SOLUBILITY ENHANCEMENT OF IBUPROFEN THROUGH MATRIX BASED HYDROGEL

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ABSTRACT

Hydrogels are crosslinked polymers having the ability to swell but remain undissolved in aqueous or biological fluids. Crosslinking can be done chemically or physically varies according to polymer properties and experimental conditions. Ibuprofen is a non-steroidal anti-inflammatory drug, an amphiphilic substance competent of self-association in aqueous solutions. In this work, cross-linking method was used to prepare hydrogel formulation in the presence of carbopol as a cross-linker for the aim of solubility enhancement of Ibuprofen drug. In preformulation study, the drug calibration curve was plotted in the various and then evaluated by UV-Spectrophotometer. All hydrogel preparations were assessed for their physical characterization such as pH, viscosity, skin irritation, drug percentage, spreadability etc.

After the preparation of hydrogels, drug release study was carried out in different mediums and the solubility of Ibuprofen was increased.

Key Words- Ibuprofen, solubility enhancement, carbopol,

INTRODUCTION

Hydrogels

Wichterle and Lim discovered the hydrogels in the late twentieth century (1960s). A water-swollen, cross-linked polymer network is product of the chemical reaction of monomer units. It can also be explained as a polymeric material having the ability to swell and retain a significant fractional amount of water within its structure, remain undissolved in water.¹² Hydrogel are reversible, for example “Inotropic” hydrogel which is formed by the interaction between a polyelectrolyte and a polyvalent ion with opposite charge, and polyelectrolyte complex formed by the interaction of opposing charged polyelectrolytes. Variation in environmental conditions such as ionic strength, temperature and pH can decay physical gels.¹²

In other words hydrogels are 3-D cross-linked networks that are capable of swelling in water or biological fluids and are able to retain a large amount of fluids in the swollen state.
Limitations

- Difficult to sterilize.
- Difficult to load.
- High cost.
- Mechanical strength is poor.
- Lens deposition in contact lenses, Hypoxia, and red eye reactions.
- Highly crystalline.
- Less soluble.
- Biodegradability is negative
- Mechanical and thermal properties are unfavourable.
- Inactive monomers.
- Toxicity of cross-linker.

Benefits

- Modification is convenient.
- In biocompatible.
- Easily injectable.
- Growth factors of time release.
- Nutrients ensure suitable tissue growth.
- Microbial cell entrapment within polyurethane hydrogel beads are less toxic.
- Environment sensitive hydrogel has the capability to sense differ of pH, temperature or the concentration of metabolite and shows activity.
- A temporal release of growth factors and nutrients provide proper milk growth.
- Natural hydrogel materials such as agarose, methylcellulose and hyaluronan have been investigated for tissue engineering.

EXPERIMENTAL

Materials

Ibuprofen was taken from (Shivalik Remedies Pvt. Ltd, Bhagwanpur, Roorkee, Uttarakhand, India) as a gift, Guar Gum, Hydroxypropyl Methyl Cellulose (HPMC), Carbopol 934, Calcium chloride and Potassium dihydrogen phosphate were purchased from (Loba Chemie Pvt. Ltd., Mumbai, Maharashtra, India), Sodium Hydroxide was buyed from (Finar Pvt. Ltd. Ahmedabad, Gujarat, India ) , Glycerine purified was purchased from (Central Drug House (P) Ltd. Daryagang, New Delhi, India), Alcohol was purchased from (Renkm Pvt. Ltd A-3, Okhla Industrial Area, Phase – 1 New Delhi, India) all other analytical grade chemicals and solvents were freshly prepared in distilled water was used during study.

Method for Preparation of the Media Solution
To prepare of the all solution media like as to 6.8 pH buffer solution, 7.4 pH buffer solution, 1.2 pH Hydrochloric acid (HCL) solution, and Calcium chloride solution (CaCl2) (for 2%, 5%, and 7%), sodium hydroxide (NaOH) solution. Prepare of all according to India Pharmacopoeia (IP) 2010 6th edition.

**Method for Preparation of the Physical Mixture**

For the preparation of physical mixture of all polymers, drug and co-solvents are weight accurately in the ratio given in formula of table – 1. And mixed properly in a 500 ml beaker with help of glass rod and after mixing the solution is ready to use for prepared hydrogel formulation.

**Method for Preparation of the Hydrogel Formulation (HF)**

Hydrogel formulations were prepared by dispersing of different concentrations of Guar gum, HPMC, Drug and Carbopol in Glycerin, NaOH, CaCl2 solution with distilled water. The reaction condition, time and composition of the crosslinking reactions were held as displayed in table-1. To the water, glycerin and drug is added in a 500 ml beaker and the solution was mixed properly and after mixing the solution HPMC, Carbopol, and Guar gum were added in the beaker as mentioned in table-1. And then the beaker stays on heating plate and the temperature was maintained at 80°C and this homogenous mixture was kept for stirring 1 hour with the help of mechanical stirrer with the speed of 2000 to 2200 rpm. The reaction was completed by mixing of this polymer, co-agents and drug. After 1 hour it was added to 10 ml solution of CaCl2 (2%, 5%, and 7% solutions) and NaOH (0.1N solution) according to table-1 and the heating plate temperature was changed at 37°C and the process is continues again in 1 hour. After total reaction time (2 hours) the sample was leaved for cooling at room temperature overnight to produce gel form. The prepared hydrogels were obtained and stored in air tied container at room temperature.

<table>
<thead>
<tr>
<th>Batch</th>
<th>Carbopol</th>
<th>Guar</th>
<th>HPMC</th>
<th>Drug</th>
<th>Glycerin</th>
<th>Cacl2</th>
<th>NaOH</th>
<th>Water</th>
<th>Reaction</th>
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</table>

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<table>
<thead>
<tr>
<th>No</th>
<th>(mg)</th>
<th>gum (mg)</th>
<th>(mg)</th>
<th>(mg)</th>
<th>(ml)</th>
<th>(ml)</th>
<th>(ml)</th>
<th>Time(Min)</th>
</tr>
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<tbody>
<tr>
<td>HF-1</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>100</td>
<td>20</td>
<td>10</td>
<td>-</td>
<td>30</td>
</tr>
<tr>
<td>HF-2</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>100</td>
<td>20</td>
<td>10</td>
<td>-</td>
<td>30</td>
</tr>
<tr>
<td>HF-3</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>100</td>
<td>20</td>
<td>-</td>
<td>25</td>
<td>30</td>
</tr>
<tr>
<td>HF-4</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>100</td>
<td>20</td>
<td>-</td>
<td>50</td>
<td>30</td>
</tr>
<tr>
<td>HF-5</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>100</td>
<td>20</td>
<td>-</td>
<td>-</td>
<td>30</td>
</tr>
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<td>HF-6</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>100</td>
<td>20</td>
<td>10</td>
<td>-</td>
<td>20</td>
</tr>
<tr>
<td>HF-7</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>100</td>
<td>20</td>
<td>10*</td>
<td>-</td>
<td>20</td>
</tr>
<tr>
<td>HF-8</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>100</td>
<td>20</td>
<td>10**</td>
<td>-</td>
<td>20</td>
</tr>
</tbody>
</table>

**Note** - 1. 2%, 5% (*), and 7% (**) Calcium Chloride Solutions (CaCl₂) are used.
2. 0.1 N Solution of Sodium Hydroxide (NaOH) is used.

Table 1 (Initial Mixture Composition and Reaction Time of Preparing for Hydrogel formulation)
Batch weight determination of all formulation
Pour all hydrogel formulations in properly pre-weighed jars and weigh using the weighing balance. The batch weight was observed and recorded.

Drug Percentage
Drug percentage of all the hydrogel formulations was calculated.

Determination of Viscosity
Brookfield digital viscometer (Brookfield Viscometer model LVDVE, USA) was used to determine viscosity of the hydrogel formulations at 37°C. For this, spindle No. 4 was used by rotating at 100, 60, 50, 30, 20, 12, 10, 6, 5, 4, 3, 2.5, 2, 1.5, 1 rpm, after rest time of 3 minutes.

Determination of Spreadability Test
Spreadability of the hydrogels was determined by glass slide apparatus. Weigh nearly 1-2 gm of developed hydrogel in the lower slide. The time taken by upper slide to totally separate from the lower slide was noted and spreadability of gel was evaluated.

RESULTS AND DISCUSSION
In this work, cross-linking method was used to prepare hydrogel formulation in the presence of carbopol as a cross-linker for the aim of solubility enhancement of Ibuprofen drug.
In preformulation study, the drug calibration curve was plotted in the various mediums like buffer 7.4pH, 6.8pH, and 1.2pH HCl at 10, 20, 30, 40, 50 and 60 µg/ml dilutions and evaluated by UV-Spectrophotometer. The scan plot of Ibuprofen was on 223 nm in all evaluated mediums and in FTIR spectra of Ibuprofen, there are no. of broad peaks in the graph at 1707 cm⁻¹ and 1421 cm⁻¹ are carboxylic acids (C=O) and other peak 1235 cm⁻¹ is a cyclohexane.
All hydrogel preparations were assessed for their physical characterization such as pH, viscosity, skin irritation, drug percentage, spreadability etc. In the developed hydrogels, percentage yield was between 55.57 to 87.31% and HF-5 attained the maximum percentage yield. The weight percentage of hydrogels was in the range of 32.197 – 74.575gm and HF-4 achieve the maximum, drug percentage of the hydrogels was in the range of 0.00133 – 0.00311mg/gm of all hydrogel formulations. The pH of every prepared hydrogel was in between 2.98 ± 0.1-0.3 to 9.40 ± 0.1-0.3, and formulations did not cause any skin irritation. The spreadability of hydrogels was found in range of 1.1 - 6.8 dispersion 2gm.cm/min was the maximum spreadability of sample 2 and sample 5 achieve the minimum spreadability.
Calibration of Ibuprofen in Phosphate Buffer 6.8 pH

Calibration of Ibuprofen in Phosphate Buffer 7.4 pH
Calibration of Ibuprofen in 0.1 N (1.2 pH) HCl.

FTIR (Fourier Transform Infrared Spectroscopy) Characterization of Ibuprofen
Percentage Yield of Hydrogels Formulations
Percentage yield was calculated by actual and theoretical yield using this formula.

\[ \% \text{ Yield} = \frac{\text{Actual Yield}}{\text{Theoretical yield}} \times 100 \]

<table>
<thead>
<tr>
<th>S.No.</th>
<th>% Yield</th>
</tr>
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<tbody>
<tr>
<td>HF 1</td>
<td>60.43</td>
</tr>
<tr>
<td>HF 6</td>
<td>55.57</td>
</tr>
<tr>
<td>HF 3</td>
<td>57.72</td>
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<tr>
<td>HF 4</td>
<td>73.79</td>
</tr>
<tr>
<td>HF 5</td>
<td>87.31</td>
</tr>
<tr>
<td>HF 6</td>
<td>63.08</td>
</tr>
<tr>
<td>HF 7</td>
<td>62.39</td>
</tr>
<tr>
<td>HF 8</td>
<td>62.83</td>
</tr>
</tbody>
</table>

Percentage Yield of Hydrogel Formulation
<table>
<thead>
<tr>
<th>S.No</th>
<th>pH</th>
<th>Drug Percentage (mg/gm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF 1</td>
<td>4.8</td>
<td>0.00269</td>
</tr>
<tr>
<td>HF 2</td>
<td>4.24</td>
<td>0.00292</td>
</tr>
<tr>
<td>HF 3</td>
<td>7.40</td>
<td>0.00226</td>
</tr>
<tr>
<td>HF 4</td>
<td>9.40</td>
<td>0.00133</td>
</tr>
<tr>
<td>HF 5</td>
<td>4.47</td>
<td>0.00222</td>
</tr>
<tr>
<td>HF 6</td>
<td>3.30</td>
<td>0.00307</td>
</tr>
<tr>
<td>HF 7</td>
<td>3.09</td>
<td>0.00311</td>
</tr>
<tr>
<td>HF 8</td>
<td>2.98</td>
<td>0.00308</td>
</tr>
</tbody>
</table>

pH, Drug Percentage of all Hydrogels Formulations
CONCLUSION

During this work the hydrogel formulations were prepared for the aim of solubility enhancement of Ibuprofen drug. Next to the preparation of all formulations of hydrogel, they were evaluated. In the FTIR spectra of Ibuprofen, there are several wide peaks in the graph, at 1707 cm^-1 and 1421 cm^-1 are carboxylic acids (C=O) and other peak 1235 cm^-1 is a cyclohexane. Hydrogel formulation-5 has the maximum percentage yield of 87.31% and the drug percentage was in the range of 0.00133 – 0.00311 mg/gm of all hydrogels formulations. The pH of every prepared hydrogel was in between 2.98 ± 0.1-0.3 to 9.40 ± 0.1-0.3

Noticable shear thinning (power law behavior) was appear from complex viscosity curves because of the structural organization of the sample as a function of given deformation. Sample 4 was least viscous while sample 5 was most viscous between all the samples. Sample 5 was also the most rigid (may have good stability) whereas sample 3 was found to be the softest (may possess low stablity than others) in long shelf life period.

The study of drug release in various mediums such as 1.2pH HCl and 7.4pH buffer was carried out and the solubility of Ibuprofen was found increased. In calculated kinetic models the finest fitted model of the maximum formulations was Makoid-Banakar model.

Thus, this is concluded that the hydrogel formulations which are prepared in our study had enhanced solubility of Ibuprofen drug that can be utilized in therapeutics field as Ibuprofen is an extensively prescribed drug.

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