DESIGN AND DEVELOPMENT OF SUSTAINED RELEASE AMBROXOL HYDROCHLORIDE MATRIX TABLETS USING THE COMBINATION GUAR GUM AND KARAYA GUM

Sunil Kumar*1, Someswara Rao B2, Suresh V Kulkarni2

1Sree Siddaganga College of Pharmacy, B H Road, Tumkur- 572102, Karnataka.
2Department of Pharmaceutics, Sree Siddaganga College of Pharmacy, B H Road, Tumkur- 572102, Karnataka.

ABSTRACT

In the present investigation, an attempt was made to design and develop of Sustained Release Ambroxol Hydrochloride Matrix Tablets using the combination Guar gum and Karaya gum, in order to improve efficacy, reduce the frequency of administration, and better patient compliance. Ambroxol hydrochloride is a potent mucolytic agent capable of inducing bronchial secretions used in the treatment of respiratory disorders. The Sustained release matrix tablets containing 75 mg Ambroxol hydrochloride were developed using different drug: polymer ratios. Sustained release matrix tablets were prepared by wet granulation method. Granules were prepared and evaluated for loose bulk density, tapped bulk density, compressibility index and angle of repose, shows satisfactory results. The prepared tablets were further evaluated for uniformity of weight, hardness, friability, thickness, content uniformity, In-vitro dissolution, drug-excipients interactions. The FT-IR studies revealed that there was no chemical interaction between drug and excipients. In-vitro release studies were carried out using USP XXII type II (paddle method) dissolution apparatus at 50 rpm by taking 900 ml of 0.1 N HCl (pH 1.2) as dissolution medium for first 2 hours and later replacing it with 900 ml pH 6.8 phosphate buffer solution for rest of the time period at 37 ± 0.5°C. The release data was fitted to various mathematical models such as, Higuchi, Korsmeyer-Peppas, First-order, and Zero order to evaluate the kinetics and mechanism of the drug release. Among all the formulations, F 4 shows 98.21 % better controlled release at the end of 11 hr. The drug release of optimized formulations F-4 follows zero order kinetics. The stability studies were carried out according to ICH
guideline which indicates that the selected formulations were stable.

**Keywords:** Ambroxol Hydrochloride, Matrix tablet, Sustained release, Karaya gum, Guar gum, Wet Granulation.

**INTRODUCTION**

Oral route is the most preferred route for administration of drugs. Tablets are the most popular oral formulation available in the market and preferred by the patients and physician alike. In long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered multiple doses and therefore have several disadvantages.\[^1\]

Sustained release drug delivery aimed at controlling the rate of release as well as maintains desired drug level in the blood that is therapeutically effective and non toxic for extended period of time, thus achieving better patient compliance and allowing a reduction of both the total dose of drug administered and the incidence of adverse side effects. It provides prolonged but not necessarily uniform release of the drug. The rationale for development of a sustained release formulation of a drug is to enhance its therapeutic benefits, minimizing its side effect while improving the management of the diseased condition.\[^2,3\]

Hydrophilic matrices are an interesting option when developing an oral sustained release formulation. The drug release from such matrices can be controlled through their physical properties. Polysaccharides are the choice of materials among the hydrophilic polymers used, because they are nontoxic and acceptable by the regulating authorities. The various polysaccharides used in drug delivery application are cellulose ethers, xanthan gum, locust bean gum and guar gum.\[^4\]

Ambroxol is a metabolite of bromhexine with similar actions and uses. It is chemically described as Trans-4-[(2-amino-3,5-dibromobenzyl)amino]-cyclohexanol. Ambroxol hydrochloride is an expectorant improver and a mucolytic agent used in the treatment of respiratory disorders such as, bronchial asthma, chronic bronchitis characterized by the production of excess or thick mucus. Ambroxol hydrochloride has also been reported to have a cough suppressing effect and anti inflammatory action. It has been successfully used for decades in the form of its hydrochloride as a secretion releasing expectorant in a variety of respiratory disorders. Its short biological half life (4 hrs) that calls for frequent daily dosing (3
to 4 times) and therapeutic use in chronic respiratory diseases necessitates its formulation in to sustained release dosage forms.\cite{5,6}

The aim of present study is to develop sustained release matrix tablets of Ambroxol hydrochloride using the combination Guar gum and Karaya gum.

**MATERIALS AND METHODS**

**Materials**

Guar Gum, Polyvinyl Pyrrolidone K 30, Lactose and Talc were purchased from SD Fine Chem. Limited, Mumbai. Karaya Gum were purchased from Research Lab Fine Chem Industries, Mumbai. Ambroxol Hydrochloride was obtained from Yarrow chemicals, Mumbai. Magnesium stearate were purchased from Loba Chemie Pvt. Ltd, Mumbai.

**Preparation of matrix tablets**

Tablet formulations were prepared by wet granulation method. Proportion of excipients with drug was as given in Table 1. The drug and all other ingredients were sifted through sieve # 60. The sifted ingredients were mixed thoroughly in a mortar with pestle for 15 min. PVP mixed with Iso propyl alcohol and added into well mixed powder till the desired wet mass was formed. This wet mass was sifted through sieve # 16. The prepared granules were dried at 60ºC for 1 hour in hot air oven, and then it was sifted through sieve # 16 and transferred the granules into a polybag. Magnesium stearate and talc were sifted through sieve # 40 and mixed with the prepared granules in a polybag for 5 min. Finally tablets were compressed at 600 mg weight on a 10 station mini rotary tableting machine (Shakti Pharmatech Pvt. Ltd, Ahmedabad) with 12.1 mm flat-shaped punches.

**Evaluation of granules**

The angle of repose was measured by using funnel method which indicates the flow ability of the granules. Loose bulk density (LBD) and tapped bulk density (TBD) were measured using the formula: LBD = weight of the powder / volume of the packing. TBD = weight of the powder / tapped volume of the packing. Compressibility index of the granules was determined by using the formula: CI(%) =\[(TBD-LBD/TBD)\]×100. The physical properties of granules were shown in Table 2.

**Evaluation of tablets**

All prepared matrix tablets were evaluated for its uniformity of weight, hardness, friability and thickness according to official methods shown in Table 3.
Uniformity of drug content
Accurately weighed quantity of the powder tablet equivalent to 100 mg of the drug was transferred to 100 ml volumetric flask. 50 ml of buffer solution of pH-6.8 was added. Mix with the aid of ultrasound for 10 min, and then the volume was made up to 100 ml with the same buffer solution, mixed solution was filtered through the membrane filter disc with an average pore diameter not greater than 0.45 µm. 5 ml of the filtrate was diluted to 100 ml with same buffer solution and examined under U.V Spectrophotometer at 210 nm.

In vitro drug release studies
In vitro drug release studies were carried out using USP XXII dissolution apparatus type II (Electrolab, Mumbai, India) at 50 rpm. The dissolution medium consist of 900 ml of pH 1.2 phosphate buffer for first two hour and pH 6.8 phosphate buffer for remaining hour, maintained at 37 ± 0.5°C. The drug release at different time intervals was measured using an ultraviolet visible spectrophotometer (Labindia, Mumbai, India) at 210 nm.

Drug Release Kinetics
The release kinetics was fitted to different mathematical models like Zero order, First order, Higuchi’s and Peppa’s plot. The kinetic treatment of selected optimized formulation F-4 shows that the regression coefficient for zero-order kinetics were found to be higher when compared with those of the first-order kinetics. The slope (n) value of Korsmeyer Peppas plots of optimized formulation F-4 were found to be 0.794 respectively, indicate that mechanism of release was Anomalous (non-Fickian) diffusion.

Table 1. Tablet composition of Ambroxol hydrochloride sustained release matrix tablets prepared with different release retardant (F-1 to F-4)

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Drug</th>
<th>Guar gum</th>
<th>Karaya gum</th>
<th>Polyvinyl Pyrrolidone K 30</th>
<th>Lactose</th>
<th>Magnesium stearate</th>
<th>Talc</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>75</td>
<td>75</td>
<td>75</td>
<td>30</td>
<td>327</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>F2</td>
<td>75</td>
<td>100</td>
<td>100</td>
<td>30</td>
<td>277</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>F3</td>
<td>75</td>
<td>150</td>
<td>150</td>
<td>30</td>
<td>177</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>F4</td>
<td>75</td>
<td>200</td>
<td>200</td>
<td>30</td>
<td>77</td>
<td>12</td>
<td>6</td>
</tr>
</tbody>
</table>

Stability Study
Selected formulations were stored at different storage conditions at elevated temperatures such as 25°C± 2°C / 60% ± 5% RH, 30°C ± 2°C / 65% ±5% RH and
40°C ± 2°C / 75% ± 5% RH for 90 days. The samples were withdrawn at intervals of fifteen days and checked for physical changes.

Table 2. Data for blend evaluation of formulation (F-1 to F-4)

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Angle of repose (°)</th>
<th>Loose bulk density (LBD)(g/ml)</th>
<th>Tapped bulk density (TBD)(g/ml)</th>
<th>Compressibility index (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>30.21 ± 1.85</td>
<td>0.236 ± 0.04</td>
<td>0.272 ± 0.02</td>
<td>13.23 ± 0.43</td>
</tr>
<tr>
<td>F2</td>
<td>31.24 ± 1.54</td>
<td>0.294 ± 0.03</td>
<td>0.343 ± 0.05</td>
<td>14.28 ± 0.72</td>
</tr>
<tr>
<td>F3</td>
<td>28.13 ± 1.25</td>
<td>0.274 ± 0.08</td>
<td>0.314 ± 0.07</td>
<td>12.73 ± 1.54</td>
</tr>
<tr>
<td>F4</td>
<td>29.17 ± 1.74</td>
<td>0.255 ± 0.06</td>
<td>0.290 ± 0.05</td>
<td>12.06 ± 1.32</td>
</tr>
</tbody>
</table>

Table 3. Physical properties of tablet formulation (F-1 to F-4)

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Thickness (mm)</th>
<th>Hardness (kg/cm²)</th>
<th>Friability (%)</th>
<th>Drug content (%)</th>
<th>Weight variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>4.20 ± 0.04</td>
<td>5.2 ± 0.23</td>
<td>0.39 ± 0.29</td>
<td>98.24 ±0.29</td>
<td>600.5</td>
</tr>
<tr>
<td>F2</td>
<td>4.25 ± 0.07</td>
<td>5.3 ± 0.19</td>
<td>0.38 ± 0.35</td>
<td>99.32 ±0.13</td>
<td>600.2</td>
</tr>
<tr>
<td>F3</td>
<td>4.27 ± 0.05</td>
<td>5.4 ± 0.16</td>
<td>0.36 ± 0.31</td>
<td>99.60 ±0.11</td>
<td>600.3</td>
</tr>
<tr>
<td>F4</td>
<td>4.45 ± 0.03</td>
<td>5.6 ± 0.21</td>
<td>0.32 ± 0.26</td>
<td>99.41 ±0.18</td>
<td>600.2</td>
</tr>
</tbody>
</table>

RESULT & DISCUSSION

FTIR spectroscopy

FTIR spectrum of Ambroxol hydrochloride showed in scan at Figure 1. Physical mixture of drug and polymers are shown in Figure 2. The characteristic peaks of the drug were observed in the spectra of drug and polymer mixture, indicates that there is no interaction between the drug and polymer mixtures. Hence these release retarding materials were selected for formulation of sustained release tablets.

Fig. 1. FTIR Spectroscopy of pure drug Ambroxol hydrochloride
Characterization of granular properties

Granules prepared for compression of matrix tablets were evaluated for their flow properties, the results were shown in Tables 2. Angle of repose was in the range 28.13 ± 1.25° to 31.24 ± 1.54°, which indicates excellent flow of the powder for all formulations. The loose bulk density of the powder formulation was in the range of 0.236 ± 0.04 to 0.294 ± 0.03 gm/ml; the tapped bulk density was in the range of 0.272 ± 0.02 to 0.343 ± 0.05 gm/ml, which indicates that the powder was not bulky. The Carr’s index was found to be in the range of 12.06 ± 1.32 to 14.28 ± 0.72; indicating compressibility of the tablet blend is good. These values indicate that the prepared granules exhibited good flow properties.

Physicochemical evaluation of matrix tablets

Tablets with a weight of 600 mg, were obtained and subjected to quality control tests such as hardness, friability and drug content (Table 3). The hardness of the tablets was found to be in the range of 5.2 ± 0.23 to 5.6 ± 0.21 Kg/cm². It was within the range of monograph specification. Thicknesses of the tablets were found to be in the range of 4.20 ± 0.04 to 4.45 ± 0.03 mm. The friability of the tablets was found to be less than 1% and it was within the range of standard specification. The drug content for all the batches was found to be in the range of 98.24 ± 0.29 to 99.60 ± 0.11. The results are given in Table 3. The punches used to compress the tablets were 12.1 mm flat-shaped punches.

In-Vitro Release Study

In vitro drug release studies were carried out using USP XXII dissolution apparatus.

Fig. 2. FTIR Spectroscopy of Ambroxol hydrochloride + Guar gum + Karaya gum
type II (Electrolab, Mumbai, India) at 50 rpm. The dissolution medium consist of 900 ml of pH 1.2 phosphate buffer for first two hour and pH 6.8 phosphate buffer for remaining hour, maintained at 37 ± 0.5°C. The drug release at different time intervals was measured using an ultraviolet visible spectrophotometer (Labindia, Mumbai, India) at 210 nm. The results were evaluated for 12 hrs. As per the results of dissolution study formulations F-1, F-2, F-3 and F-4 showed 96.43, 96.15, 97.69 and 98.21% respectively. The drug release from the tablet was sustained for 9 to 11 hr. Formulation F4 found to be most promising formulation as they showed sustained release (98.21% upto 11 hrs) as well as maintained excellent matrix integrity during the period of 11 hr study. Hence formulation F4 was selected as the optimized formulation.

Fig. 3. *In Vitro* Dissolution Profile of F1 to F4 Formulations

**Determination of the release kinetics**

The release data was fitted to various mathematical models to evaluate the kinetics and mechanism of drug release. The kinetic data of all formulations F-1 to F-4 could be best expressed by zero order equation as the plots showed highest linearity (R²: 0.995 to 0.998), than first order release kinetics (R²: 0.764 to 0.815). The n values obtained from Korsmeyer Peppas plots range from (0.725 to 0.794) indicate that mechanism of release of formulations F-1 to F-4 was Anomalous (non-Fickian) diffusion.
Table 4. Release kinetics parameters of sustained release matrix tablets of Ambroxol hydrochloride.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Zero Order $R^2$</th>
<th>First Order $R^2$</th>
<th>Higuchi $R^2$</th>
<th>Peppas-model $R^2$</th>
<th>Slope $n$</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.995</td>
<td>0.770</td>
<td>0.988</td>
<td>0.998</td>
<td>0.725</td>
</tr>
<tr>
<td>F2</td>
<td>0.998</td>
<td>0.815</td>
<td>0.980</td>
<td>0.997</td>
<td>0.765</td>
</tr>
<tr>
<td>F3</td>
<td>0.997</td>
<td>0.779</td>
<td>0.968</td>
<td>0.992</td>
<td>0.777</td>
</tr>
<tr>
<td>F4</td>
<td>0.998</td>
<td>0.764</td>
<td>0.974</td>
<td>0.991</td>
<td>0.794</td>
</tr>
</tbody>
</table>

CONCLUSION

The matrix tablets were found to be effective in sustaining the drug release up to 11 hr. This is mainly due to formation of a thick gel structure that delays drug release from tablet matrix. Drug release was found to be diffusion coupled with erosion. Stability studies revealed that there was no significant change in drug content and dissolution profile of matrix tablets. FTIR studies revealed that there was no shift in peaks, indicating there is no interaction between Ambroxol hydrochloride and other ingredients used. It can be concluded that stable formulation could be developed by incorporating Guar gum and Karaya gum in a definite proportion, so that the controlled released profile is maintained for an extended period.

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REFERENCES

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