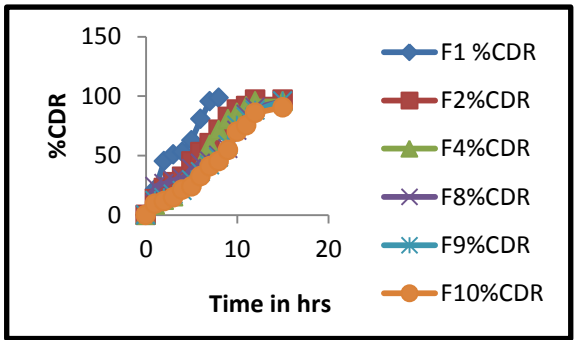


Fig. 14: Cumulative % of drug release Vs Time of F1, Vs Time of F1, F2, F4, F5, F6, and F7

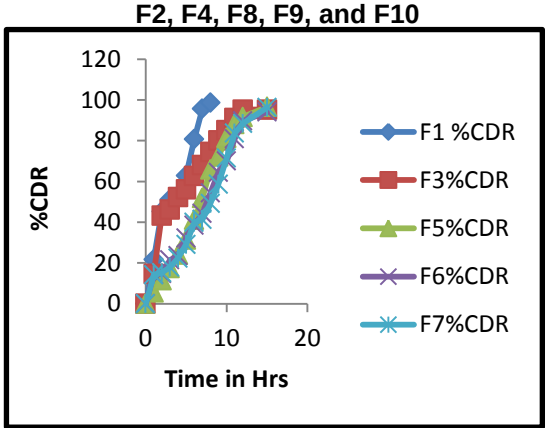


Fig. 15: Cumulative% of drug release Vs of F1, F3, F8, F9, and F10

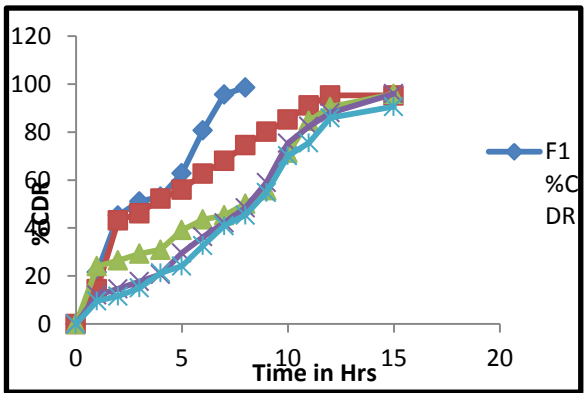


Fig. 16: Cumulative % of drug release Vs time Time of F1, F3, F5, F6, and F7

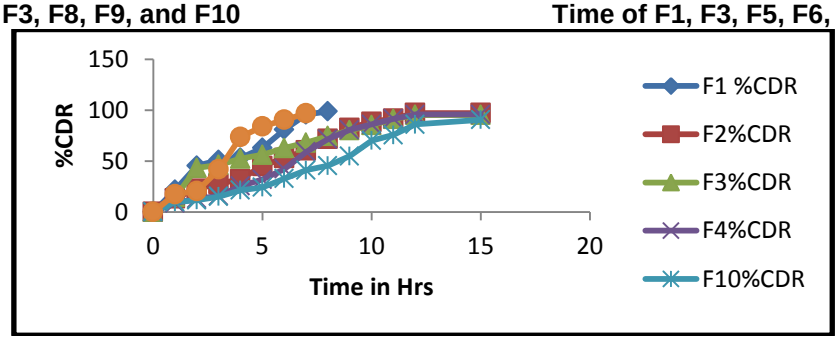


Fig. 17: cumulative % of drug release Vs Time of F1,F2,F3,F4,F10

Release Kinetics.

Table 11: Kinetics of drug release of Gabapentin OCRDDS

Code.	Zero Order. (R^2)	First Order. (R^2)	Higuchhi (Matrix). (R^2)	Peppas. (R^2)	Hixon Crowen. (R^2)	Best Fit Model.
F1.	0.9657	0.9735	0.9682	0.9782	0.9711	Peppa's
F2.	0.9704	0.9758	0.9473	0.9903	0.9742	Peppa's
F3.	0.8694	0.8950	0.9879	0.9608	0.8869	Matrix
F4.	0.9731	0.9733	0.9008	0.9804	0.9733	Peppa's
F5.	0.9845	0.9841	0.9017	0.9950	0.9844	Peppa's
F6.	0.9889	0.9883	0.9126	0.9665	0.9886	Zero – order
F7.	0.9856	0.9831	0.8958	0.9560	0.9841	Zero – order
F8.	0.9611	0.9660	0.9312	0.9317	0.9647	First – order
F9.	0.9851	0.9823	0.8909	0.9646	0.9834	Zero – order
F10	**0.9838**	**0.9804**	**0.8825**	**0.9718**	**0.9817**	**Zero-order**

The cross linked hydrogel matrix tablet F6 to f10 have shown near Zero order release when analysed using PCP- Disso V2.08 soft ware, except formulation F8. The 'n' and 'R' values for all the formulations.

CONCLUSION

The FTIR studies indicated that the drug was compatible with the polymers and other excipients used in the dosage form.DSC studies along with FTIR spectra confirmed the crosslinking of chitosan. Pre-compression parameter results showed good flow properties. Post-Compression parameter results were found to be optimum. Hardness of the tablets is sufficient to withstand the shock. All the formulated tablets were found be within the official limit for weight uniformity. The drug content was uniform in all the tablet formulations indicating uniform distribution of drug within the matrices. Based on the *in- vitro* dissolution studies formulations F10 containing HPMC K100 150mg , CHAL 150mg was found to be promising and showed a drug release profile 90.01% when compared to other formulations. All the formulations were subjected for kinetic studies and showed near Zero order model indicating that the drug release was by anomalous transport. Finally, it was concluded that the Hydrogel based CDDTs of Gabapentin, formulations F10 containing HPMC K100 150mg , CHAL 150mg are showed Swelling time and *in-vitro* drug release study slower than the other formulations. Selected formulations were found to be complying with all the properties of tablets and the formulations were satisfactory.

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