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

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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. 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. Modified chitosan hydrogels have been proven to be a potential carriers for delivery of different drug molecules with respect to size and type.

Gabapentin, 2-[1-(aminomethyl) cyclohexyl] 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 seizures in adults with epilepsy and for the management of post hepatic neuralgia. It is rapidly absorbed following oral dose and has a relatively short half-life (5h), requiring three doses per day in most of the patients. 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.

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 cellulose (HPMC K100) gift sample from On top Pharmaceutical Pvt Ltd Bangalore, Microcrystalline cellulose (MCC), Talc, acetaldehyde from Sdine 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 °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 °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

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
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<tr>
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<td>---</td>
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</tbody>
</table>

**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 °C at a heating rate of 10° 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 (Θ)**
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.

\[ Θ = \tan^{-1} \left( \frac{h}{r} \right) \]

Where,

- Θ = 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.

\[
\text{Bulk-density} = \frac{\text{Mass of the powder}}{\text{Bulk volume}}
\]

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.

\[
\text{Tapped-density} = \frac{\text{Mass of the powder}}{\text{Tapped volume}}
\]

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

\[
\text{Carr’s Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100
\]

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

\[
\text{Hausner’s ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}
\]

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,

\[
F = (W_{\text{initial}} - W_{\text{final}}) / W_{\text{initial}} \times 100
\]

Where,
- \( F \) = Percentage friability
- \( W_{\text{initial}} \) = Initial weight before friability test.
- \( W_{\text{final}} \) = 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.

\[
PD = \frac{W_{\text{avg}} - W_{\text{initial}}}{W_{\text{avg}}} \times 100
\]

Where,
- \( PD \) = Percentage deviation,
- \( W_{\text{avg}} \) = Average weight of tablet,
- \( W_{\text{initial}} \) = 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:

\[
\% \text{ (S.I.)} = \frac{(M_t) - (M_o)}{(M_o)} \times 100
\]

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 spectrophotometer 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°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**
a) FTIR spectrum to establish cross-linking between chitosan & acetaldehyde.
FTIR analysis: The FTIR spectra of CH and CHAL given in figure 14 and 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 1084 cm⁻¹ is due to C-O stretching of ether group. While in case of CHAL, peak at 3424 cm⁻¹ is assigned for stretching vibration of hydroxyl group. The peak at 2927 cm⁻¹ is due to stretching vibrations of –CH group, the peak at 1652 cm⁻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 –NH₃⁺ stretching vibrations. The peak at 3425 cm⁻¹ might be attributed to stretching vibration of –OH group. The peak at 2151 cm⁻¹ corresponds to the distinct side chain and/or CN stretching vibrations of Gabapentin, polymorphs. The peaks in the region of 1700-1500 cm⁻¹ could be assigned as the ionised asymmetric carboxylate and NH₃⁺ deformation vibration. The peaks at 1472, 1452, 1421, 1399 cm⁻¹ corresponds to asymmetric carboxylate band and/or CH₂ 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

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 °C while CHAL at 104.75°C. 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 become 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

<table>
<thead>
<tr>
<th>Batch no</th>
<th>Weight Variation (mg) ±SD</th>
<th>Friability% ±SD</th>
<th>Hardness (Kg/cm²) ±SD</th>
<th>Thickness (mm)</th>
<th>Drug content ±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>500±1.135</td>
<td>0.120±0.049</td>
<td>5.93±0.850</td>
<td>4.14</td>
<td>96.63±1.70</td>
</tr>
<tr>
<td>F2</td>
<td>500±1.197</td>
<td>0.452±0.040</td>
<td>5.8±0.929</td>
<td>4.11</td>
<td>95.54±0.334</td>
</tr>
<tr>
<td>F3</td>
<td>500±1.125</td>
<td>0.245±0.035</td>
<td>5.4±0.305</td>
<td>4.19</td>
<td>98.93±0.305</td>
</tr>
<tr>
<td>F4</td>
<td>501±1.315</td>
<td>0.746±0.041</td>
<td>5.5±0.208</td>
<td>4.34</td>
<td>95.63±0.335</td>
</tr>
<tr>
<td>F5</td>
<td>500±1.152</td>
<td>0.341±0.040</td>
<td>5.46±0.305</td>
<td>4.12</td>
<td>97.50±0.252</td>
</tr>
<tr>
<td>F6</td>
<td>501±1.129</td>
<td>0.359±0.040</td>
<td>5.4±1.00</td>
<td>4.22</td>
<td>95.50±0.301</td>
</tr>
<tr>
<td>F7</td>
<td>500±1.136</td>
<td>0.136±0.032</td>
<td>5.71±0.090</td>
<td>4.25</td>
<td>97.63±0.384</td>
</tr>
<tr>
<td>F8</td>
<td>500±1.325</td>
<td>0.365±0.030</td>
<td>5.71±0.268</td>
<td>4.17</td>
<td>94.63±0.361</td>
</tr>
<tr>
<td>F9</td>
<td>500±1.856</td>
<td>0.236±0.025</td>
<td>5.36±0.251</td>
<td>4.11</td>
<td>98.36±0.238</td>
</tr>
<tr>
<td>F10</td>
<td>500±1.965</td>
<td>0.357±0.036</td>
<td>5.73±0.122</td>
<td>4.23</td>
<td>97.53±0.235</td>
</tr>
</tbody>
</table>

For all the formulations angle of repose was found in the range of 23.32° ±0.225 to 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

<table>
<thead>
<tr>
<th>Batch no</th>
<th>Weight Variation(mg) ±SD</th>
<th>Friability% ±SD</th>
<th>Hardness (Kg/cm²) ±SD</th>
<th>Thickness (mm)</th>
<th>Drug content ±SD</th>
</tr>
</thead>
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<tr>
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<tr>
<td>F6</td>
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<td>5.73±0.122</td>
<td>4.23</td>
<td>97.53±0.235</td>
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</table>
The tablet thickness of all the formulations lie within the range of 4.11 to 4.34 mm. The tablet hardness was found to be in the range of 5.36 ± 0.251 to 5.93 ± 0.850 kg/cm². 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 ± 0.335%.

5.5 SWELLING INDEX

Table 8: Swelling Index of formulations F1 to F10

<table>
<thead>
<tr>
<th>Time Hour</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
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<td>3.488</td>
<td>3.454</td>
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<td>1.92</td>
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<td>1.96</td>
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<td>2</td>
<td>22.33</td>
<td>23.84</td>
<td>12.85</td>
<td>17.61</td>
<td>7.089</td>
<td>8.211</td>
<td>6.003</td>
<td>22.7</td>
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<td>4.22</td>
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<tr>
<td>3</td>
<td>17.92</td>
<td>23.04</td>
<td>10.91</td>
<td>12.21</td>
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<td>4</td>
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<td>12.56</td>
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</table>

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, whereas 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 DISSOLUTION 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%, 96.91±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±0.63 Respectively. 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, F2, F4, F5, F6, and F7

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

Fig. 16: Cumulative % of drug release Vs time 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

<table>
<thead>
<tr>
<th>Code</th>
<th>Zero Order. (R²)</th>
<th>First Order. (R²)</th>
<th>Higuchi (Matrix). (R²)</th>
<th>Peppas. (R²)</th>
<th>Hixon Crowen. (R²)</th>
<th>Best Fit Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.9657</td>
<td>0.9735</td>
<td>0.9682</td>
<td>0.9782</td>
<td>0.9711</td>
<td>Peppa’s</td>
</tr>
<tr>
<td>F2</td>
<td>0.9704</td>
<td>0.9758</td>
<td>0.9473</td>
<td>0.9803</td>
<td>0.9742</td>
<td>Peppa’s</td>
</tr>
<tr>
<td>F3</td>
<td>0.8694</td>
<td>0.8950</td>
<td>0.9879</td>
<td>0.9608</td>
<td>0.9869</td>
<td>Matrix</td>
</tr>
<tr>
<td>F4</td>
<td>0.9731</td>
<td>0.9733</td>
<td>0.9008</td>
<td>0.9804</td>
<td>0.9733</td>
<td>Peppa’s</td>
</tr>
<tr>
<td>F5</td>
<td>0.9845</td>
<td>0.9841</td>
<td>0.9017</td>
<td>0.9950</td>
<td>0.9844</td>
<td>Peppa’s</td>
</tr>
<tr>
<td>F6</td>
<td>0.9889</td>
<td>0.9883</td>
<td>0.9126</td>
<td>0.9665</td>
<td>0.9886</td>
<td>Zero – order</td>
</tr>
<tr>
<td>F7</td>
<td>0.9856</td>
<td>0.9831</td>
<td>0.8958</td>
<td>0.9560</td>
<td>0.9841</td>
<td>Zero – order</td>
</tr>
<tr>
<td>F8</td>
<td>0.9611</td>
<td>0.9660</td>
<td>0.9312</td>
<td>0.9317</td>
<td>0.9647</td>
<td>First – order</td>
</tr>
<tr>
<td>F9</td>
<td>0.9851</td>
<td>0.9823</td>
<td>0.8909</td>
<td>0.9846</td>
<td>0.9834</td>
<td>Zero – order</td>
</tr>
<tr>
<td>F10</td>
<td>0.9838</td>
<td>0.9804</td>
<td>0.8825</td>
<td>0.9718</td>
<td>0.9817</td>
<td>Zero – order</td>
</tr>
</tbody>
</table>

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.

ACKNOWLEDGEMENT
I am thankful to the faculty members, Department of Pharmaceutics, H.S.K. College of Pharmacy, Bagalkot. For providing necessary facilities to carry out this research work.

REFERENCES