FORMULATION DEVELOPMENT AND OPTIMIZATION OF LORATIDINE TABLETS EMPLOYING SOLID DISPERSIONS IN MCC PH102 AND POLOXAMER188 AS PER 2^2 FACTORIAL DESIGN

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ABSTRACT
Loratadine has anti-histamine that reduces the effect of natural chemical histamine in the body. Histamine can produce symptoms of sneezing, itching, watery eyes and runny nose. Loratadine is used to treat sneezing, runny nose, watery eyes haves skin rash, itching & other cold or allergy symptoms. The present investigation concerns the formulation development & optimization of loratadine which after oral regulation or disintegration to enhance the solubility of solution and increase drug bioavailability. The loratadine prescribes anti histamic drug belongs to class-II and BCS classification & exhibit low and variable oral bioavailability due to its poor aqueous solubility. In the present study solid dispersion in microcrystalline cellulose and Poloxamer188 tried alone and in combination to enhance dissolution rate of loratadine in its tablet formulation development. The objective of the present study is to optimize loratadine in its tablet formulation by 2^2 factorial design using solid dispersions. MCC PH 102 and Poloxamer188 (surfactant) to achieve NLT 85% dissolution in 15 minutes. For optimization of loratadine tablet or 2^2 factorial design using solid dispersion MCC PH
102 and Poloxamer188 are considered as two factors the two levels of the A (MCC) are 1:1 and 1:5 ratio of Drug:MCC PH 102 at the two levels of factor B (Poloxamer188) are 1% and 5% of drug content. Four loratadine tablet formulations employing selected combination of two factors i.e. MCC PH 102 and Poloxamer188 as per $2^2$ factorial design were formulated. Solid dispersions of loratadine in combined carries were initially prepared and were used to prepare the tablets. The tablets were prepared by direct compression method and were evaluated. Loratadine tablet formulations LSDFa disintegrated rapidly with in 25 seconds and gave very rapid dissolution of loratadine, 100% in 15 min. The increasing order of dissolution rate ($K_1$) observed with various formulations was LSDFb, LSDFab, LSDFa, LSDF. The polynomial equation describing the relationship between the response, Y and the variables $X_1$ & $X_2$ based on the observed data was found to be $Y= 60.73+37.93(X_1)+4.49(X_2)-5.83(X_1X_2)$. Based on the above polynomial equation, the optimized loratadine tablet formulations with NLT 86.42% dissolution in 15 min could be formulated employing MCC PH 102 at 1: 4.52 ratio of drug : MCC PH 102 , Polaxamer188 at 3% of drug content. The optimized loratadine tablet formulations gave 86.42% of dissolution in 15 min fulfilling the target dissolution set. Hence optimization by $2^2$ factorial design employing solid dispersion MCC PH 102 and Poloxamer 188 could be used to formulate loratadine tablets with the desired dissolution i.e ..., NLT 85% and 15 min.

**KEYWORDS**: Optimization, Loratadine tablets, Factorial design, Solid dispersion, MCC PH102, Poloxamer188.

**INTRODUCTION**

Loratadine has anti-histamine that reduces the effect of natural chemical histamine in the body. Histamine can produce symptoms of sneezing, itching, watery eyes and runny nose. Loratadine is used to treat sneezing, runny nose, watery eyes haves skin rash, itching & other cold or allergy symptoms. The loratadine prescribes antihistaminc drug belongs to class-II and BCS classification & exhibit low and variable oral bioavailability due to its poor aqueous solubility. In the present study solid dispersion in microcrystalline cellulose and Poloxamer188 tried alone and in combination to enhance dissolution rate of loratadine in it’s tablet formulation development. It needs enhancement in the dissolution rate in its formulation development to derive its maximum therapeutic efficacy. Among various techniques cyclodextrin complexation$^{[1-4]}$, solid dispersion and solvent deposition techniques$^{[5,6]}$, use of superdisintegrants$^{[7,8]}$ and surfactants$^{[9-11]}$ are widely accepted in
industry for enhancing the dissolution rate of poorly soluble drugs from solid dosage forms. In solid dispersions the poorly soluble drug is dispersed in an inert water-soluble carrier such as urea, polyethylene glycol, poly vinyl pyrrolidone and surfactants at solid state. In the case of solvent deposited dispersions the drug is deposited in minuscule form on an inert water insoluble excipient such as MCC, silica gel, starch and modified starches at solid state.

The present investigation concerns the formulation development & optimization of loratadine which after oral regulation or disintegration to enhance the solubility of solution and increase drug bioavailability. The objective of the present study is to optimize loratadine in its tablet formulation by $2^2$ factorial design using solid dispersions. MCC PH 102 and Poloxamer 188 (surfactant) to achieve NLT 85% dissolution in 10 minutes.

Optimization\(^{(12)}\) of pharmaceutical formulations involves choosing and combining ingredients that will result in a formulation whose attributes confirm with certain prerequisite requirements. The choice of the nature and qualities of additives (excipients) to be used in a new formulation shall be on a rational basis. The application of formulation optimization techniques is relatively new to the practice of pharmacy.

In general the procedure consists of preparing a series of formulations, varying the concentrations of the formulation ingredients in some systematic manner. These formulations are then evaluated according to one or more attributes, such as hardness, dissolution, appearance, stability, taste and so on. Based on the results of these tests, a particular formulation (or series of formulations) may be predicted to be optimal. The optimization procedure is facilitated by applying factorial designs and by the fitting of an empirical polynomial equation to the experimental results. The predicted optimal formulation has to be prepared and evaluated to confirm its quality.

**EXPERIMENTAL**

**Materials**

Loratadine was a gift sample from M/s Hetero Laboratories Ltd., Hyderabad. Micro crystalline cellulose (MCC PH102) and Poloxamer188 were gift samples from M/s Aurobindo Pharmaceuticals., Hyderabad. Talc and magnesium stearate were procured from commercial sources. All other materials used were of Pharmacopoeial grade.
Methods

Estimation of Loratadine

An UV Spectrophotometric method based on the measurement of absorbance at 248 nm in phosphate buffer of pH 6.8 was used for the estimation of Loratadine. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beer’s law in the concentration range of 1 – 10 µg/ ml. When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variance were found to be 0.85% and 1.10% respectively. No interference by the excipients used in the study was observed.

Formulation of Loratadine Tablets\(^1\)

For optimization of Loratadine tablets as per \(2^2\) factorial design using solid dispersions the MCC PH102 and Poloxamer188 are considered as the two factors. The two levels of the factor A (MCC) are 1:1 and 1:5 ratio of drug: MCC and the two levels of the factor B (Poloxamer188) are 1% and 5% of drug content. Four Loratadine tablet formulations employing selected combinations of the two factors i.e. MCC and Poloxamer188 as per \(2^2\) factorial design were formulated. Solid dispersions of Loratadine in combined carriers were initially prepared and were used to prepare the tablets by direct compression method.

Preparation of Solid Dispersions in Combined Carriers\(^1\)

Solid dispersions of Loratadine in MCC and Poloxamer 188 as per \(2^2\) factorial design were prepared by kneading method. The required quantities of drug and Poloxamer 188 were dissolved in the solvent methanol to get a clear solution in a dry mortar. MCC was added to the drug- surfactant solution in the motor and mixed. The mixture was kneaded for 30 min by continuous trituration. Small volume of the solvent was added to maintain the mixture as thick slurry during kneading process. Trituration was continued until a dry mass was obtained. The mass obtained was further dried at 50\(^0\)C for 1 hour in a hot air oven. The dried product was powdered and passed through mesh no. 100 in each case and was used for the preparation of Loratadine tablets.

Preparation of Loratadine Tablets

Loratadine (40 mg) tablets were prepared by direct compression method as per the formula given in Table1. Solid dispersions employing the required quantities of Loratadine, MCC and Poloxamer188 as per the formula were initially prepared as described above and were taken in a closed polyethene bag. Talc and magnesium stearate were then added by passing through mesh no.80 and blended. The blend of ingredients was then compressed directly into tablets.
using an 8-station RIMEK tablet punching machine employing 9 mm round and flat punches.

Evaluation of Tablets
All the Loratadine tablets prepared were evaluated for drug content, hardness, friability, disintegration time and dissolution rate as follows.

1. Hardness
Hardness of the tablet was determined using the Monsanto hardness tester (Make: Adarsh). The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by tuning threaded bolts until the tablet fractured. Then the final reading was recorded. The hardness was computed by deducing the initial pressure from the final pressure.

2. Friability
The roche friability test apparatus was used to determine the friability of the tablets. About 10 tablets were selected, dedusted and weighed. Then they were placed in a drum and rotated for 100 times. The tablets were dedusted to remove loose dust and were reweighed. The percentage friability was calculated by the formulae.

\[
\% \text{ friability} = \frac{\text{initial wt} - \text{final wt}}{\text{initial wt}} \times 100
\]

3. Disintegration time
Disintegration time of the tablets was determined using single unit disintegration test apparatus (Make: ELCON) employing water as test fluid.

4. Drug Content
Weighed tablets (5) were powdered using a glass mortar and pestle. An accurately weighed quantity of powder equivalent to 20 mg of Loratadine was taken into 100 ml volumetric flask, dissolved in phosphate buffer of pH 6.8 and the solution was filtered through Whatman filter paper no.41. The filtrate was collected and suitably diluted with phosphate buffer of pH 6.8 and assayed for Loratadine at 248 nm.

Dissolution Rate Study
Dissolution rate of Loratadine tablets prepared was studied in phosphate buffer of pH 6.8 (900 ml) employing eight station dissolution rate test apparatus (ELITE, DS 8000) using
paddle stirrer at 50 rpm and at a temperature of 37°C ± 1°C. One tablet was used in each test. Samples of dissolution fluid (5 ml) were withdrawn through a filter at different time intervals and assayed for Loratadine at 248 nm. The sample of dissolution fluid withdrawn at each time was replaced with fresh drug free dissolution fluid and a suitable correction was made for the amount of drug present in the samples withdrawn in calculating percent dissolved at various times. Each dissolution experiment was run in triplicate (n=3).

Analysis of Data
The dissolution data were analyzed as per zero order and first order kinetic models. Dissolution efficiency (DE \(_{30}\)) values were estimated as suggested by Khan.\[15]\] Dissolution rate (K\(_1\)) values were analyzed as per ANOVA of 2\(^2\) factorial experiments.

RESULTS AND DISCUSSION
The objective of the present study is to optimize the Loratadine tablet formulation employing solid dispersions in MCC PH102 and Poloxamer188 by 2\(^2\) factorial design to achieve NLT 85% dissolution in 10 min. For optimization of Loratadine tablets as per 2\(^2\) factorial design using solid dispersions, the MCC PH102 and Poloxamer188 are considered as the two factors. The two levels of the factor A (MCC) are 1:1 and 1:5 ratio of drug: MCC and the two levels of the factor B (Poloxamer188) are 1% and 5% of drug content. Four Loratadine tablet formulations employing selected combinations of the two factors i.e. MCC and Poloxamer188 as per 2\(^2\) factorial design were formulated. Solid dispersions of Loratadine in combined carriers were initially prepared and were used to prepare the tablets by direct compression method.

Tablets were prepared by direct compression method as per the formulae given in Table 1 and were evaluated for drug content, hardness, friability, disintegration time and dissolution rate characteristics. The dissolution rate (K\(_1\)) values were analyzed as per ANOVA of 2\(^2\) factorial design to find out the significance of the individual and combined effects of the two factors involved on the dissolution rate of Loratadine tablets formulated.

The physical parameters of the Loratadine tablets prepared are given in Table 2. The hardness of the tablets was in the range 4.5-5.2 kg/cm\(^2\). Weight loss in the friability test was less than 0.93% in all the cases. Loratadine content of the tablets prepared was within 100±3 %. Much variations were observed in the disintegration and dissolution characteristics of the Loratadine tablets prepared. The disintegration times were in the range 25 sec to 6 min 25
sec. Loratadine tablet formulations LSDFₐ disintegrated rapidly with in 25 sec. All other tablets disintegrated rather slowly in about 3 min to 6 min 20 sec. All the Loratadine tablets prepared fulfilled the official (IP 2010) requirements with regard to drug content, hardness, friability and disintegration time specified for uncoated tablets.

Dissolution rate of Loratadine tablets prepared was studied in phosphate buffer pH 6.8. The dissolution profiles of the tablets are shown in Fig.1 and the dissolution parameters are given in Table 3. Dissolution of Loratadine from all the tablets prepared followed first order kinetics with coefficient of determination (R²) values above 0.962. The first order dissolution rate constant (K₁) values were estimated from the slope of the first order linear plots. Much variations were observed in the dissolution rate (K₁) and DE₃₀ values of the tablets prepared due to formulation variables. ANOVA of K₁ values (Table 4) indicated that the individual and combined effects of the two factors, MCC PH102 and Poloxamer188 in influencing the dissolution rate of Loratadine tablets are highly significant (P < 0.01). Loratadine tablet formulations LSDFₐ and LSDFₐₖ gave very rapid dissolution of Loratadine than others. These tablets gave above 95% dissolution in 15 min. The increasing order of dissolution rate (K₁) observed with various formulations was LSDFₐ > LSDFₐₖ > LSDFₐ > LSDF₂₂.

Optimization

For optimization, percent drug dissolved in 10 min was taken as response (Y) and level of MCC PH102 as (X₁) and level of Poloxamer188 (X₂). The polynomial equation describing the relationship between the response, Y and the variables, X₁ and X₂ based on the observed data was found to be Y = 60.73 + 37.93(X₁) + 4.49(X₂) + 5.83(X₁X₂). Based on the above polynomial equation, the optimized Loratadine tablet formulation with NLT 85% dissolution in 15 min could be formulated employing MCC at 1: 4.52 ratio of drug: MCC PH102, and Poloxamer188 at 3% of drug content. To verify Loratadine tablets were formulated employing the optimized levels of MCC PH102 and Poloxamer188. The formula of the optimized Loratadine tablets is given in Table 1. The optimized Loratadine tablet formulation was prepared by direct compression method and the tablets were evaluated. The physical parameters of the optimized formulation are given in Table 2 and dissolution parameters are given in Table 3. The hardness of the optimized Loratadine tablets was 5.0 kg/sq.cm. Friability (percent weight loss) was less than 0.86%. Disintegration time of the tablets was 25 sec. The optimized Loratadine tablet formulation gave 86.42% dissolution in 15 min fulfilling the target dissolution set.
Table 1: Formulae of Loratadine Tablets Prepared Employing Solid Dispersions in MCC and Poloxamer188 as per 2² Factorial Design

<table>
<thead>
<tr>
<th>Ingredient (mg/tab)</th>
<th>LDF₁</th>
<th>LDFₐ</th>
<th>LDFₐ</th>
<th>LDFₐb</th>
<th>Fₜₐp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loratadine</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>MCC PH102</td>
<td>10</td>
<td>50</td>
<td>10</td>
<td>50</td>
<td>45.2</td>
</tr>
<tr>
<td>Poloxamer188</td>
<td>0.1</td>
<td>0.1</td>
<td>0.5</td>
<td>0.5</td>
<td>6.3</td>
</tr>
<tr>
<td>Talc</td>
<td>0.40</td>
<td>1.2</td>
<td>0.41</td>
<td>1.21</td>
<td>1.11</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.40</td>
<td>1.2</td>
<td>0.41</td>
<td>1.21</td>
<td>1.11</td>
</tr>
<tr>
<td>Total weight (mg)</td>
<td>20.9</td>
<td>62.5</td>
<td>21.32</td>
<td>62.92</td>
<td>57.70</td>
</tr>
</tbody>
</table>

Table 2: Physical Parameters of Loratadine Tablets Prepared Employing Solid Dispersions in MCC and Poloxamer188 as per 2² Factorial Design

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Hardness (Kg/cm²)</th>
<th>Friability (% Wt loss)</th>
<th>Disintegration Time (min-sec)</th>
<th>Drug Content (mg/tablet)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDF₁</td>
<td>5.4±0.20</td>
<td>0.82±0.02</td>
<td>6-25</td>
<td>98.3±0.26</td>
</tr>
<tr>
<td>LDFₐ</td>
<td>4.7±0.20</td>
<td>0.88±0.02</td>
<td>0-25</td>
<td>99.6±0.20</td>
</tr>
<tr>
<td>LDFₐb</td>
<td>5.2±0.15</td>
<td>0.87±0.02</td>
<td>5-30</td>
<td>98.4±0.20</td>
</tr>
<tr>
<td>LDFₐb</td>
<td>4.5±0.15</td>
<td>0.93±0.01</td>
<td>3-30</td>
<td>98.5±0.26</td>
</tr>
<tr>
<td>Fₜₐp</td>
<td>5.0±0.10</td>
<td>0.86±0.01</td>
<td>0-25</td>
<td>98.3±0.26</td>
</tr>
</tbody>
</table>

Table 3: Dissolution Parameters of Loratadine Tablets Prepared Employing Solid Dispersions in MCC and Poloxamer188 as per 2² Factorial Design

<table>
<thead>
<tr>
<th>Formulation</th>
<th>PD₁₅ (%)</th>
<th>Tₕ₀ (min)</th>
<th>T₉₀ (min)</th>
<th>DE₃₀ (%) (x±s d)</th>
<th>K₁ X 10⁻¹ (min⁻¹) (x±s d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDF₁</td>
<td>12.46</td>
<td>2</td>
<td>3.5</td>
<td>13.6±0.26</td>
<td>0.3684±0.01</td>
</tr>
<tr>
<td>LDFₐ</td>
<td>100</td>
<td>3</td>
<td>7.5</td>
<td>74.82±0.026</td>
<td>5.6269±0.03</td>
</tr>
<tr>
<td>LDFₐb</td>
<td>33.13</td>
<td>24.5</td>
<td>51</td>
<td>29.7±0.17</td>
<td>0.5143±0.01</td>
</tr>
<tr>
<td>LDFₐb</td>
<td>97.32</td>
<td>51.5</td>
<td>83</td>
<td>71.1±0.1</td>
<td>2.4335±0.01</td>
</tr>
<tr>
<td>Fₜₐp</td>
<td>86.42</td>
<td>2.8</td>
<td>10.5</td>
<td>86.29±0.56</td>
<td>1.542±0.36</td>
</tr>
</tbody>
</table>

Table 4: ANOVA of Dissolution Rates (K₁) of Loratadine Tablets Prepared Employing Solid Dispersions in MCC and Poloxamer188 as per 2² Factorial Design

<table>
<thead>
<tr>
<th>Source of Variation</th>
<th>DF</th>
<th>SS</th>
<th>MSS</th>
<th>F-ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>11</td>
<td>4793.7</td>
<td>435.79</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>3</td>
<td>22350.18</td>
<td>7450.06</td>
<td>3.395</td>
</tr>
<tr>
<td>Error</td>
<td>8</td>
<td>17556.48</td>
<td>2194.56</td>
<td></td>
</tr>
<tr>
<td>Fₐ</td>
<td>1</td>
<td>27263.19</td>
<td>27263.19</td>
<td>12.42</td>
</tr>
<tr>
<td>F₂</td>
<td>1</td>
<td>9001.11</td>
<td>9001.11</td>
<td>4.10</td>
</tr>
<tr>
<td>Fₐb</td>
<td>1</td>
<td>11565.00</td>
<td>11565.00</td>
<td>5.26</td>
</tr>
</tbody>
</table>

F₀.₀₁(1,10) = 8.53; F₀.₀₅ (1,10) = 4.49
CONCLUSIONS

1. Loratadine tablet formulations LSDF<sub>a</sub> disintegrated rapidly with in 25 sec and gave very rapid dissolution of Loratadine, 100% in 15 min.
2. The increasing order of dissolution rate (K<sub>i</sub>) observed with various formulations was LSDF<sub>a</sub> > LSDF<sub>ab</sub> > LSD F<sub>b</sub> > LSDF<sub>i</sub>.
3. The polynomial equation describing the relationship between the response, Y and the variables, X<sub>1</sub> and X<sub>2</sub> based on the observed data was found to be Y = 60.73+37.93(X<sub>1</sub>)+4.49(X<sub>2</sub>)-5.83(X<sub>1</sub>X<sub>2</sub>). Based on the above polynomial equation, the optimized Loratadine tablet formulation with NLT 85% dissolution in 10 min could be formulated employing MCC at 1: 4.36 ratio of drug: MCC PH102, and Poloxamer188 at 3% of drug content.
4. The optimized Loratadine tablet formulation gave 86.42% dissolution in 10min
5. fulfilling the target dissolution set.
6. Hence optimization by 2<sup>2</sup> factorial design employing solid dispersions in MCC PH102 and Poloxamer188 could be used to formulate Loratadine tablets with the desired dissolution i.e., NLT 85% in 15 min.

REFERENCES