ORAL SUSTAINED DELIVERY OF SALBUTAMOL USING IN-SITU GELATION OF SODIUM ALGINATE

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ABSTRACT

The purpose of this study was to evaluate the potential for the oral sustained delivery of sodium alginate formulation with in situ gelation properties of salbutamol sulphate. Sodium alginate insitu gelling sols were prepared in five different concentrations such as 1, 1.5, 2, 2.5, and 3% (w/v). The formulated insitu gelling sols were evaluated for rheological properties, drug content and stability. The invitro release study was performed in acidic medium followed by basic medium for about 8hrs. The stability studies were carried out for 4 month and the drug content and appearance of the formulated sols were examined.

Key words: Salbutamol, In situ, Sodium Alginate, Stability, Sols.

INTRODUCTION

Some hydrophilic polymers have ion properties. Among these alginate which belong to a family of un-branched binary copolymers of (1, 4)-linked β-D-mannuronic acid and α-L-glucuronic acid residues. The later may be present in various proportions altering the physico-chemical properties of the polymer formed. Alginates show characteristic ion binding for multivalent cations and this forms the basis for their gelling properties. The alginate binding leads to the formation of covalent bonds leading to the perception of the insoluble hydrogel. Such crosslinking processes stiffens and roughens the polymer and reduces the swelling in solvents. This generally leads to a reduction in the permeability of different solutes hindering the release of encapsulated drugs in alginate matrices, allowing these systems to be used in controlling the drug release. The soluble sodium alginate was cross-linked with calcium chloride resulting in the formation of the insoluble calcium alginate. This system had been used successfully to delay the release of some drugs. Different investigators reached a consensus that similar systems are only appropriately hinder the release of large molecular weight drugs while fail short to do so with smaller molecular weight compounds. Salbutamol is a β-adrenergic receptor agonist used as a bronchodilator. It can be specifically indicated in case of acute asthma and also for symptom relief during maintenance therapy of asthma and other conditions with reversible airways obstruction (including COPD). This drug has a daily dose of 4-8 mg because of shorter biological half-life (1.2 hrs); it needs multiple administrations, which often results in dose related side effects and poor patient compliance. Also, in the commercially available preparations 10 ml of the formulation should be taken 3 or 4 times daily. In order to overcome a sustained drug delivery system is necessary which can improve the patient’s compliance but as in tablet form it is difficult to administer to pediatric and pediatric patients. So on considering the above factors we have planned to formulate an oral insitu gelling vehicle for the sustained delivery of salbutamol which are to be administered in liquid form and to form gels insitu in the acidic environment of the stomach.

MATERIAL AND METHODS

Salbutamol sulphate (Tablets India Ltd), Sodium citrate (Rainbow 2000, B -Pura Laboratories, Chennai), Calcium chloride (Rankem, Ranbaxy fine chemicals, New Delhi). Hydro chloric acids, Potassium dihydrogen phosphate, Sodium hydroxide, Potassium chloride used for the preparation are of analytical grade.

Preparation of sol

Sodium alginate (1%w/v) solution was prepared with distilled water and stirred continuously with magnetic stirrer. Then sodium citrate (0.25% W/V), calcium chloride (0.075% W/V) and salbutamol (400mg) were added and heated to 60ºC for about 30mins then the prepared sol is allowed to cool. This sol is stored in room temperature until further use.

Study on drug to polymer ratio

Four different batches of insitu gelling sols were prepared by varying the concentration of sodium alginate polymer. Sodium alginate solutions (1, 1.5, 2, 2.5 and 3% W/V) were prepared with distilled water and stirred continuously with magnetic stirrer. Then sodium citrate (0.25% W/V), calcium chloride (0.075% W/V) and salbutamol (400mg) were added and heated to 60ºC for about 30mins then the prepared sols were allowed to cool. These prepared sols were stored in room temperature until further use.

Evaluation of the formulated sols

Physicochemical properties

The formulated sols were visually observed. It was found that the sols were clear without any dispersed particles.

Measurement of viscosity of the formulated sols

The rheological behaviors of the prepared sols were determined by Brookfield viscometer. The spindle S34 was selected for the study. The samples containing 0.1, 0.15, 0.2, 2.5 and 3%, w/v sodium alginate sols were filled in the sample holder and the spindle was immersed in the samples. The study was carried out at 25°C with 150rpm. Measurements on each sample were performed in triplicate, to analyze the result.

Determination of drug content

A known quantity (40 mg) of the prepared sols was stirred with 100 ml of buffer solution pH 6.8 for 6 hrs. The sample was then centrifuged at 5000 rpm and the filtrate was measured spectrophotometrically at 276.1 nm.

In vitro drug release studies

For the determination of invitro drug release, USP Dissolution Apparatus-II was used. Diffusion method was employed to maintain different pH conditions in the dissolution studies. 10 ml (40 mg of drug) of the solution was added to 750 ml of buffer solution of pH 1.2, contained in the dissolution flask and the temperature was
maintained at 37°C with 50 rpm. Aliquots of 5 ml were withdrawn at frequent intervals and equal amount of fresh medium was replaced after each sampling up to 2hrs. At the end of 2 hrs, the medium was changed to pH 7.2. The dissolution was continued in this medium up to 8 hrs. The collected samples were analysed for the drug content through UV spectrophotometer at 276.1 nm.\textsuperscript{19, 20}

### Stability studies

Stability studies were carried out at room temperature (32-37°C). The sols prepared were stored in room temperature for about four months. The sols were observed for their physical appearance and drug content at four different intervals.\textsuperscript{21, 22}

### RESULTS AND DISCUSSION

Although gelation of sodium alginate will occur in the presence of H+ ions, the soft alginic acid gels that are formed are generally suitable as vehicles for drug delivery. In this study Ca++ ions were included in the formulation for induction of alginate gelation. However, for ease of administration we required the formulation to be in the fluid (sol) state.\textsuperscript{23} This was achieved by addition of sufficient sodium citrate to the formulation to form a complex with all of the Ca++ ions present in the formulation and hence to effectively remove them from solution. In the acidic environment of the stomach the complex is broken down and the Ca++ ions released cause gelation to occur.\textsuperscript{24}

The optimum quantities of calcium chloride and sodium citrate which maintained fluidity of the formulation before administration and resulted in gelation when the formulation was added to simulated gastric fluid (pH 1.2), were found from the literatures. The sols formed were clear and viscous with a pleasant appearance.\textsuperscript{25}

#### Study on drug to polymer ratio

Sodium alginate sols in the concentrations of 1, 1.5, 2, 2.5 and 3% w/v were prepared respectively and their drug loading capacity was determined. From the result it was observed that on increase in polymer concentration the drug loading capacity also increased but after the concentration (2%w/v) the drug loading decreased. This is possibly due to the saturation in the binding sites.\textsuperscript{26}

#### Physicochemical

The sols formed were clear and viscous with a pleasant appearance. The sols when transferred to buffer pH1.2 it was converted to gel. This is due to the acidic environment of the buffer the complex is broken down and the Ca++ ions released causing gelation to occur.

#### Determination of viscosity

The viscosities of the samples were studied through Brookfield viscometer and the viscosities of the samples were found to be 82.5 to 148.2 cps. On increase in polymer concentration the viscosity were also found to be increased.\textsuperscript{27} (Table-1)

#### Determination of drug content

The drug content of the samples were found to be from 37 to 39% for all the batches but the batch SAL-IV showed the highest concentration of drug loading such as 39.96mg. Whereas other batches were found to be comparatively low. (Table-I)

#### Invitro release study

When a solution is administered orally, it first reaches the stomach and it passes in to small intestine, where the pH is alkaline. Hence invitro drug release under gastric pH 1.2 and intestinal pH 7.2 conditions were studied. The amount of drug release from 1, 1.5, 2, 2.5 and 3% w/v sodium alginate was found to be 72.5, 73.5, 69.7, 81.1, and 72.5% W/V at the end of 8hrs. Figure 2 show significant influence of sodium alginate concentration on the invitro release. The reason for this difference in release behavior is attributable to the large difference in the H+ ion concentrations of the two dissolution medium. The H+ ion concentration at pH6.8 is insufficient to cause the formation of rigid gel.\textsuperscript{28} (Fig-2)

#### Stability studies

The stabilities were determined for a period of four months and the results were reported in the table no 3. All the batches showed a slight reduction in the drug content whereas the formulated batch SAL-IV was found to have a least drug loss when compared to other batches.\textsuperscript{29, 30} and the batches SAL IV and SAL V loosed its sol properties and converted to gel on storage at the fourth month analysis.

### Table 1: Physiochemical properties

<table>
<thead>
<tr>
<th>S. no.</th>
<th>Formulation code (%w/v)</th>
<th>Viscosity (CPS)</th>
<th>Drug content (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>SAL I (1%w/v)</td>
<td>82.5</td>
<td>37.45±0.07</td>
</tr>
<tr>
<td>2.</td>
<td>SAL II(1.5)%w/v)</td>
<td>84.4</td>
<td>37.89±0.23</td>
</tr>
<tr>
<td>3.</td>
<td>SAL III (2%w/v)</td>
<td>104.5</td>
<td>38.86±0.18</td>
</tr>
<tr>
<td>4.</td>
<td>SAL IV (2.5%w/v)</td>
<td>120.6</td>
<td>39.92±0.07</td>
</tr>
<tr>
<td>5.</td>
<td>SAL V (3%w/v)</td>
<td>148.2</td>
<td>39.02±0.46</td>
</tr>
</tbody>
</table>
Fig. 2: Invitro dissolution study of formulated insitu gelling sodium alginate sols from different batches

Table 2: Invitro release kinetics

<table>
<thead>
<tr>
<th>Sample</th>
<th>Higuchi</th>
<th>Peppa’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAL I (1%w/v)</td>
<td>0.975914</td>
<td>0.983415</td>
</tr>
<tr>
<td>SAL II (1.5%w/v)</td>
<td>0.958899</td>
<td>0.973904</td>
</tr>
<tr>
<td>SAL III (2%w/v)</td>
<td>0.980695</td>
<td>0.469255</td>
</tr>
<tr>
<td>SAL IV (2.5%w/v)</td>
<td>0.987379</td>
<td>0.990639</td>
</tr>
<tr>
<td>SAL V (3%w/v)</td>
<td>0.96572</td>
<td>0.977456</td>
</tr>
</tbody>
</table>

Table 3: Data after stability study

<table>
<thead>
<tr>
<th>S. no</th>
<th>Months</th>
<th>Sal I (1%W/V)</th>
<th>Sal II (1.5%W/V)</th>
<th>Sal III (2%W/V)</th>
<th>Sal IV (2.5%W/V)</th>
<th>Sal V (3%W/V)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>APR</td>
<td>DC</td>
<td>APR</td>
<td>DC</td>
<td>APR</td>
<td>DC</td>
</tr>
<tr>
<td>1.</td>
<td>1st Month</td>
<td>NC 37.45±0.07</td>
<td>NC 37.89±0.23</td>
<td>NC 38.86±0.18</td>
<td>NC 39.96±0.07</td>
<td>NC 39.02±0.46</td>
</tr>
<tr>
<td>2.</td>
<td>2nd Month</td>
<td>NC 32.45±0.14</td>
<td>NC 33.31±0.84</td>
<td>NC 33.98±0.09</td>
<td>NC 38.52±0.19</td>
<td>NC 31.77±0.29</td>
</tr>
<tr>
<td>3.</td>
<td>3rd Month</td>
<td>NC 30.17±0.46</td>
<td>NC 29.49±0.46</td>
<td>NC 31.45±0.13</td>
<td>NC 37.07±0.68</td>
<td>NC 30.12±0.96</td>
</tr>
<tr>
<td>4.</td>
<td>4th Month</td>
<td>NC 28.39±0.67</td>
<td>SCG 28.78±0.50</td>
<td>SCG 30.92±0.02</td>
<td>SCG 36.33±0.59</td>
<td>SCG 28.66±0.06</td>
</tr>
</tbody>
</table>

DC: Drug content, APR: Appearance, NC: No Characteristic Change, SCG: Sol is converted into Gel

CONCLUSION

This study has demonstrated the feasibility of forming gels in the stomach by the oral administration of aqueous solutions of sodium alginate containing Ca++ ions in a complexed form. Furthermore, a sustained release of the drug, salbutamol is achievable from the gel vehicles over a period of at least 8 h. so we may conclude that sodium alginate may be a useful oral sustained release vehicle to improve patient compliance and bioavailability and which may be most useful for pediatrics and geriatrics patients.

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