RESEARCH AND REVIEWS: JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES

Formulation and Evaluation of Floatable In-situ Gel for Stomach-Specific Drug Delivery of Carbamazapine.

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Received: 09/11/2013
Revised : 05/12/2013
Accepted: 13/12/2013

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Keywords: Carbamazapine; in-situ gel, Sodium alginate; floating.

ABSTRACT

The present investigation deals with the formulation and evaluation of sodium alginate and HPMC based floating oral in-situ gel of carbamazapine. Sodium alginate and HPMC were used as a polymer and CaCO3 was used as a cross-linking agent to form in-situ gels. The drug gets released in sustained and controlled manner from these types of formulations for prolonged duration thus reduces the dosing frequency of the drug. Formulation method of present study utilizes the polymers that exhibit sol-to-gel phase transition due to change in specific physicochemical parameters. Developed formulations were evaluated for their suitability to control the drug release and ease of administration by measuring the amount of drug entrapped, floatation duration, rate of drug release and pH and viscosity during sol gel transition etc. Results of the study indicated among the different batches of formulations with range of polymeric concentration and gelling stimuli, the formulation batch F5 was most suitable preparation being able to control the drug release for 24hrs duration with administration and physiological suitability in terms of pH and Viscosity. Thus results of the study concluded that very useful antiepileptic drugs like carbamazapine can be reformulated into more patient friendly and therapeutically beneficial formulations using these types of oral in-situ floatable gel systems, which reduces manufacturing cost and duration.

INTRODUCTION

The present research is about gastro retentive drug delivery systems in the form of in-situ gels. Advanced research is carried out to develop novel drug delivery systems to alter the pharmacokinetics of the drugs. Drug release from the delivery devices are usually sustained at the target sites for many drugs using current release technologies. The main accent during the development of oral controlled release dosage forms is to prolong the residence time of the dosage form in the stomach or upper gastrointestinal (GI) tract until the drug is completely released[1]. To achieve the retention of dosage unit in stomach many approaches have emerged like bioadhesive systems, swelling and expanding systems, floating systems,modified shape systems, high-density systems and other delayed gastric emptying devices[2,3,4].

FFDS are widely explored for gastro retention purposes and have a bulk density lower than gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on gastric contents, the drug is released slowly at a desired rate from the system. The gel formed from in situ gelling system, being lighter than gastric fluids, floats over the stomach contents or adhere to gastric mucosa due to presence of bioadhesive nature of polymer and produce gastric retention of dosage form and increase gastric residence time resulting in prolonged drug delivery in gastrointestinal tract[5,6]. In situ forming gels are formulations, applied as a solution, which undergoes gelation after instillation due to physicochemical changes inherent to the biological fluids. In this way, the polymers, which show sol-gel phase transition and thus trigger drug release in response to external stimuli, are the most investigated. In-situ hydrogels are providing such “sensor” properties and can undergo reversible sol-gel phase transitions upon changes in the environmental condition[7]. These “intelligent” or “smart” polymers play important role in drug delivery since they may dictate not...
only where a drug is delivered, but also when and with which interval it is released. Sodium alginate (SA) is a widely used natural polymer in various drug delivery systems. It exhibits favourable biological properties such as non-toxicity, biocompatibility, biodegradability and ulcer healing traits. Moreover, gelation of dilute solutions of SA occurs on addition of di-and trivalent ions by a co-operative process involving consecutive G-residues in the α-L-guluronic acid blocks of the alginate chain in a manner described by the ‘egg-box’ model[8,9].

Carbamazepine is used for anticonvulsant and antineuralgic effects. The popularity of this drug is related to several beneficial properties, including, proven efficacy in controlling different types of seizures. It is poorly soluble in water with erratic oral absorption and bioavailability less than 70%. Moreover carbamazepine has a narrow therapeutic range and shows bioavailability differences [10,11]. In efforts to reduce the frequency of dosing required for chronic carbamazepine therapy and to decrease variability in plasma concentration, various extended release formulations have been developed by many researchers [12]. Preparing the drug in a floating in-situ gel dosage form can control the extent of bioavailability for such poorly water soluble drug. The objective of the present investigation is to develop floating in-situ gels containing carbamazepine which are helpful in long term treatment of chronic seizures.

MATERIALS AND METHODS

Materials

Sodium citrate, Sodium alginate, CaCl2 and CaCO3 were obtained from Qualigens Fine chemicals, Mumbai. HPMC K4M was gift sample from Manb rovepharma, Mumbai. Gift sample of Carbamazepine was kindly provided by Sun pharmaceuticals Ltd, Vadodara, Gujarat. All the other ingredients used were of analytical grade and used as received.

Method of preparation of in-situ gelling solutions[4,5]

Sodium alginate solutions of concentrations 0.25, 0.5, 1.0, 1.5 and 2.0% (w/v) were prepared by adding the alginate to deionized water, the HPMC K4M, HPMC K15M and HPMC K100M were also added in respective batch in different concentration, containing 0.25% (w/v) sodium citrate with stirring and calcium carbonate (prescreened by 60 #) was dissolved in another beaker along with Methyl Paraben and Propyl Paraben in 2:0.2 ratios in purified water in sufficient quantity. Carbamazepine (2000 mg) was initially dissolved in hot propylene glycol solution, then dissolved in 10 ml of 0.1N HCl solution (pH 1.2) and added to above solution. Concentrations of cations in solution were sufficient to hold the molecular chains together and inhibit hydration. Sodium alginate solution was heated to 70°C with stirring. After cooling to below 40°C, different concentrations of calcium carbonate and the drug solution were added and dispersed well with continuous stirring. This results in sodium alginate in-situ gelling solution containing carbamazepine which were checked for lag time, viscosity and gelling property. To achieve repeatability in gelation we used a source of Ca++ ions in the solution itself. Due to the free calcium ions being complexed with sodium citrate, gelation was delayed until the administered solution reached the acidic environment of the stomach. Gelation was then occurred as the complex broke down and the Ca++ ions were released. The calcium carbonate present in the gelling formulation released carbon dioxide in gastric environment thereby making the formulation porous and buoyant and prolonging the residence time.

UV Absorbance Maxima and Calibration Curve of Carbamazapine in 0.1 N HCl

Stock solution of Carbamazapine in methanol with proper dilution was initially scanned in UV visible spectrophotometer within wavelength of 200-700 nm. For calibration, 100 mg of Carbamazapine was dissolved in 100 ml of 0.1N HCl. The solution was then diluted with 0.1 N HCl to obtain 10, 20, 30, 40, 50 and 60 µg/ml solution. It was then measured by UV visible spectrophotometer at 286nm.

Identification of Drug by FTIR

Fourier-transform infrared (FT-IR) spectra were obtained using an FT-IR spectrometer (Shimadzu 8400S, Japan). The pure carbamazapinewere mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:5 (Sample: KBr) ratio, respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press. Forty scans were obtained at a resolution of 4 cm-1, from 4000 to 400 cm-1.

Identification of Drug by DSC

The DSC study was carried out using DSC-60 (Shimadzu, Tokyo, Japan). The instrument comprises of calorimeter, flow controller, thermal analyzer and operating software. The drug were heated in sealed aluminum pans under air flow (30 ml/min) at a scanning rate of 20°C/min from 50 to 300°C. Empty aluminum pan was used as a reference. The heat flow as a function of temperature was measured for the samples.
Physical Appearance and pH

All the prepared batches of polymeric solutions of carbamazapinewere checked for their clarity and the pH. After administration of the prepared solutions in 0.1 mol L⁻¹HCl, pH 1.2, the time required for gel formation and consistency of gel formed was checked visually. The pH was also measured in each of the solution of sodium alginate based in situ solutions of Carbamazapine, using a calibrated digital pH meter at 25°C.

Viscosity measurement of the in-situ gelling solutions

Viscosity of the sols were determined using a Brookfield digital viscometer (Model no LVDV 2P230) with the spindle number 1. The temperature of the 5 mL samples was kept at 28 ±1 °C during each measurement which lasted 30 sec, and the experiments were performed in triplicate.

In-vitro buoyancy

The in-vitro buoyancy study was performed using the 100 mL of simulated gastric fluid (pH = 1.2) in a beaker kept under slow stirring using magnetic stirrer. The medium temperature was kept at 37°C. A 10 mL sample of the prepared solution (in-situ gelling formulation) was drawn up with the help of a disposable syringe and injected into the beaker containing the medium without much turbulence[7]. The time for the gel to come to surface (floating lag time) and the time the gel remained floated on the medium surface (floating time) were recorded.

In-Vitro Gelling Capacity[5,7]

The in-vitro gelling capacity of prepared formulations was measured by placing five ml of the gelation solution (0.1N HCl, pH 1.2) in a 35 ml borosilicate glass test tube and maintained at 37±1°C temperature. One ml of gel formulation solution was added with the help of pipette. As the solution comes in contact with gelation solution, it was immediately converted into stiff gel like structure. The gelling capacity of solution was evaluated on the basis of stiffness of formed gel and time period for which they formed gel remains as such. The in-vitro gelling capacity was graded on the basis of gelation time and time period for which they formed gel remains.

Drug Content

Ten mL of the solution was added to 900 mL of simulated gastric fluid (0.1 mol L⁻¹HCl, pH 1.2) and stirred for 1 h on a magnetic stirrer. The solution was filtered, suitably diluted with simulated gastric fluid and the drug concentration was determined using a UV-visible spectrophotometer a (UV-1601 Shimadzu, Japan) at 286 nm against a suitable blank solution.

Swelling Index[5]

A gel of 100mg was weighed accurately (W1). It was kept in a petridishand 50ml of 0.1 N HCl was added. The petridish was kept aside for 24 hrs. The weight of swollen matrix gel (W2) was measured and swelling index was calculated using following formulae: Swelling Index= (W2-W1/W1)*100 Where, W1 = initial weight of gel (100mg), W2 = weight of swollen matrix after 24 hrs.

In-Vitro Drug Release[13,14]

The release of drug from the formulations was determined using a USP/24 dissolution test apparatus with a paddle stirrer at 50 rpm. The dissolution medium used was 900 mL of simulated gastric fluid (0.1 mol L⁻¹HCl, pH 1.2) and temperature was maintained at 37 ± 0.2 °C. Ten mL of the formulation was added into the dissolution vessel containing simulated gastric fluid avoiding any disturbance using testtube. At each time interval, a precisely measured sample of the dissolution medium was pipetted out and replenished with fresh medium. Carbamazepine concentration in the aliquot was determined spectrophotometrically. Each study was conducted in triplicate.

Analysis of the drug release kinetics[16,17,18]

The in-vitro drug release data were analyzed by fitting them into different kinetic models in order to investigate the release mechanism of carbamazapine from the gel systems. The cumulative amount of drugs released from the systems at different time intervals was fitted to different kinetic model of Zero order, First order, Higuchi model, Hixson-Crowell model and Korsmeyer-Peppas model to find out whether the drug release from the systems provides a constant drug release pattern. The correlation coefficient (R²), and Release constant were calculated to find the fitness of the data to different kinetic models.
RESULTS AND DISCUSSION

Absorbance Maxima and Calibration Curve of Carbamazapine in 0.1 N HCl

Absorption spectrum of carbamazapine indicated \( \lambda_{\text{max}} \) at 286 nm which is very close to its reported \( \lambda_{\text{max}} \) value that is 285 nm.

![Figure 1: Calibration Curve of Carbamazepine](image)

\[
y = 0.023x \\
R^2 = 0.996
\]

Identification of Drug by FTIR

Identification of drug was performed using FTIR spectrophotometer. The characteristic absorption peaks of pure drug obtained in the spectra correlates with the peaks of official spectrum of Pharmacopeia which confirms the purity of drug. The stability of the drug and sodium alginate in presence of each other was studied by IR spectroscopy and DSC. The characteristic peaks remain unaltered in the combination formulation, which indicated that no major interaction occurred between the functional groups of drug with the other ingredients.

![Figure 2: FT-IR spectra of A) Carbamazepine pure drug B) Sodium alginate and C) Both in combination.](image)
FTIR spectrum of carbamazepine which shows a sharp peak at 3244 and another peak at 2941 cm$^{-1}$ ($\text{–NH}$ valence vibration), peak at 1597 cm$^{-1}$ ($\text{–CO}$–$\text{R}$ vibration), and another one at 1509 cm$^{-1}$ ($\text{–C}=$$\text{C}$– vibration). There was no much change in these vibration peaks at combination formulation with sodium alginate also. Thus minimum interaction between drug and excipient was observed from spectral peaks.

Identification of Drug by DSC Spectra

The DSC thermograph of the pure drug, sodium alginate, and combination formulation were obtained (Figure 3). The DSC thermogram analyses was conducted to explore the melting activities of drug. DSC analysis figure (3-a) showed a endothermic onset of peak at 174.5ºC and a sharp endothermic onset of peak at 189.5ºC corresponding to carbamazepine melting point as indicated by Florey K [3].

![Figure 3: DSC thermograph of the pure drug, sodium alginate, and combination](image)

Physical Appearance and pH

Physical characterization parameters are reported in table 1. All the formulation had off white to pale yellow colored solution. They had pH in the range of 6.9 -7.2.

Viscosity of In Situ Gelling Solutions

The viscosity of the formulations increased with an increase in sodium alginate and HPMC concentration. This phenomenon is a consequence of increasing chain interaction with an increase in polymer concentration. Calcium carbonate, which is the source of cations, increased the viscosity of the formulation. This change in viscosity is due to the proportional increase in the amount of dispersed calcium carbonate. Formulation viscosities are tabulated in table 1.

Floating Behavior

The buoyancy lag time varied with the formulation variables. Formulation F5 exhibited the least buoyancy lag time (28s) while formulation F1 exhibited the highest lag time (111 s). Irrespective of formulation variables, buoyancy duration was more than 20 hours. All the prepared batches were evaluated for their floating properties in simulated gastric fluid. The time for formulation to come to the medium surface (floating lag time) and the time period for which the formulation maintained floated on the medium surface (duration of floating) were determined (Table 1).

Upon contact with an acidic medium, calcium carbonate effervesced, releasing carbon dioxide and calcium ions. Then, gelation and cross-linking by Ca++ ions took place to provide a gel barrier at the surface of the formulation. The released carbon dioxide was entrapped in the gel network producing a buoyant preparation, which resulted in extended floating. In-vitro gelling capacity and % Swelling index of various formulations were reported in table no.1. The Drug content of all (F1-F5) formulations is given in table no 1. It ranges in between 99% - 97.5%. The values are acceptable as per united states pharmacopeia standards.
Table 1: Table indicating the results of physical and formulation properties of optimum formulations

<table>
<thead>
<tr>
<th>Evaluation Parameters</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
</tr>
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<tbody>
<tr>
<td>pH</td>
<td>7.1</td>
<td>7.05</td>
<td>7.2</td>
<td>6.9</td>
<td>7.15</td>
</tr>
<tr>
<td>Viscosity (cp)</td>
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<td>311</td>
<td>290</td>
<td>295</td>
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<tr>
<td>In-Situ Gelling Time (Sec)</td>
<td>29</td>
<td>25</td>
<td>32</td>
<td>35</td>
<td>37</td>
</tr>
<tr>
<td>Floating Lag Time (min)</td>
<td>&lt;2</td>
<td>&lt;2</td>
<td>&lt;1</td>
<td>&lt;2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Floating Time (Hrs)</td>
<td>Stiff, &gt; 24hrs</td>
<td>Stiff, &gt; 24hrs</td>
<td>Stiff, &gt; 24hrs</td>
<td>Stiff, &gt; 24hrs</td>
<td>Stiff, &gt; 24hrs</td>
</tr>
<tr>
<td>Type of gel and gelling capacity (Hrs)</td>
<td>Stiff, &gt; 24hrs</td>
<td>Stiff, &gt; 24hrs</td>
<td>Stiff, &gt; 24hrs</td>
<td>Stiff, &gt; 24hrs</td>
<td>Stiff, &gt; 24hrs</td>
</tr>
<tr>
<td>Swelling Index (%)</td>
<td>82.79 ± 3.25</td>
<td>88.41 ± 2.73</td>
<td>88.54 ± 2.51</td>
<td>81.44 ± 1.73</td>
<td>89.58 ± 1.887</td>
</tr>
<tr>
<td>% Drug Content</td>
<td>97.94 ± 0.40</td>
<td>98.94 ± 0.40</td>
<td>98.75 ± 0.33</td>
<td>97.68 ± 0.27</td>
<td>98.75 ± 0.33</td>
</tr>
</tbody>
</table>

In-Vitro Drug Release

The in-vitro drug release of the in situ floating gel were carried in 0.1N HCl from 0 to 24 hrs by USP type-II apparatus. The plot of % Cumulative drug release v/s time (hrs) was plotted and depicted as shown in figure no.4.

![Figure 4: Graph of In-vitro drug release behavior from optimized formulations](image)

Initially, the drug was released at a faster rate due to the burst effect. As the percentage of calcium carbonate increased, the release rate decreased due to the stronger gel formation occurred. The lowest amount of calcium carbonate which produced a buoyant gel system for the 24 hrs duration of drug release study was found to be 0.7% at all polymer levels. On increasing the calcium carbonate concentration, the floating time was reduced significantly. Increasing calcium carbonate concentration in formulations increased the viscosity at all polymer concentrations studied. The drug release from the gel was characterized by an initial phase of high release (burst effect). However, drug was released at a slower rate in the second phase due to swelling of gelation polymer, i.e. a moderate release rate. The initial burst effect was considerably reduced with an increase in polymer concentration.

Kinetic of Drug Release

The dissolution drug release profile was plotted as cumulative % drug release v/s time curve as shown in figure 4. The dissolution data so obtained was fitted to various kinetic models like Zero Order, First order, Higuchi, Korsmeyer-Peppas models. Results were shown in table 2. The release of drug from the in-situ gel followed zero and higuchi model and the release process was found to occur by an non fickian diffusion-controlled mechanism as n value obtained for the best fit model was above 0.45 and below 0.85. The correlation coefficient (R2), Sum of square (SSQ) and Release constant also calculated to find the fitness of the data to different kinetic models were tabulated in table no.2.
Table 2: Table showing the release kinetic model with values of rate constant and regression coefficient.

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Zero-order Model</th>
<th>First-order Model</th>
<th>Higuchi Model</th>
<th>Kors-peppas Model</th>
<th>Best-Fit Model</th>
</tr>
</thead>
<tbody>
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<td>$K_0$</td>
<td>$R^2$</td>
<td>$K_l$</td>
<td>$R^2$</td>
<td>$K_H$</td>
</tr>
<tr>
<td>F1</td>
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<td>0.941</td>
<td>0.0733</td>
<td>0.867</td>
<td>0.0304</td>
</tr>
<tr>
<td>F2</td>
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<td>0.918</td>
<td>0.0694</td>
<td>0.877</td>
<td>0.0302</td>
</tr>
<tr>
<td>F3</td>
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<td>0.973</td>
<td>0.0701</td>
<td>0.792</td>
<td>0.0412</td>
</tr>
<tr>
<td>F4</td>
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<td>0.0677</td>
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</tr>
<tr>
<td>F5</td>
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<td>0.9613</td>
<td>0.0432</td>
<td>0.892</td>
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ACKNOWLEDGEMENT

Authors wish to thank JNCE Trust and Principal GRY Institute of Pharmacy, (India), for extending all the required laboratory facilities for the present work.

REFERENCES