FORMULATION AND IN VITRO EVALUATION OF FAST DISSOLVING TABLET OF VERAPAMIL HYDROCHLORIDE

DATTATRAYA M. SHINKAR*, POOJA S. AHER, PARAG D. KOTHAWADE, AVISH D. MARU
Department of Pharmaceutics, Loknete Dr. J. D. Pawar College of Pharmacy, Manur, Tal. Kalwan, Dist Nashik, Maharashtra 423501
Email: dattashinkar@gmail.com

ABSTRACT
Objective: The main objective of this research work was to formulate and evaluate fast dissolving tablet of verapamil hydrochloride for the treatment of hypertension.
Methods: In this study, fast dissolving tablet were prepared by wet granulation method by using croscarmellose sodium and sodium starch glycolate as superdisintegrants in the concentration of 2%, 4%, and 6%. Polyvinyl pyrrolidone K30 is used as a binder. The designed tablets were subjected to various assessment parameters like friability test, hardness test, disintegration test, wetting time, in vitro drug release and drug content.
Results: All the prepared formulations were subjected to various assessment parameters, and the findings obtained within the prescribed limit. The calibration curve of pure drug using various solvents like distilled water, phosphate buffer pH 6.8 was plotted. F1-F9 containing croscarmellose sodium and sodium starch glycolate in various concentration demonstrate the minimum disintegration time. Among all these formulations F8 shows disintegration time up to 19±0.06 seconds due to the high concentration of superdisintegrants. In vitro drug release was tested in phosphate buffer pH 6.8 at a time interval of 0, 1, 3, 6, 9, 12, 15 min. The F8 shows drug release 98.5±0.567%. Accelerated stability study of optimized formulation (F8) up to 2 mo showed there was no change in disintegration time and percentage drug release.
Conclusion: The results obtained in the research work clearly showed a promising potential of fast dissolving tablets containing a specific ratio of croscarmellose sodium and sodium starch glycolate as superdisintegrants for the effective treatment of hypertension.
Keywords: Fast dissolving tablet, Verapamil hydrochloride, Superdisintegrants, Bioavailability, Calcium channel blocker

INTRODUCTION
Oral drug delivery remains the preferred route for administration of various drugs. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain evasion and most importantly the patient compliance. Tablets and capsules are the most popular dosage forms. But one important drawback of such dosage forms is dysphagia or difficulty in swallowing. To solve the above-mentioned problem, pharmaceutical technologists have put in their best efforts to develop a fast dissolving drug delivery, i.e. mouth dissolving tablet that disintegrates and dissolves rapidly in the saliva, within a few seconds without the need of drinking water or chewing. Such formulations provide an opportunity for product line extension in the many elderly persons will have difficulties in taking conventional oral dosage forms (viz., solutions, suspensions, tablets, and capsules) because of hand tremors and dysphagia. Other groups that may experience problems using conventional oral dosage forms include the mentally ill, the developmentally disabled and patients who are uncooperative, on reduced liquid-intake plans, or are nauseated. The technologies utilized for fabrication of fast dissolving tablet include lyophilization, molding, direct compression, cotton candy process, spray drying, sublimation, mass extrusion, nanonization, and quick dissolve film formation.

In case of geriatric and pediatric patients, there is a problem of dysphasia i.e. difficulty in swallowing. The oral bioavailability of verapamil hydrochloride is 35% due to first pass metabolism; therefore the bioavailability of the drug is increased by formulating fast-dissolving drug delivery system. Bioavailability is increased due to absorption from mouth to pharynx and pharynx to the esophagus. Thus, in the present investigation, it was planned to formulate and evaluate fast dissolving tablet of verapamil hydrochloride [1-11].

MATERIALS AND METHODS
Materials
Verapamil hydrochloride procured from Swapnroop drug agency, Aurangabad. All the other reagents used were of analytical grade.

Methods
Determination of λ max of verapamil hydrochloride
The UV spectrum of verapamil hydrochloride was obtained by using a UV-visible spectrometer (UV 3000). Accurately weigh 10 mg of the drug was added to 100 ml of volumetric flask. Volume was made up to 100 ml with water (100 μg/ml). This solution was used as a stock solution. From the stock solution, 1 ml of aliquots was withdrawn, and the volume was made up to 10 ml using water to obtain the concentration of 10 μg/ml. The resultant solution was scanned from 400 to 200 nm, and the spectrum was recorded to obtain the value of the maximum wavelength in respective solvents [12].

Drug excipients compatibility study
Infrared spectrum
The infrared (IR) spectrum of verapamil hydrochloride was recorded with potassium bromide (KBr) discover the wave number of 4000 to 400 cm⁻¹ by using fourier transform infrared spectrophotometer (FTIR) [13].

Formulation of fast dissolving tablets
Weighed a required quantity of all powdered material and mixed properly. Then granules were prepared by the addition of binder solution in the powdered material until dump mass is get formed. These dump mass is screened properly to obtain pellets or granules. After drying milling of the dried mass and then mixed with other ingredients like lubricant or glidant.

Formulation optimization
A 3² factorial design was applied to a formulation that shows the satisfactory results to see the effect of varying concentration of independent variables croscarmellose sodium (X₁), sodium starch glycolate (X₂) on dependent variables like disintegration time and cumulative drug release [14].
Hausner’s ratio = $\frac{\rho_{t}}{\rho_{b}}$

Where $\rho_{t}$ is tapped density and $\rho_{b}$ is bulk density.

Carr’s compressibility index

The compressibility index of the granules was determined by the Carr’s compressibility index. (%) Carr’s Index can be calculated by using the following formula [15].

\[
\text{carr’s index} = \left( \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \right) \times 100
\]
and time taken for complete wetting is noted. Averages of triplicate readings were taken [18].

Drug content uniformity
Randomly ten tablets from each batch were weighed accurately and powdered; the equivalent weight of 100 mg of verapamil hydrochloride was taken and made the volume up to 100 ml with phosphate buffer pH 6.8 in 100 ml volumetric flask and kept aside with constant shaking for 24 h to extract the total drug present in the tablet. Then the solution was filtered, and the volume was made with phosphate buffer pH 6.8 and analyzed for drug content at λmax of 278 nm. Averages of triplicate were taken [19].

In vitro drug release
Release of the drug in vitro, was determined by estimating the dissolution profile, USP 2 paddle apparatus was used and the paddle was allowed to rotate at 50 rpm, phosphate buffer (pH 6.8) (900 ml) was used as a dissolution medium. At specific time intervals of 0, 1, 3, 9, 12, 15 min 5 ml of samples were withdrawn and measured the absorbance at 278 nm after suitable dilution with pH 6.8 phosphate buffer. Average of three readings was taken [20-23].

Stability study
Stability study was conducted as per ICH guidelines 40°C ± 2°C, 75% ± 2% RH to test the chemical and physical stability of fast dissolving tablets for the period of 2 mo [24].

RESULTS AND DISCUSSION
Determination of λ max of verapamil hydrochloride
λ max of verapamil hydrochloride was determined in water. The calibration curve of verapamil hydrochloride shown linearity as per Beers Lambert’s law at 278 nm represented in fig. 1.
Drug excipients compatibility study

IR spectrometer study

The IR spectra of verapamil hydrochloride, polymers, and physical mixture are shown in figures. The IR absorption bands observed in the IR spectrum of drug and polymers resembles with that of found in physical mixture proves compatibility of the drug with polymers. In fig. 2 absorption spectrum of drug and crosscarmellose sodium and in fig. 3 absorption spectrum of drug and sodium starch glycolate.

Precompression evaluation parameters of powder

Angle of repose

The angle of repose is an inactive parameter of powder flow ability from the hopper to die cavity. An angle of repose between 25° to 30° indicates excellent flowability of the powder bed. In this work, the angle of repose was found to be varying between 22.56°-31.68° when glidants were incorporated. These studies indicated that the powder beds of all formulations are easily flowable. All the precompression parameters were found to be within the acceptable limit.

Table 3: Precompression parameters for fast dissolving tablets of F1 to F9

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>*Angle of repose (°)</th>
<th>*Bulk density (g/ml)</th>
<th>*Tapped density (g/ml)</th>
<th>Carr’s index (%)</th>
<th>Hausner’s ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>31.44±0.14</td>
<td>0.35±0.07</td>
<td>0.39±0.109</td>
<td>10.25</td>
<td>1.11</td>
</tr>
<tr>
<td>F2</td>
<td>24.72±0.02</td>
<td>0.39±0.11</td>
<td>0.42±0.098</td>
<td>7.14</td>
<td>1.07</td>
</tr>
<tr>
<td>F3</td>
<td>27.58±0.09</td>
<td>0.36±0.096</td>
<td>0.41±0.069</td>
<td>12.19</td>
<td>1.13</td>
</tr>
<tr>
<td>F4</td>
<td>25.52±0.43</td>
<td>0.29±0.108</td>
<td>0.32±0.023</td>
<td>9.375</td>
<td>1.10</td>
</tr>
<tr>
<td>F5</td>
<td>28.73±0.24</td>
<td>0.52±0.135</td>
<td>0.59±0.207</td>
<td>11.86</td>
<td>1.13</td>
</tr>
<tr>
<td>F6</td>
<td>33.85±0.16</td>
<td>0.5±0.160</td>
<td>0.53±0.239</td>
<td>5.6</td>
<td>1.06</td>
</tr>
<tr>
<td>F7</td>
<td>30.2±0.04</td>
<td>0.45±0.195</td>
<td>0.48±0.108</td>
<td>8.16</td>
<td>1.08</td>
</tr>
<tr>
<td>F8</td>
<td>22.5±0.42</td>
<td>0.26±0.17</td>
<td>0.28±0.1858</td>
<td>7.14</td>
<td>1.07</td>
</tr>
<tr>
<td>F9</td>
<td>31.68±0.05</td>
<td>0.33±0.145</td>
<td>0.37±0.138</td>
<td>10.81</td>
<td>1.12</td>
</tr>
</tbody>
</table>

*All values are mean±SD of three determinations. SD: Standard deviation

Post-compression evaluation of fast dissolving tablets of verapamil hydrochloride

Hardness

Hardness of the tablets varied between 2.8±0.11 Kg/cm² to 3.1±0.25 Kg/cm² indicating good binding and satisfactory strength of tablets to withstand stresses during transportation and also may offer good dissolution property.

% friability

The % friability was found in the range of 0.50±0.12% to 0.82±0.01%. The weight variation ranges from 149.7±0.44 to 151±1.06 mg which passes the standard.

Thickness

The thickness of the tablets was found to be uniform, between 2.68±0.19 mm to 2.84±0.02 mm for (F1 to F9).

Drug content

Drug content found in the fast dissolving tablets resembling that of literature value. Range of drug content is 90.8%-99.1%. Therefore uniformity of content was maintained in all formulations. Drug content of all formulations is listed in table 4.

Weight variation

The weight of the formulated tablets of verapamil hydrochloride (F1 to F9) was found to be uniform with low standard deviation values from 149.2±1.25 to 151.3±0.69 mg. The prepared formulations comply with the weight variation test as per IP. The results are given in table 4.

Wetting time

It is the time required for complete wetting of tablet. The wetting time was found in the range of 16±0.55 to 25±0.57 sec.

Disintegration time

It is the time required for complete disintegration of the tablet. The disintegration time was found in the range of 19±0.06 to 27±0.57 sec.

% cumulative drug release

% cumulative drug release was found in the range of 87.12±0.599 to 98.5±0.567 %

Table 4: Post-compression parameters for fast dissolving tablets of F1 to F9

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Hardness (Kg/cm²±SD)</th>
<th>Thickness (mm±SD)</th>
<th>Friability %a (mean±SD)</th>
<th>Weight variation (Mg±mean±SD)</th>
<th>Wetting time* (Sec±mean±SD)</th>
<th>Disintegration time (Sec±mean±SD)</th>
<th>Drug content %a (mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>3.3±0.20</td>
<td>2.04±0.02</td>
<td>0.67±0.02</td>
<td>150.9±0.17</td>
<td>25±0.57</td>
<td>27±0.57</td>
<td>90.8±0.92</td>
</tr>
<tr>
<td>F2</td>
<td>3.2±0.05</td>
<td>2.8±0.04</td>
<td>0.50±0.12</td>
<td>151±0.06</td>
<td>20±0.03</td>
<td>23±0.53</td>
<td>93.2±0.81</td>
</tr>
<tr>
<td>F3</td>
<td>2.9±0.05</td>
<td>2.83±0.08</td>
<td>0.63±0.05</td>
<td>150.1±0.63</td>
<td>22±0.57</td>
<td>26±1.15</td>
<td>95.8±0.50</td>
</tr>
<tr>
<td>F4</td>
<td>3.1±0.23</td>
<td>2.82±0.15</td>
<td>0.72±1.35</td>
<td>149.2±1.25</td>
<td>18±1</td>
<td>20±0.28</td>
<td>94.7±0.62</td>
</tr>
<tr>
<td>F5</td>
<td>2.9±0.11</td>
<td>2.70±0.07</td>
<td>0.59±0.13</td>
<td>151±0.86</td>
<td>20±0.17</td>
<td>23±0.79</td>
<td>97.2±0.88</td>
</tr>
<tr>
<td>F6</td>
<td>3.2±0.15</td>
<td>2.68±0.19</td>
<td>0.82±0.01</td>
<td>149.7±0.44</td>
<td>24±0.28</td>
<td>27±0.55</td>
<td>96.5±0.71</td>
</tr>
<tr>
<td>F7</td>
<td>3.1±0.25</td>
<td>2.74±0.21</td>
<td>0.68±0.16</td>
<td>151±0.69</td>
<td>18±0.32</td>
<td>21±0.27</td>
<td>97.5±0.87</td>
</tr>
<tr>
<td>F8</td>
<td>2.8±0.11</td>
<td>2.77±0.06</td>
<td>0.59±0.10</td>
<td>150±0.73</td>
<td>16±0.55</td>
<td>19±0.06</td>
<td>99.1±0.94</td>
</tr>
<tr>
<td>F9</td>
<td>3.3±0.45</td>
<td>2.80±0.26</td>
<td>0.67±0.17</td>
<td>150.1±0.68</td>
<td>19±0.29</td>
<td>23±0.36</td>
<td>98.9±0.79</td>
</tr>
</tbody>
</table>

*aAll values are mean±SD of three determinations. SD: Standard deviation
% cumulative drug release of the different formulations is shown in Fig. 4. In this formulations as the level of croscarmellose sodium and sodium starch glycolate is increased the drug release will also increases. Release of the drug in vitro, was determined by estimating the dissolution profile, USP 2 paddle apparatus was used and the paddle was allowed to rotate at 50 rpm, phosphate buffer (pH 6.8) (900 ml) was used as a dissolution medium.

Table 5: Stability study of the optimized formulation

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Observations</th>
<th>Before stability * (mean±SD)</th>
<th>Stability testing interval days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 mo *(mean±SD)</td>
<td>2 mo *(mean±SD)</td>
</tr>
<tr>
<td>1</td>
<td>Visual Appearance</td>
<td>White</td>
<td>White</td>
</tr>
<tr>
<td>2</td>
<td>disintegration time (sec)</td>
<td>19±0.06</td>
<td>19±0.30</td>
</tr>
<tr>
<td>3</td>
<td>drug content</td>
<td>99.1±0.94</td>
<td>99.02±0.499</td>
</tr>
</tbody>
</table>

*All values are mean±SD of three determinations. SD: Standard deviation

Stability study

Results of the stability studies showed that there is no change in the physical parameters of the formulation. Drug content of the formulation was also found to be same as that before stability testing. Stability data is shown in table 5.

Optimization

The purpose of 3² factorial design was to conduct the comprehensive study of the effect of process parameters like croscarmellose sodium (X₁) and sodium starch glycolate (X₂) and their interactions using a suitable statistical tool (Design expert software version 9.0.2.0) by applying one way ANOVA at 0.05 levels. Mathematical modeling was carried out; the polynomial equation was obtained depending on significant influence among two factors on their experimental design.

The influence of the main effect on responses was further elucidated by response surface methodology. It is a widely used tool in the development and design of the dosage form. The three-dimensional response surface plot and the corresponding two-dimensional contour plot were generated by software as shown in Fig. 5, 6, 7 and 8. The response surface plot is very useful for the determination of the main and interaction effects of the independent variables whereas the two-dimensional plot gives a visual representation of values of responses.

In case of in vitro drug release, the three-dimensional surface response plot depicted the increase in the drug release and disintegration time as increasing the concentration of superdisintegrants. The two-dimensional contour plot relating X₁X₂ (interaction between croscarmellose sodium and sodium starch glycolate) was nonlinear indicating interaction between two variables.
DISCUSSION

Prepared formulations were subjected to various assessment parameters and the findings obtained were within the limits which are depicted in table 4. The hardness of all the tablets indicating good binding and satisfactory strength of tablets to withstand stresses during transportation and may offer good dissolution property. The thickness of the tablets was found to be uniform, and drug content of all formulations shows uniformity in the content of drug in each tablet. All the prepared formulations comply
disintegration and weight variation test as per IP. The F8 formulation containing croscarmellose sodium and sodium starch glycolate in the ratio of (9:6) was selected as optimized formulation on the basis of the result of in vitro dissolution test. It is seen that in vitro drug release and disintegration increases as an enhancement of the concentration of superdisintegrants like croscarmellose sodium and sodium starch glycolate.

CONCLUSION

The current studies are aimed at successful development and optimization of the fast dissolving tablet of verapamil hydrochloride. Disintegration and in vitro drug release studies as per IP. The F8 formulation was selected as optimized formulation. The concentration of super disintegrants like croscarmellose sodium and sodium starch glycolate increases the disintegration and in vitro drug release.

The current studies are aimed at successful development and optimization of the fast dissolving tablet of verapamil hydrochloride. Disintegration and in vitro drug release studies as per IP. The F8 formulation was selected as optimized formulation. The concentration of super disintegrants like croscarmellose sodium and sodium starch glycolate increases the disintegration and in vitro drug release.

Thus, drug release from the fast dissolving tablet was increased by using the increased concentration of super disintegrants, assisting in faster disintegration in the oral cavity. As the drug having fast disintegration may leads to more drug availability for dissolution, resulting in faster absorption and possibly bioavailability leads to the quick onset of action in the systemic circulation.

ACKNOWLEDGMENT

Authors are thankful to management and Principal of L. N. Dr. J. D. Pawar, College of Pharmacy, Manur, Khalwan, Dist.-Nashik, Maharashtra for their constant support and providing facilities.

AUTHORS CONTRIBUTIONS

Experimental design, guidance, supervision for the research was done by Mr. D. M. Shinkar, Mr. P. D. Kothawade. Support and guidance for the work by Dr. A. D. Maru. Literature review, experimental work, development, optimization of the formulations and interpretation of results was done by Miss. Pooja S. Aher and writing of this manuscript by Mr. D. M. Shinkar. All authors read and approve the final manuscript.

CONFLICT OF INTERESTS

All authors have none to declare.

REFERENCES