Development of Nifedipine sublingual tablets using disintegrants as release modifiers

Swapna G\textsuperscript{1,2}, Sesha Maheswaramma K\textsuperscript{3}, Hemalatha S\textsuperscript{4}, Bhaskar Reddy K\textsuperscript{*2}

\textsuperscript{1}Research Scholar, JNTUA, Anantapur- 515002, Andhra Pradesh, India
\textsuperscript{2}Department of Pharmaceutics, Sri Venkateswara College of Pharmacy, Centre for Pharmaceutical Nanotechnology, RVS Nagar, Tirupati Road, Chittoor – 517127, Andhra Pradesh, India
\textsuperscript{3}Department of Chemistry, Jawaharlal Nehru Technological University, Anantapur College of Engineering, Pulivendula- 516390, Andhra Pradesh, India
\textsuperscript{4}Department of Pharmacognosy, Sri Venkateswara College of Pharmacy, RVS Nagar, Tirupati Road, Chittoor – 517127, Andhra Pradesh, India

Keywords: Chronic hypertension, Nifedipine, Sublimation, Sublingual, Super disintegrants

\textsuperscript{*}Corresponding Author
Name: Bhaskar Reddy K
Phone: 7729999180
Email: bhaskurra@gmail.com
ISSN: 0975-7538
DOI: https://doi.org/10.26452/ijrps.v11i4.4886

\textbf{INTRODUCTION}

Nifedipine is derived from dihydropyridine, a yellowish color substance having a crystalline structure. The chemical name of the compound is a 3,5-pyridine dicarboxylic acid, 1,4-dihydropyridine-2,6-dimethyl-4-(2-nitrophenyl)-dimethyl ester. Chowdhury Hafizul reviewed stated that 1,4-dihydropyridine ring is very effective towards calcium channel blocker (Ahsan and Hafizul, 1993). Nifedipine also actively work as an antianginal...
agent by inhibiting calcium ion influx. Nifedipine inhibits the transmembrane influx of calcium ions into cardiac muscle and smooth muscles without changing serum calcium levels (Kuriyama et al., 1982; Jetley and Weston, 1980). The hypothetical mechanism action of Nifedipine behind hypertension is due to the relaxation and prevention of coronary artery spasm, which reduces in oxygen utilization (Opie et al., 2013). Nifedipine having a 1,4-dihydropyridine ring is considered a slow and powerful calcium blocker than non-dihydropyridine blockers (Kuriyama et al., 1982; Jetley and Weston, 1980).

Nifedipine comes under BSC class II drug having low solubility and limited bioavailability. Nifedipine is well absorbed through intestine mucosa, nasal and oral mucosal membranes. The pharmacokinetics of Nifedipine could be increased by adapting a new formulation technique compared to a commercially available old technique. In this regard, researchers have been focused on sublingual tablets (SLTs), which can disintegrate firstly and shows increased bioavailability towards the early treatment of the disease. In the development of the SLTs, various techniques are adapted, e.g. dry granulation, direct compression, freeze-drying, spray drying, sublimation etc.

In this current study, a direct compression technique with a combination of super disintegrants and sublimation method has been introduced to formulate Nifedipine SLTs. These techniques are commonly used by most of researchers due to their cost-effectiveness, ease of being carried out in labs at atmospheric temperature, utilization of conventional equipment to achieve the better property of SLTs (Basu et al., 2011; Yadav et al., 2009). SLTs is one of the emerging and very popular formulations and are widely accepted by pediatric and geriatric patients. The sublimation method helps in the formation of pores on the surface of the tablet, which readily helps in the absorption of aqueous media and disintegrate the tablet immediately. SLTs can be taken by the patient in the absence of water during the journey because saliva can disintegrate the tablet easily in the buccal cavity. The main aim of the research work is to formulate nifedipine loaded SLTs, which will take very less time to disintegrate the tablet and produce an immediate effect in the treatment of hypertension (Simon et al., 2001).

**MATERIALS AND METHODS**

Nifedipine powder was a gift sample from Emcure Pharma, Pune, India. Croscarmellose sodium and sodium starch glycolate are obtained from Signet, Mumbai. Similarly, camphor, aspartame, microcrystalline cellulose, magnesium stearate and talc were of analytical research-grade and used as received from Divya Chemicals, India.

**Formulation of nifedipine SLTs**

Nifedipine and Super disintegrants (Croscarmellose sodium (CS) and sodium starch glycolate (SSG)) at different proportions were weighed and passed through a #80 mesh screen prior to mixing. The screened substances were transferred into a mortar and mixed intimately with a pestle. Weighed the number of excipients added gradually to the mixture until a homogeneous mixture was obtained in Table 1. The powder blend was slugged and compressed into tablets using a single punch tablet machine. Formulated tablets were dried at 60°C for 8 h (sublimation of camphor) until a constant weight was obtained and make tablets porous in their structure (Okhuelegbe et al., 2015).

**Pre-formulation study of prepared mixture**

The homogeneous mixture prepared as per Table 1 were subjected for pre-formulation studies such as bulk density, tapped density, Carr’s index and Hausner’s ratio and angle of repose. This parameter is helpful to find out the flowability, compressibility, size distribution of the particle. Above discussed parameters are calculated for each formulation of Nifedipine loaded SLTs and reported in Table 2.

**Drug compatibility study**

**FTIR study**

In Fourier-transform infrared spectroscopy (FTIR) analysis sample has been analyzed in the wavenumber between 4000-400 cm⁻¹. KBr pallets is prepared for the FTIR analysis. KBr is added with the sample and finally, a pallet has been formed and submitted to the FTIR analysis. Potassium bromide (KBr) is the commonest alkali halide used in the pellets due to its high transparency. FT-IR analysis can be used for the identification of unknown materials, determination of quality and compatibility of the sample in a mixture. FTIR absorption spectra of pure drug super disintegrants and their combination were characterized by IR-Affinity-1 (Shimadzu, Japan) (Thulluru et al., 2019; Bhosale and Kolte, 2019).

**DSC study**

Differential Scanning Colorimetry (DSC) is a thermal analysis technique used in research labs and many industries to analyse pharmaceutical formulations, polymers, nanomaterials and food products. DSC (SDTQ600, USA) is a thermoanalytical method used to study the drug and excipients interaction. The
drug and superdisintegrants were scanned individually and their combination to check the compatibility between drug and superdisintegrants (Ayshath et al., 2015; Han et al., 2020). DSC mainly focused on the heat capacity of material and the physical changes observed due to the temperature (10°C/min from 0 to 700°C under nitrogen flow rate 50ml/min).

**Evaluation of Nifedipine loaded SLTs.**

**Weight variation**

Twenty tablets were selected randomly from each formulation and weighed individually using a digital balance. The average weights were calculated and mean values were determined.

**Tablet thickness test**

To determine the uniformity and physical dimension of tablets, thickness is measured by Vernier caliper’s for randomly selected 20 tablets from each formulation.

**Hardness**

Hardness is one of the important factors having a significance role in transportation. The hardness of the tablets was determined using a Monsanto hardness tester. The hardness of ten tablets was measured using a Pfizer hardness tester. It is expressed in kg/cm².

**Friability**

The tablets were tested for friability testing using Roche friabilator. For this test, twenty tablets from each formulation have been selected. All tablets weighed properly and were subjected to the drum of Roche friabilator, revolving at 25 rpm for 4 min, and the tablets were reweighed after dedusted. The weight was measured and friability was calculated in % based on loss in weight.

**Drug content**

Twenty tablets were crushed into powder, the quantity of powder equivalent to the average weight of formulation was weighed and taken in a volumetric flask dissolved in 15 ml of methanol, the solution is filtered through Whatman filter paper, from this 1 ml of solution is withdrawn and after suitable dilution analyzed by UV spectrophotometer at 237nm for Nifedipine (Dinakaran et al., 2013).

**Wetting time**

A piece of tissue paper was kept inside a petri dish containing 6ml water. Nifedipine loaded SLT was placed on the paper and the time is noted till it gets wet completely.

**Surface pH**

The surface pH of SLTs is an important factor to be investigated to find out any possibility of irritation or toxicity, which could lead to a decrease in drug absorption (Devarakonda et al., 2004). Excess alkaline or acidic pH of the formulated SLTs may cause irritation and uneasiness during the drug delivery.

**Tablet disintegration study**

SLTs, which disintegrates firstly, is a more acceptable form of drug delivery in the buccal cavity in the presence of saliva. SLT, after placing under the tongue it disintegrates within few seconds to a few minutes without the presence of water. The presence of super disintegrants and the pores due to the sublimation method enhance the disintegration rate of a formulated SLTs in the buccal cavity.

This study was carried out by taking 6 tablets at a time under an aqueous buffer pH 6.8. The temperature was maintained at 37 ± 0.5°C. The time taken by the tablet to disintegrate completely was noted for each formulation (Bi et al., 1996).

**In vitro dissolution study**

The dissolution study is an important study that gives an idea about the % of drug release at different time intervals (Kito et al., 2019). For SLT, super disintegrants affect the rate of dissolution. The dissolution (USP type I) apparatus contain 900 ml buffer pH 6.8 (Abouhussein et al., 2019; Pandey et al., 2010) at 37 ± 0.5°C temperature and the shaft rotate at 100 rpm. Randomly selected tablets from each batch have been considered for the dissolution test. Predetermined time intervals 5 ml sample is pipetted and replaced by the fresh buffer. After a suitable dilution, the collected sample was analyzed under UV Spectrophotometer at 237 nm.

**Stability study**

Stability study involves several concepts such as physical, chemical and therapeutical. To find out the chemical stability of the finished product is an integral part of the formulation. It produces important information such as shelf-life of the formulation, proper storage condition, active drug and its compatibility with excipients etc. As per the ICH (international conference of harmonization) guideline, the selected SLT was subjected for stability study for 3 months. Stability study carried out as per Indian weather condition in a stability chamber at 40°C ± 2°C / 75% ± 5% RH. Various stability parameters, e.g. physical appearance, drug content, disintegration time and in-vitro drug release, were evaluated in triplicate.

**RESULTS AND DISCUSSION**

**Properties of mixture**

To determine the nature and size of the compound,
Table 1: Formulation of NIF loaded SLTs

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Batches</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>10</td>
</tr>
<tr>
<td>Croscarmellose sodium</td>
<td>15</td>
</tr>
<tr>
<td>Sodium starch glycolate</td>
<td>-</td>
</tr>
<tr>
<td>Camphor</td>
<td>-</td>
</tr>
<tr>
<td>Aspartame</td>
<td>4</td>
</tr>
<tr>
<td>Mcc</td>
<td>11</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>5</td>
</tr>
<tr>
<td>Talc</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 2: Pre-formulation study for NIF loaded mixtures (Formulation F1- F6)

<table>
<thead>
<tr>
<th>Pre-Compression Parameter</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulk density</td>
<td>0.29±0.01</td>
<td>0.32±0.08</td>
<td>0.34±0.11</td>
<td>0.37±1.02</td>
<td>0.40±0.07</td>
<td>0.41±0.29</td>
</tr>
<tr>
<td>Tapped density</td>
<td>0.39±0.73</td>
<td>0.36±1.52</td>
<td>0.45±0.91</td>
<td>0.39±1.72</td>
<td>0.43±0.83</td>
<td>0.46±0.31</td>
</tr>
<tr>
<td>Angle of repose</td>
<td>27.21±0.1</td>
<td>24.01±0.72</td>
<td>29.8±0.09</td>
<td>25.32±1.11</td>
<td>27.09±0.08</td>
<td>30.21±0.05</td>
</tr>
<tr>
<td>Carr’s index</td>
<td>23.33±0.76</td>
<td>10.83±0.03</td>
<td>23.77±1.99</td>
<td>4.8±1.09</td>
<td>6.5±1.71</td>
<td>9.78±0.02</td>
</tr>
<tr>
<td>Hausner’s ratio</td>
<td>1.3±0.06</td>
<td>1.12±0.01</td>
<td>1.31±0.02</td>
<td>1.05±0.01</td>
<td>1.06±0.03</td>
<td>1.1±0.03</td>
</tr>
</tbody>
</table>

Table 3: Post-compression parameters for Nifedipine loaded SLTs formulation F1-F6

<table>
<thead>
<tr>
<th>Batch no</th>
<th>Tablet Weight variation (mg)</th>
<th>Tablet Thickness (mm)</th>
<th>Tablet Hardness (kg/cm²)</th>
<th>Tablet Friability (%)</th>
<th>Drug content (%)</th>
<th>Wetting time (sec)</th>
<th>Disintegration time (sec)</th>
<th>Surface pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>59.33±2.11</td>
<td>2.97±1.03</td>
<td>3.03±0.06</td>
<td>0.52±0.51</td>
<td>97.09±0.85</td>
<td>2.02±0.02</td>
<td>20±0.02</td>
<td>6.14±0.2</td>
</tr>
<tr>
<td>F2</td>
<td>58.11±1.06</td>
<td>3.31±0.93</td>
<td>2.51±0.7</td>
<td>0.61±0.09</td>
<td>98.01±0.76</td>
<td>3.01±0.01</td>
<td>29±0.01</td>
<td>5.04±0.11</td>
</tr>
<tr>
<td>F3</td>
<td>60.03±1.7</td>
<td>2.28±0.37</td>
<td>2.09±0.28</td>
<td>0.59±0.43</td>
<td>99.3±0.11</td>
<td>2.01±0.10</td>
<td>16±0.02</td>
<td>6.61±0.06</td>
</tr>
<tr>
<td>F4</td>
<td>57.09±1.91</td>
<td>2.96±0.09</td>
<td>3.81±0.11</td>
<td>0.71±0.07</td>
<td>99.87±0.93</td>
<td>2.5±0.01</td>
<td>19±0.02</td>
<td>5.68±0.07</td>
</tr>
<tr>
<td>F5</td>
<td>59.13±0.01</td>
<td>3.31±0.01</td>
<td>2.93±0.19</td>
<td>0.63±0.01</td>
<td>99.42±0.81</td>
<td>2.01±0.01</td>
<td>13±0.01</td>
<td>5.93±0.28</td>
</tr>
<tr>
<td>F6</td>
<td>59.19±1.37</td>
<td>2.99±0.48</td>
<td>2.79±0.85</td>
<td>0.63±0.07</td>
<td>98.92±0.47</td>
<td>2.5±0.02</td>
<td>38±0.02</td>
<td>6.7±0.014</td>
</tr>
</tbody>
</table>

Results are expressed as of mean ±SD (n=3)

Table 4: Stability studies of best formulation of Nifedipine sublingual tablet

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Drug</th>
<th>1st month</th>
<th>2nd month</th>
<th>3rd month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical appearance drug &amp; excipients</td>
<td>NIF</td>
<td>NSC</td>
<td>NSC</td>
<td>NSC</td>
</tr>
<tr>
<td>Drug content %</td>
<td>NIF (F5)</td>
<td>99.42%</td>
<td>98%</td>
<td>97.38%</td>
</tr>
<tr>
<td>Disintegration time</td>
<td>NIF (F5)</td>
<td>13 sec</td>
<td>12 sec</td>
<td>12 sec</td>
</tr>
<tr>
<td>In-vitro drug release %</td>
<td>NIF (F5)</td>
<td>99.99%</td>
<td>96.03%</td>
<td>95.87%</td>
</tr>
</tbody>
</table>

All values are expressed as mean ± standard deviation, (n=3), NSC: No Significant Change
bulk density and tapped density are the important parameters to be conducted. These properties of a compound may vary due to the crystallization and homogeneous mixing of the compounds. The density of the solid also affects their compression and flow property after final production. Precompression results of Nifedipine loaded mixtures from each batch has been reported in Table 2. The bulk density of the formulations was found to be 0.29 to 0.41 gm/ml, tapped density shows the range between 0.36 to 0.46 gm/ml, angle of repose in the range between 24.01 to 30.21, Carr’s index within the range of 4.8 to 23.77 and Hauser’s ratio value lies in between 1.05 to 1.31. Obtained results were within limits and observed excellent flowability.

**FTIR study**
To maintain the safety, effectiveness and physical appearance of the active drug compatibility is a very important parameter to be evaluated. The active drug, super disintegrants and their mixtures were taken into consideration to find out the compatibility. The FTIR spectrum of individual active drugs (Nifedipine), super disintegrants (Croscarmellose sodium and Sodium starch glycolate) and their combinations has shown in Figure 1. Obtained result reveals that individual super disintegrants...
and active drug shows different spectra which are different from each other.

When the drug-super disintegrants combination has been taken into consideration, it is observed that there is no shifting or change in the spectra of Nifedipine. The FTIR spectra reveal no chemical interaction between drug-super disintegrants mixture and found compatible for the formulation of SLTs.

**DSC study**

Similarly, as FTIR, the DSC technique is used to study the compatibility of the active drug with different super disintegrants and their compositions. In the DSC study, samples are heated thermally in an equal ratio between drug and superdisintegrants to confirm the chemical compatibility. Obtained results provide either exothermic or endothermic peaks of the submitted samples. Resultant spectra compared within parent samples and their physical mixtures. A slight change in the peak shape, intensity and width could be the indication of incompatibility. DSC curve of the pure drug (Nifedipine), super disintegrants (Croscarmellose sodium and Sodium starch glycolate) and their mixtures has shown in Figure 2, indicating that superdisintegrants are compatible with pure drug.

**Digital Image**

NIF loaded SLT images has been shown in Figure 3, which gives a clear view that the surface of each tablet is rough. This could be due to the sublimation method, in which camphor and moisture present in the tablet are evaporated at 60°C.

The morphology study for the best formulation F5 is carried out by SEM analysis shown in Figure 4. The SEM image provides a complete surface morphology and confirms the pore formation due to the sublimation method (highlighted as a red circle in the image). Figure 5 represents in vitro dispersion time for all formulations.

**Evaluation of Nifedipine loaded SLTs**

An evaluation study has been performed for NIF loaded SLTs formulation F1-F6 and is listed in Table 3. The average weight for all formulations was found to be in the range of 57 to 60 mg. Vernier calliper was used to measure the thickness of the formulated tablets. Thickness for all formulations found within the range of 2.28 to 3.31mm. The hardness of SLTs is within the range of 2.51 to 3.81kg/cm². Friability ranges below 1%. These parameters represent the strength of the tablet.

Similarly, drug content % ranges between 97.09 to 99.87%, surface pH between 5 to 6 and wetting time lies between 2 to 3 seconds. Disintegration time for all the formulations are lies in the range between 13 to 38 seconds. The physical properties of all formulations were found to be optimum as per Indian pharmacopoeia.

**Dissolution study**

Different super disintegrants bound Nifedipine loaded SLTs were formulated formulation (F1 to F6). In-vitro dissolution time for formulation F1 to F6 SLTs shows variation in release period ranging from 9 min to 14 min shown in Figure 6. The difference may be attributed to the nature of super disintegrants and their different concentration in various proportions in formulations. The different concentrations of super disintegrants in the formulation have shown immediate release of the nifedipine drug than individual super disintegrants. Direct compression technique also played a vital role in the formulation of the sublingual tablet of Nifedipine which disintegrates within a short interval of time. The sublimation method is one more added advantage to achieve the desired release rate in the buccal area. When camphor is sublimated at 60°C from the formulation, a pore has been formed on the surface shown in the SEM image. The pores present on the surface of the SLT allow the aqueous solution to get inside the tablet easily and helps to disintegrate the tablet within a fraction of a second. Mostly sublingual tablets kept under the tongue, with the contact of saliva tablet break instantly and produce a better pharmacological effect. Phosphate buffer pH 6.8, similar to saliva pH taken as a buffering agent to find out the % of drug release from different formulations of nifedipine loaded SLTs. Formulation F1 and F2 contain superdisintegrants such as CS and SSG individually in respective formulations. Formulation F1 shows complete release at 12 min, whereas 97% drug release was observed in formulation F2. F3, F4 and F5 contain different compositions between the two super disintegrants and found complete release in 10 min, 11 min and 9 min, respectively. Formulation F5 has shown complete release within less time as compared to other formulations. This formulation contains an equal ratio of super disintegrants, which perform better than individual super disintegrants. In formulation F6, which was formulated without any super disintegrants, it has shown 99% drug release in 14 min. The time taken for the complete release of the drug is higher as compare to all other formulations. So super disintegrants have played an important role in the formulation of sublingual tablets. Formulation F5 is considered as the best formulation among all other formulations due to the complete release of the drug in a shorter duration.
of time.

**Stability study**

Formulation F5 was selected for stability study and confirms that there are significant changes observed in colour, shape and morphology of the tablet. Negligible deviation in results for drug content %, disintegration time and *in-vitro* drug release % is shown in Table 4.

Stability study confirms that Nifedipine loaded SLTs are stable.

**CONCLUSIONS**

Nifedipine has shown low solubility and its fast pass metabolism is also limited. To improve the pharmacokinetic property and pharmacological effect, a novel drug delivery system should be incorporated. Nifedipine bioavailability can be improved by converting it into a Sublingual fast dissolving tablet. In this current study, we have introduced the direct compression technique and sublimation method combinedly to develop a better sublingual tablet that disintegrates the tablet within a few seconds and could be a life saviour. Due to the sublimation of camphor, pores have been developed in the tablet. This could easily disintegrate the tablets in the buccal cavity in the presence of saliva. Superdisintegrants played a vital role in the formulation of the sublingual tablet. In this study, CS and SSG have been taken in different ratios to enhance the disintegration and dissolution property of the sublingual tablet. Formulation F5, considered as the best formulation (100% drug release at 9 min), confirms that the presence of super disintegrants in equal ratio perform better than individual super disintegrants. Formulation F6 without any super disintegrants has taken more time for the complete release of the drug. FTIR and DSC study confirms the compatibility between drug-super disintegrants. Evaluation parameters for all formulations are optimum and within the limit of Indian pharmacopoeia.

**ACKNOWLEDGEMENT**

The authors thank the management of Sri Venkateswara College of pharmacy for their continuous support and encouragement. The authors also acknowledge the DST-FIST program (F.No.SR/FST/college-280/18.11.2015) to the department Sri Venkateswara College of Pharmacy for the providing of instrumentation facilities.

**Funding Support**

The authors declare that they have no funding support for this study.

**Conflict of Interest**

The authors declare that they have no conflict of interest for this study.

**REFERENCES**


