FORMULATION AND EVALUATION OF DULOXETINE HYDROCHLORIDE BY USING PRESS COATING TECHNOLOGY

R. Naresh Babu1*, D. Bindu Madhuri1, P. Sambasiva Rao2, G. Raveendra Babu3, B. Sivasai Kiran4

1*Department of Pharmaceutics, Nirmala College of Pharmacy, Atmakuru-522503, A.P., India.
2Department of pharmaceutics, Vijaya College of Pharmacy, Hayathanagar- 501511, Telangana, India.
3Department of Pharmaceutical Analysis, A. K. R. G. College of Pharmacy, Nallajerla-534112, A.P., India.
4Department of Pharmaceutical Analysis, D. C. R. M. Pharmacy College, Inkolлу-532167, A.P., India.

ABSTRACT

Enteric coated tablets of duloxetine hydrochloride was developed to get resistance from gastric juice when it is present in stomach, because duloxetine is incompatible with gastric juice. The tablets are prepared by using direct compression technique using polymer hydroxyl propyl methylcellulose phthalate, sodium starch glycolate and other excipients like talc, calcium phosphate, magnesium stearate. Hydroxyl propyl methylcellulose phthalate used for preventing drug release in stomach. Sodium starch glycolate used to reduce the disintegration time of tablet in intestine. Core tablet was optimized with 6% concentrations of super disintegrates like sodium starch glycolate press coated tablets were prepared with different concentrations of enteric coated material like hydroxyl propyl methylcellulose phthalate. Press coated tablets were evaluated in terms of their precompression parameters, physical characteristics, weight variation, hardness, drug content and further tablets were evaluated for in-vitro drug release, for 3hrs that is first 2 hrs no drug release was observed and gradually drug release was increased up to 45 min. The present formulation no drug release was observed in F30, F31 in acidic medium at first 2hrs. Gradually drug release was increased in alkaline medium. This
study concluded that enteric coated tablets by press coating technology can be prepared by using different concentrations of polymer studied and we can reduce the gastrointestinal tract side effects.

KEYWORDS: Duloxetine, Tablets, Preparation, Evaluation.

INTRODUCTION

Diabetic neuropathy, a common complication of diabetes, is damage to the nerves that allow you to feel things such as pain. There are several ways that diabetes damages the nerves, but they all seem related to blood sugar being too high for a long period of time 347 million people worldwide has diabetes. Diabetes increases the risk of heart disease and stroke 50% of people with diabetes. Diabetic polyneuropathy is the most common neuropathy in the Western world. Clinical and subclinical neuropathy has been estimated to occur in 10 to 100 percent of diabetic patients, depending upon the diagnostic criteria and patient populations examined. Diabetic neuropathy is classified into distinct clinical syndromes. A characteristic set of symptoms and signs exist for each syndrome, depending on the component of the peripheral nervous system that is affected.[1-3] Duloxetine hydrochloride (Figure 1) chemical name was (+)-(S)-N methyl (naphthalene-1yloxy)3-(thiophen-2-yl) propa-l-amine and it was an anti depressant drug and It was a serotonin-nor epinephrine reuptake inhibitor. Duloxetine also has approval for use in osteoarthritis and musculoskeletal pain. It can also relieve the symptoms of painful peripheral neuropathy, particularly diabetic neuropathy, and it is used to control the symptoms of fibromyalgia.[4-8] The main objective of the present work was to develop enteric coated tablets of duloxetine hydrochloride using different polymers like Hydroxyl propyl methylcellulose phthalate, Sodium starch glycolate, Talc, Calcium phosphate and Magnesium stearate.[9-10] The enteric coated tablets were prepared and evaluated for different physiochemical parameters such as weight variation test, moisture content test and drug content, hardness, friability, drug content and in vitro release.[11-12] The result showed all the parameters were the limits in case of in-vitro drug release, formulation F44. The drug release of formulations F44, F45, F46 were found more than 75% of the drug within 45 minutes in basic medium which are formulated by using different concentrations of hydroxyl propyl methylcellulose phthalate where as other formulations release drug within 120 minutes in acidic medium which were formulated by using low concentrations of hydroxyl propyl methylcellulose phthalate. Among all these formulations F44 shows better results.[13-14]
MATERIALS AND METHODS

Materials
Duloxetine hydrochloride (Cygnus Chemicals Pvt Ltd, Mumbai-400607) was used as a model drug. Hydroxyl propyl methylcellulose phthalate (HPMC Phthalate Dow Chemicals, Chennai-600020) was selected as a dispersion base. Sodium starch glycolate was a good disintegrating agent (SD Fine Chemicals Ltd., Mumbai-400102). Magnesium stearate was a good lubricant (Signet Chemical Corporation Pvt Ltd, Mumbai) preventing for sticking in manufacturing equipments. Calcium carbonate and Talc (Choudary and company, Udaipur-324001) diluent and absorbent was added to promote drug dispersion and increase the bulk amount of the product. All solvents used were of analytical grade.

Preparation of stock solution
Weighed accurately 10mg of duloxetine hydrochloride pure drug was dissolved in 10ml of 6.8 phosphate buffer 0.1ml of solution was taken and make up with 100ml of 6.8 phosphate buffer.

Preparation of standard solution
The stock solution was subsequently diluted with 6.8 phosphate buffer to obtain a series of dilutions containing 10, 20, 30, 40, 50, µg/ml of Duloxetine hydrochloride per ml of solution. The absorbance of the above dilutions was measured at 290 nm by using UV Spectrophotometer taking 6.8 phosphate buffer as blank. Then a graph was plotted by taking a concentration on x axis and absorbance on y axis which gives a straight line. The standard solution of duloxetine hydrochloride was prepared by accurately weighing 10mg of the drug diluted in 100 ml volumetric flask with distilled water to give a range of solutions with final concentration of 5-50ug/ml. The absorbance of each solution was determined at 290nm corresponding to 5-25 µg were taken in a series of 10 ml volumetric flask and volume made up with methanol. The absorbance measurements of these solutions were carried out against methanol as blank at 292 nm and a calibration curve was plotted.

In-vitro dissolution studies
Weigh and transfer the tablets equivalent to 650 mg of duloxetine individually in each of the 6 dissolution flasks, containing 900ml of 0.1N hydrochloric acid and previously adjust the temperature to 37°C± 0.5°C. Collect the samples for every 5, 10, 20, 30, 45, 60 min and later replace the medium with phosphate buffer 6.8 and collect the samples for remaining 30 min from a zone midway between the surface of the medium and the top of the rotating blade and
not less than 1cm from the vessel wall and filter through filter by discarding the first 5ml. The absorbance is measured at 291nm by using UV-spectrophotometer.

RESULTS AND DISCUSSION

Preformulation studies

Six formulations were prepared with the different level addition of HPMCP, Magnesium stearate, Talc, calcium phosphate. Mixture of excipients was prepared and evaluated for various parameters as follows, the bulk density of various powders mixed blends were found in the range 0.515-0.525 kg/cm³. The tapped density of various powder mixed blends was found in the range 0.610 – 0.617 gm/cm³. The compressibility index of various powders mixed blends were found in the range 14.56 – 16.57%. The Hausner’s ratio of various powders mixed blends were found in the range 1.170 – 1.189. Tablets were prepared using direct compression technique. Since the material was free flowing, tablets were obtained of uniform weight due to uniform die fill tablets were obtained in the range with acceptable weight varying as per pharmacopoeia specifications, less than 7.5%. The thickness of the tablets was found in the range 3.6-3.8 mm. Uniformity thickness was obtained due to uniform die fill. Hardness of the tablets was found in the range 4.55-4.75 Kg/cm². Uniform hardness was obtained due to equal compression force. Friability of tablets was observed in the range 0.29 - 0.65%. Tablets were evaluated by using an assay method. The drug was obtained in the acceptable limit. The drug content was found in the range 98.1 – 102.6% are shown in Figures 3, 4, 5 and Table 1.

In-vitro dissolution studies

In vitro drug release studies were conducted for the formulation using the USP dissolution apparatus type-II (paddle), at 100 rpm. The percentage drug release at the end of 2hrs 30 min was found in the range 80 – 94.5 %. Among all these formulations F44 shows better results. Drug polymer interactions studied by comparing IR spectra of the pure drug were compared with the mixture of the drug with other ingredients are shown in Figures 6, 7, 8, 9 and Table 2 and 3. Duloxetine gives the peak in IR spectrum nearby 3273 cm⁻¹, due to the presence of the secondary amine group. The peaks at 3077cm⁻¹ also observed due to the presence of methane group. The peaks present in the Duloxetine drug, excipients physical mixture also shows the peaks of nearby at 1571.2cm⁻¹, 1235cm⁻¹. The frequencies of functional groups of pure drug remained unaffected in a physical mixture containing different polymers and other
ingredients. Hence there was no interaction between the drug and excipients used in the study.

Figure 1: Duloxetine Hydrochloride

![Duloxetine Hydrochloride](image)

Figure 2: Duloxetine Hydrochloride Calibration Curve

![Duloxetine Hydrochloride Calibration Curve](image)

Figure 3: Percentage of Drug Release of F41, F42, F43

![Percentage of Drug Release of F41, F42, F43](image)
Figure 4: Percentage of Drug Release of F44, F45, F46

Figure 5: Percentage of Drug Release of F43, F44, F45, F46

Figure 6: FT-IR Spectrum of Pure Drug

Figure 7: FT-IR Spectrum of Pure Drug and HPMC
Figure 8: FT-IR Spectrum of Pure Drug and SSG

Figure 9: FT-IR Spectrum of Pure Drug and Excipients

Figure 10: Core Tablets of Duloxetine Hydrochloride

Table 1: Preformulation Studies of Duloxetine Hydrochloride

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Bulk density (gm/cm³)</th>
<th>Tapped density (gm/cm³)</th>
<th>Angle of repose (°)</th>
<th>Compressibility Index (%)</th>
<th>Hausner’s Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>F41</td>
<td>0.515</td>
<td>0.610</td>
<td>30.48</td>
<td>15.57</td>
<td>1.18</td>
</tr>
<tr>
<td>F42</td>
<td>0.523</td>
<td>0.615</td>
<td>31.24</td>
<td>14.95</td>
<td>1.175</td>
</tr>
<tr>
<td>F43</td>
<td>0.518</td>
<td>0.612</td>
<td>30.86</td>
<td>15.35</td>
<td>1.181</td>
</tr>
<tr>
<td>F44</td>
<td>0.517</td>
<td>0.613</td>
<td>33.28</td>
<td>15.66</td>
<td>1.189</td>
</tr>
<tr>
<td>F45</td>
<td>0.525</td>
<td>0.617</td>
<td>32.19</td>
<td>14.91</td>
<td>1.175</td>
</tr>
<tr>
<td>F46</td>
<td>0.522</td>
<td>0.611</td>
<td>31.10</td>
<td>14.56</td>
<td>1.170</td>
</tr>
</tbody>
</table>
Table 2: Dissolution Profile of Duloxetine Hydrochloride in Acidic Medium

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>F41</th>
<th>F42</th>
<th>F43</th>
<th>F44</th>
<th>F45</th>
<th>F46</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>15</td>
<td>8.96</td>
<td>5.79</td>
<td>2.26</td>
<td>0.27</td>
<td>0.059</td>
<td>0.00</td>
</tr>
<tr>
<td>30</td>
<td>92.08</td>
<td>5.88</td>
<td>2.71</td>
<td>0.99</td>
<td>0.081</td>
<td>0.054</td>
</tr>
<tr>
<td>60</td>
<td>95.07</td>
<td>6.51</td>
<td>3.80</td>
<td>1.53</td>
<td>0.181</td>
<td>0.063</td>
</tr>
<tr>
<td>90</td>
<td>95.52</td>
<td>89.81</td>
<td>4.52</td>
<td>2.08</td>
<td>0.226</td>
<td>0.135</td>
</tr>
<tr>
<td>120</td>
<td>96</td>
<td>93.98</td>
<td>4.79</td>
<td>3.89</td>
<td>0.380</td>
<td>0.289</td>
</tr>
</tbody>
</table>

Table 3: Dissolution Profile of Duloxetine Hydrochloride in Basic Medium

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>F41</th>
<th>F42</th>
<th>F43</th>
<th>F44</th>
<th>F45</th>
<th>F46</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0</td>
<td>39.07</td>
<td>35.53</td>
<td>34.08</td>
<td>30.7</td>
</tr>
<tr>
<td>15</td>
<td>0</td>
<td>0</td>
<td>72.70</td>
<td>62.35</td>
<td>53.35</td>
<td>52.7</td>
</tr>
<tr>
<td>30</td>
<td>0</td>
<td>0</td>
<td>85.97</td>
<td>83.98</td>
<td>59.8</td>
<td>75.3</td>
</tr>
<tr>
<td>45</td>
<td>0</td>
<td>0</td>
<td>92.51</td>
<td>90.43</td>
<td>62.6</td>
<td>88.0</td>
</tr>
<tr>
<td>60</td>
<td>0</td>
<td>0</td>
<td>94.86</td>
<td>93.88</td>
<td>92.5</td>
<td>88.0</td>
</tr>
</tbody>
</table>

**CONCLUSION**

Tablets were prepared by using press coating technology. The finished products were evaluated in preformulation studies and *in vitro* drug release studies. The formulations (F44, F45, and F46) were developed to sustain the drug release from the tablet dosage form. The drug release of formulations F44, F45, F46 were found more than 75% of the drug within 45 minutes in basic medium which are formulated by using different concentrations of HPMCP where as other formulations release drug within 120 minutes in acidic medium which were formulated by using low concentrations of HPMCP. Among all these formulations F44 shows better results and it fulfills all the requirements of enteric coated pellets and performed long term stability study on this formulation.

**REFERENCES**


