FORMULATION AND IN-VITRO EVALUATION OF NIFEDIPINE SUSTAINED RELEASE TABLETS

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ABSTRACT
In the present study, Nifedipine was chosen as a model drug which is an Anti-Hypertensive. Because of its short life (2hr) and its high water solubility it was chosen as a suitable candidate for sustained release matrix tablet formulation. It was formulated in to matrix tablet using polymer such as Sodium alginate & HPMC K100 as release retardants. All the pre-compression parameters (angle of repose, Hausner’s ratio and Carr’s index) were found to be within the standard limits. Tablets were evaluated for hardness, friability, thickness, drug content, in-vitro release. The effect of polymer concentration binary polymer mixture on drug release profile was studied. It was observed that the polymer concentration has influence the drug release from matrix tablet. Matrix tablet content a blend of HPMC K100 and Sodium Alginate successfully sustained the release of Nifedipine for a period of 12hr. Pre and Post compression Studies clearly show that a sudden rise in the drug plasma concentration results in an increase in heart rate and drug-specific side effects. Sublingual Nifedipine has previously been used in hypertensive emergencies, however, was found to be dangerous, and has been abandoned. Therefore, it has been generally accepted that sustained-release (SR) formulations are most efficient for routine hypertension therapy with Nifedipine. The study indicates that the matrix tablets of Nifedipine prepared using HPMC K100 and Sodium Alginate can successfully be employed as twice-a-day oral sustained release dosage form in order to improve patient compliance.

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INTRODUCTION
Nifedipine, a calcium-channel blocking agent, is widely used in the treatment of angina pectoris and systemic hypertension [1]. Half life of the drug is comparatively short [2]. Clinical experiences gained with oral Nifedipine formulations with immediate-release (IR) characteristics clearly show that a sudden rise in the drug plasma concentration results in an increase in heart rate and drug-specific side effects [3,4]. Sublingual Nifedipine has previously been used in hypertensive emergencies, however, was found to be dangerous, and has been abandoned. Therefore, it has been generally accepted that sustained-release (SR) formulations are most efficient for routine hypertension therapy with Nifedipine. The SR dosage forms should primarily reduce the occurrence of steep rises in plasma concentration of the drug. Another important therapeutic goal that can be achieved with SR formulations is the improvement of chronic therapy compliance by prolongation of the dosing intervals. The matrix tablet by direct compression has attracted much attention due to its technological simplicity in comparison with other controlled release systems. It require fewer unit operations, less machinery reduced number of personnel and processing time, increased product stability and production rate [5]. Hydrophophilic polymer matrix systems are widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile, cost effectiveness and broad regulatory acceptance. The purpose of controlled release systems is
to maintain drug concentration in the blood or in the target tissues at desired value as long as possible. HPMC is the dominant hydrophilic vehicle used for the preparation of oral controlled drug delivery [6]. While HPMC could potentially (and therefore control) the release of a soluble drug, it could also facilitate the release of relatively insoluble drug (e.g. Nifedipine). In the later case, insolubility of the drug molecule would be the rate limiting step in its release and HPMC’s solubilizing effect would facilitate the release. The net result is controlled drug delivery for a prolonged period of time [7].

MATERIALS AND METHODS

Materials
Nifedipine was provided by Doctors Life sciences INNOVATOR-Nicardia Retard J.B chemicals and pharmaceuticals Ltd; Lactose, Sodium Alginate, HPMC K100, Talc (Oxford laboratory).Hydrogen chloride, Chloroform, Sodium hydroxide (Ranken RFCL Ltd), Starch (Spectrum Reagents and chemicals Pvt Ltd), Methanol (Hayman Ltd), Potassium dihydrogen phosphate (SDFC.Ltd. fine-Chemicals Ltd).

Methods

Method of Preparation of Nifedipine SR Tablets:
Nifedipine granules were prepared by wet granulation method. Microcrystalline cellulose, Lactose, Sodium Alginate, HPMC K100 were weighed and screened through 40 mesh sieves. Then Sodium Alginate, HPMC K100, Microcrystalline cellulose and Lactose were mixed with Nifedipine and wet granules were prepared by adding starch paste (%/w/v sol) as binding solution and sheared by pestle and formed as damp mass and passed through #16 mesh sieve. Granules were dried at 45-50oC by using a hot air oven for 20min. Dried granules were screened through #80 mesh sieve. Dried granules were mixed with Magnesium stearate and Talc. Then they were compressed by using Single tablet punching machine [8].

PRE-FORMULATION STUDIES FOR API [9]:

Physical appearance:
A small quantity of Nifedipine powder was taken in butter paper and viewed in well illuminated place. Finally the colour, odour and texture were observed. Solubility: A semi-quantitative determination of the solubility was made by adding solvent in small incremental amount to a test tube containing fixed quantity of solute or vice versa. After each addition, the system vigorously shaken and examined visually for any undissolved solute particles. The solubility was expressed in terms of ratio of solute and solvent.

Determination of Bulk density and Tapped density:
It refers to a measurement to describe packing of particles and also used to determine the amount of drug that occupies the volume in mg/ml before tapping and after tapping an accurately weighed quantity of the powder (W), was carefully poured into the graduated cylinder and the volume (Vo) was measured, then the graduated cylinder was closed with lid, set into the density determination apparatus. The density apparatus was set for 100 taps and after that, the volume (Vf) was measured and continued operation till the two consecutive readings were equal. The bulk density and tapped density were calculated using the following formula:

\[
\text{Bulk density} = \frac{W}{V_0}, \text{Tapped density} = \frac{W}{V_f}
\]

Where,
\( W \) = weight of the powder, \( V_0 = \) initial volume, \( V_f = \) final volume

Compressibility index:
Compressibility was calculated from the powder density using the following formula:

\[
\% \text{ Compressibility} = \left[ \frac{\text{Pt} - \text{Po}}{\text{Pt}} \right] \times 100
\]

Where,
\( \text{Pt} \) = Tapped density and \( \text{Po} = \) Bulk density

Angle of Repose:

The angle of repose was determined by the funnel method. Accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powders. The powders were allowed to pass through the funnel freely onto the surface. The diameter and height of the powder cone was measured and angle of repose was calculated by using the given formula.

\[
\tan \theta = \frac{h}{r}
\]

Where,
\( h = \) height of the heap, \( r = \) radius of the powder cone

PRE-COMPRESSION STUDIES FOR GRANULES [10]:

Angle of repose:

A quantity of 4gms of granules from each formula was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was tapped continuously until no further change in volume was observed.

\[
\text{BD} = \frac{\text{Weight of the powder/Initial volume, TD} = \frac{\text{Weight of the powder/Tapped volume}}{\text{Total density}}}
\]

Carr’s index:
The Compressibility of the granules was determined by Carr’s compressibility index. It is indirectly related to the relative flow rate, cohesiveness and particle size.

\[
\text{Carr’s index} = \frac{\text{Total density}}{\text{Bulk density} \times 100}
\]

Hauser’s ratio:
The Hauser’s ratio is a number that is correlated to the flowability of a powder or granular material. It is calculated by using the given formula.

\[
\text{Hauser’s ratio} = \frac{\text{Total density}}{\text{Bulk density}}
\]

POST-COMPRESSION STUDIES [11]:

Thickness:
Tablet thickness can be measured using digital vernier calipers. 3 tablets were taken and their thickness was measured and the average thickness for each tablet was calculated.

Hardness:
In the present study the crushing strength of the tablet was measured using Monsanto hardness tester. An average of three observations is reported.

Friability test:
Friability of the tablets was determined using Roche friability. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Preweighed sample of tablets was placed in the friabilitator and were subjected to 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. Conventional tablets that lose less than 1% of their weight are acceptable.

\[
\% \text{ Friability} = \left[ \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \right] \times 100
\]
### Table No.1: Formulation of Nifedipine Sustained Release Tablets

<table>
<thead>
<tr>
<th>INGREDIENTS (mg)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nifedipine</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>HPMC K100</td>
<td>5 (2.5%)</td>
<td>5 (2.5%)</td>
<td>5 (2.5%)</td>
<td>10 (5%)</td>
<td>10 (5%)</td>
<td>10 (5%)</td>
<td>20 (10%)</td>
<td>20 (10%)</td>
<td>20 (10%)</td>
</tr>
<tr>
<td>Sodium Alginate</td>
<td>5 (2.5%)</td>
<td>10 (5%)</td>
<td>20 (10%)</td>
<td>5 (2.5%)</td>
<td>10 (5%)</td>
<td>20 (5%)</td>
<td>10 (10%)</td>
<td>20 (10%)</td>
<td>20 (10%)</td>
</tr>
<tr>
<td>Lactose</td>
<td>132</td>
<td>117</td>
<td>107</td>
<td>117</td>
<td>112</td>
<td>102</td>
<td>107</td>
<td>107</td>
<td>92</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Starch</td>
<td>5% w/v Sol</td>
<td>5% w/v Sol</td>
<td>5% w/v Sol</td>
<td>5% w/v Sol</td>
<td>5% w/v Sol</td>
<td>5% w/v Sol</td>
<td>5% w/v Sol</td>
<td>5% w/v Sol</td>
<td>5% w/v Sol</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Talc</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Total weight</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
</tbody>
</table>

### Weight variation:
The weight variation test is done by weighing 10 tablets individually, calculating average weight and comparing the individual tablet weights to the average.

\[
\text{% Weight variation} = \left(\frac{\text{Average weight} - \text{Initial weight}}{\text{Average weight}}\right) \times 100
\]

### Drug content:
Five tablets were taken and powdered; the powder equivalent to 20 mg of Nifedipine was dissolved in 100 ml of 0.1 M HCl of pH 1.2, filtered and analyzed at 350nm using UV-Visible spectrophotometer.

### In vitro dissolution studies:
**Apparatus:** USP APPARATUS - II
**Medium:** 0.1N HCl up to 1st two hours, 6.8 pH Phosphate buffer for remaining 10hr.
**Sampling interval:** 1st hr, 2nd hr, 4th hr, 6th hr, 8th hr, 10th hr & 12th hr
**Rpm:** 100
**Temperature:** 37°C± 0.5°C

**Procedure**

*In vitro* dissolution studies of Nifedipine SR tablets were conducted with the USP Type-II apparatus. The dissolution studies were performed using 900 ml of 0.1 M HCl of pH 1.2 as dissolution medium at 37±0.5°C with 100 rpm speed for the first 2hr and the replaced with 6.8 PH phosphate buffer for the remaining 10hr. A tablet of each formulation containing 20 mg of drug was added into the dissolution medium. The sample of 5ml aliquots were withdrawn at regular intervals. The withdrawn sample was replaced every time with same quantity of fresh dissolution medium. The sample solutions were diluted and analyzed for their drug release by using UV-Spectrophotometer at wavelength of 350nm. Percentage of drug dissolved was calculated by plotting time on X axis against percent cumulative drug release on Y axis.
RESULTS & DISCUSSION:

Comparison of Optimized formulation with Marketed formulation:
The In-vitro dissolution profile of the optimized formulation was compared against In-vitro dissolution profile of marketed formulation under similar experimental conditions [13].

The Following are the Details of the Innovator Product

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>OBSERVATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Name</td>
<td>Nicardia Retard 20</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>J.B. Chemicals &amp; Pharmaceuticals LTD</td>
</tr>
<tr>
<td>Dosage Form</td>
<td>Sustained Release Tablet</td>
</tr>
<tr>
<td>Active and label claim</td>
<td>Nifedipine 20mg</td>
</tr>
</tbody>
</table>

RESULTS & DISCUSSION:

The bulk density of all formulations, powder blend containing excipients was found to be in the range of 0.71 to 0.79 gm/ml, whereas the tapped density was observed between 0.82 to 0.90 gm/ml. From the values of bulk density and tapped density the values for compressibility index and Hausner’s ratio were calculated. The values for compressibility index were found between 11.76 to 17.77%. The values for Hausner’s ratio were found in between 0.220 to 0.814. Friability test was conducted for all formulations, % friability was found to be in the range of 0.220 to 0.814. Friability test for all formulations indicated that % friability was less than 1%, which showed the LP specification and reveals that all formulations have possessed good physical strength and can withstand the mechanical shocks that can be observed during handling, shipping and transportation.

Drug content of all formulations was observed between 96.25 to 101.05%. Drug content for all formulations were within the range which indicated that there was uniform flow and uniform distribution of drug.

In-vitro dissolution studies on all the formulations had been conducted. The results were compared with that of the innovator product. From the above data it can be confirmed that formulation F5 was similar to the innovator product.
Drug Content
Table No.5: Drug content of all formulations

<table>
<thead>
<tr>
<th>S.No</th>
<th>Formulation code</th>
<th>Drug content</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F1</td>
<td>97.66</td>
</tr>
<tr>
<td>2</td>
<td>F2</td>
<td>96.25</td>
</tr>
<tr>
<td>3</td>
<td>F3</td>
<td>98.33</td>
</tr>
<tr>
<td>4</td>
<td>F4</td>
<td>98.45</td>
</tr>
<tr>
<td>5</td>
<td>F5</td>
<td>99.86</td>
</tr>
<tr>
<td>6</td>
<td>F6</td>
<td>97.45</td>
</tr>
<tr>
<td>7</td>
<td>F7</td>
<td>101.05</td>
</tr>
<tr>
<td>8</td>
<td>F8</td>
<td>98.66</td>
</tr>
<tr>
<td>9</td>
<td>F9</td>
<td>96.98</td>
</tr>
</tbody>
</table>

In-Vitro Drug Release Studies:
Table No.6: Dissolution data of Nifedipine SR Tablets

<table>
<thead>
<tr>
<th>S.No</th>
<th>Time (hrs)</th>
<th>% Cumulative drug release</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>23.80, 22.80, 18.14, 19.21</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>32.26, 32.20, 37.40, 38.36</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>54.50, 55.61, 55.12, 57.67</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>62.14, 64.27, 59.17, 60.23</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>71.87, 73.54, 70.24, 72.09</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>80.49, 82.21, 83.69, 81.38</td>
</tr>
<tr>
<td>7</td>
<td>12</td>
<td>92.90, 90.30, 93.40, 91.30</td>
</tr>
</tbody>
</table>

Fig 3: Dissolution Profile of all Nifedipine SR Tablets
Fig 4: Dissolution Profile of Innovator
Fig 5: Dissolution Profile of Best formulation (F5) & Innovator

CONCLUSION

The present work aimed at developing Sustained Release Tablets of Nifedipine by wet granulation method. After 12th hour the percentage drug release from the formulations were 92.3%, 90.3%, 93.4%, 91.3%, 98.2%, 85.2%, 89.8%, 81.4%, 87.9% for the formulations containing HPMC K100 & SA 2.5% & 2.5%, 2.5% & 5%, 2.5% & 10%, 5% & 2.5%, 5% & 5%, 5% & 10%, 10% & 2.5%, 10% & 5% and 10% & 10% respectively. Formulation F5 was identified to be the best as it showed sustained action for 12hr and as it matches well with the innovator. Accordingly it can be concluded that the F5 (5% & 5% w/w HPMC K100 & SA) is robust one.

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