FORMULATION AND EVALUATION OF SUBLINGUAL TABLETS OF FELODIPINE FOR THE TREATMENT OF HYPERTENSION
Mohd Abdul Hadi

Assistant Professor, Department of Pharmaceutics, Nizam Institute of Pharmacy, Deshmukhi (V), Pochampally (M), Behind Mount Opera, Yadadri Bhuvanagiri (Dist)-508284, Telangana, India.

Abstract:
Sublingual administration of the drug means placement of the drug under the tongue and drug reaches directly into the bloodstream through the ventral surface of the tongue and floor of the mouth. The concept of formulating sublingual tablets of Felodipine (antihypertensive drug) offer suitable and practical approach in serving the desired objective of faster disintegration and dissolution characteristic with increase bioavailability and to know the effects of two synthetic superdisintegrants (crospovidone and sodium starch glycollate). In the present work comparison between crospovidone and sodium starch glycollate was done by taking different ratios. Prepared tablets were subjected to different evaluation parameters such as hardness, thickness, friability, weight variation, and drug content uniformity, in vitro disintegration time, wetting time, in vitro dissolution studies and stability studies are carried out by using best formulation. Thus, sublingual tablet of Felodipine could be an alternative route to avoid gastrointestinal side effect as well as bypass hepatic first pass metabolism. The formulated sublingual tablets may act as a potential alternate for the Felodipine oral tablet.

Keywords: Felodipine, Crospovidone, Sodium starch glycollate, Sublingual Tablet, Hypertension

Corresponding author:
Mohd Abdul Hadi
Assistant Professor,
Department of Pharmaceutics,
Nizam Institute of Pharmacy, Deshmukhi (V),
Pochampally (M), Behind Mount Opera,
Yadadri Bhuvanagiri (Dist)-508284, Telangana, India.
E-mail - hadisultan19@gmail.com
Contact No:- 8801191475

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INTRODUCTION:
Amongst the various routes of drug delivery, oral route is perhaps the most preferred to the patient and the clinician alike. However, peroral administration of drug has disadvantages such as hepatic first pass metabolism and enzymatic degradation within the GI tract that limits oral administration of certain classes of drug like peptides and proteins. So, other absorptive mucosa is considered as potential sites for drug administration. Trans-mucosal routes of drug delivery (i.e. the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity) offer several advantages over peroral administration for systemic delivery. These advantages include possible bypass of first pass effect, avoidance of pre-systemic elimination in GI tract and depending on drug suitable enzymatic flora for drug absorption [1-5].

Many patients, particularly children and the elderly population find it inconvenient to ingest conventional solid dosage forms such as tablets and capsules due to an impaired ability to swallow. This leads to patient noncompliance and potentially prolonged duration of treatment. This issue can be addressed through the development of sublingual dosage forms that disperse or dissolve in the saliva and are swallowed without water [6-8].

Drugs have been applied to the mucosa for topical application for many years. However, recently there has been interest in exploiting the oral cavity as a portal for delivering drugs to the systemic circulation. Notwithstanding the relatively poor permeability characteristics of the epithelium, a number are offered by this route of administration. Foremost among these are the avoidance of first pass metabolism, ease of access to the delivery site, and the opportunity of sustained drug delivery predominantly via the buccal tissues [9-15].

Oral mucosal drug delivery is an alternative method of systemic drug delivery that offers several advantages over both injectable and enteral methods. Because the oral mucosa is highly vascularised, drugs that are absorbed through the oral mucosa directly enter the systemic circulation, by passing the gastrointestinal tract and first-pass metabolism in the liver. For some drugs, this results in rapid onset of action via a more comfortable and convenient delivery route than the intravenous route. Not all drugs, however, can be administered through the oral mucosa because of the characteristics of the oral mucosa and the physicochemical properties of the drug [16-20].

The oral route of administration is considered as the most widely accepted route. The unique environment of the oral cavity offers its potential as a site for drug delivery. Because rich blood supply and direct access to systemic circulation, the oral mucosal route is suitable for drugs, which are susceptible to acid hydrolysis in the stomach or which are extensively metabolized in the liver. The continuous secretion of saliva results in rapid removal of released drug and this may desire that the oral cavity be restricted to the delivery of drugs, which have a short systemic circulation [21-25].

The mucin film, which exists on the surface of the oral mucosa, may provide an opportunity to retain a drug delivery system in contact with the mucosa for prolonged periods if it is designed to be mucoadhesive. Such system ensures a close contact with absorbing membrane, thus optimizing the drug concentration gradient across the biological membrane and reducing the differential pathway. The oral mucosa may be potential site for controlled or sustained drug delivery. Oral route is most preferred route by medical practitioners and manufacturer due to highest acceptability of patients. About 60% of all dosage forms available are the oral solid dosage form [26-30].

The lower bioavailability, long onset time and dysphasia patients turned the manufacturer to the parenterals and liquid orals. But the liquid orals (syrup, suspension, emulsion etc) have the problem of accurate dosing mainly and parenterals are painful drug delivery, so most patient incompliance2. The target sites for local drug delivery in the oral cavity include the following: Buccal, Sublingual, Periodontal region, Tongue, Gum. Other desirable targeting sites adjacent to oral cavity include pharynx, larynx, adenoids and tonsils [31-38].

Within the oral cavity, delivery of drugs via the membranes of the oral cavity is classified into three categories:

i) Sublingual delivery which is systemic delivery of drugs through the mucosal membranes the floor of the mouth to the systemic circulation;

ii) Buccal delivery which is drug administration through the mucosal membranes lining the cheeks and the area between the gums and upper and lower lips to the systemic circulation.

iii) Local delivery which is drug delivery to periodontal, gingival, delivery for the local treatment of ulcers, bacterial and fungal infections and periodontal disease.
AIM AND OBJECTIVE:
1) Formulation development and Evaluation of sublingual tablets of felodipine and optimize the formula.
2) To see the effect of super disintegrant concentration on the disintegration and drug release profile.

MATERIALS:
The following excipients were procured from different sources and utilized in the formulation development.

<table>
<thead>
<tr>
<th>No.</th>
<th>Excipient</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Crospovidone</td>
</tr>
<tr>
<td>2</td>
<td>SSG</td>
</tr>
<tr>
<td>3</td>
<td>Sodium saccharine</td>
</tr>
<tr>
<td>4</td>
<td>Mannitol</td>
</tr>
<tr>
<td>5</td>
<td>Micro crystalline cellulose</td>
</tr>
<tr>
<td>6</td>
<td>Talc</td>
</tr>
<tr>
<td>7</td>
<td>Magnesium stearate</td>
</tr>
</tbody>
</table>

Table1. List of excipients used in the formulation development.

DRUG PROFILE:
Felodipine
Felodipine is a long-acting 1,4-dihydropyridine calcium channel blocker (CCB). It acts primarily on vascular smooth muscle cells by stabilizing voltage-gated L-type calcium channels in their inactive conformation. By inhibiting the influx of calcium in smooth muscle cells, felodipine prevents calcium-dependent myocyte contraction and vasoconstriction. Felodipine is the most potent CCB in use and is unique in that it exhibits fluorescent activity.

In addition to binding to L-type calcium channels, felodipine binds to a number of calcium-binding proteins, exhibits competitive antagonism of the mineralocorticoid receptor, inhibits the activity of calmodulin-dependent cyclic nucleotide phosphodiesterase, and blocks calcium influx through voltage-gated T-type calcium channels. Felodipine is used to treat mild to moderate essential hypertension.

Chemical Structure

![Chemical Structure](image)

Chemical formula: C_{18}H_{19}Cl_{2}NO_{4}
IUPAC Name: 3-ethyl 5-methyl 4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate.
Melting point: 145 °C
Water solubility: 19.7 mg/L
LogP: 3.86

Mechanism of action: Felodipine decreases arterial smooth muscle contractility and subsequent vasoconstriction by inhibiting the influx of calcium ions through voltage-gated L-type calcium channels. It reversibly competes against nitrendipine and other DHP CCBs for DHP binding sites in vascular smooth muscle and cultured rabbit atrial cells. Calcium ions entering the cell through these channels bind to calmodulin.

Calcium-bound calmodulin then binds to and activates myosin light chain kinase (MLCK). Activated MLCK catalyzes the phosphorylation of the regulatory light chain subunit of myosin, a key step in muscle contraction. Signal amplification is achieved by calcium-induced calcium release from the sarcoplasmic reticulum through ryanodine receptors. Inhibition of the initial influx of calcium decreases the contractile activity of arterial smooth muscle cells and results in vasodilation. The vasodilatory effects of felodipine result in an overall decrease in blood pressure. Felodipine may be used to treat mild to moderate essential hypertension.

Absorption: Is completely absorbed from the gastrointestinal tract; however, extensive first-pass metabolism through the portal circulation results in a low systemic availability of 15%. Bioavailability is unaffected by food.
Volume of distribution: 10 L/kg
Protein binding: 99%, primarily to the albumin fraction.

Metabolism: Hepatic metabolism primarily via cytochrome P450 3A4. Six metabolites with no appreciable vasodilatory effects have been identified.
Route of elimination: Although higher concentrations of the metabolites are present in the plasma due to decreased urinary excretion, these are inactive.
Animal studies have demonstrated that felodipine crosses the blood-brain barrier and the placenta.
Half life: 17.5-31.5 hours in hypertensive patients; 19.1-35.9 hours in elderly hypertensive patients; 8.5-19.7 in healthy volunteers.
Clearance: 0.8 L/min [Young healthy subjects]
METHODS
The methods used for preparation and evaluation of sublingual tablets of felodipine were described in this chapter.

PREPARATION OF SUBLINGUAL TABLETS
Felodipine sublingual tablets were prepared by the direct compression method using different excipients. The excipients used were Micro crystalline cellulose (binding agent), Mannitol (diluents), saccharine sodium (sweetening agent), crospovidone (super disintegrant). Different concentration of excipients was used to prepare different group of sublingual tablets. Compositions of various formulations are shown in Table 02.

Table 2: Formulation Composition of Sublingual Tablets of felodipine

<table>
<thead>
<tr>
<th>Ingredients (mg)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Felodipine</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>4</td>
<td>8</td>
<td>0</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>Sodium saccharine</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Mannitol</td>
<td>85</td>
<td>85</td>
<td>85</td>
<td>85</td>
<td>85</td>
</tr>
<tr>
<td>Micro crystalline cellulose</td>
<td>90</td>
<td>86</td>
<td>86</td>
<td>82</td>
<td>78</td>
</tr>
<tr>
<td>Talc</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
</tbody>
</table>

Preparation of calibration curve of felodipine in phosphate buffer solution (pH 6.8)
25mg of Felodipine was accurately weighed and dissolved in 25ml of phosphate buffer into a volumetric flask (1000 mcg/ml) respectively. 1 ml of this solution was taken and made up to 100 ml with phosphate buffer solution, which gives 10 mcg/ml concentrations (stock solution). From this stock solution, concentration of 10, 20, 30, 40,50mcg/ml in phosphate buffer solution were prepared. The absorbance of the diluted solution was measured at 364 nm in UV spectrophotometer and a standard plot was drawn using the data obtained.

PRE-COMPRESSIONAL EVALUATION OF TABLETS
The powder blends of tablets from different formulation (F1 to F5) were subjected to pre-formulations studies (Bulk density, Tapped density, Hausner’s ratio, Angle of Repose and Percent compressibility etc.).

POST-COMPRESSIONAL EVALUATION OF TABLETS
HARDNESS:
The test was done as per the standard methods. The hardness of three randomly selected tablets from each formulation (F1 to F5) was determined by placing each tablet diagonally between the two plungers of tablet hardness tester (with the nozzle) and applying pressure until the tablet broke down into two parts completely and the reading on the scale was noted down in Kg/cm².

THICKNESS:
The thickness of three randomly selected tablets from each formulation was determined in mm using a digital vernier caliper. The average values were calculated.

UNIFORMITY OF WEIGHT:
Weight variation test was done as per standard procedure. Twenty tablets from each formulation (F1 to F5) were weighed using an electronic balance and the average weight was calculated. The average weight of one tablet is determined from the collective weight and find out % variation as per table 3.

Table 3: Weight variation of tablets

<table>
<thead>
<tr>
<th>Average weight of Tablets(mg)</th>
<th>Maximum % different allowed</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 or less</td>
<td>10</td>
</tr>
<tr>
<td>80 - 250</td>
<td>7.5</td>
</tr>
<tr>
<td>More than 250</td>
<td>5</td>
</tr>
</tbody>
</table>

FRIABILITY:
The friability of tablets was measured using a Roche Fribaiator. Tablets were rotated at 25 rpm for 4 minutes or up to 100 revolutions. The tablets were taken out, dedusted and reweighted. The percentage friability was calculated from the loss in weight as given in equation below. The weight loss should not more than 1%. The results are shown in Table 4.

\[
\%\text{Friability} = \frac{\text{(initial weight- final weight)}}{\text{(Initial weight)}} \times 100
\]

DRUG CONTENT
Ten tablets from each batch were finely powdered and the powder equivalent to 5mg of felodipine was weighed and dissolved in suitable quantity of methanol. The solution was filtered, suitably diluted and the drug content was analyzed spectrophotometrically at 364nm.

WETTING TIME:
The tablet was placed at the centre of two layers of absorbent paper fitted into a dish. After the paper was
thoroughly wetted with saline phosphate buffer (pH-6.8), excess water was completely drained out of the dish. The time required for the water to diffuse from the wetted absorbent paper throughout the entire tablet was then recorded using a stopwatch.

**WATER ABSORPTION RATIO:**
A piece of tissue paper folded twice was placed in a small petridish containing 6 ml of saline phosphate buffer (pH-6.8). A tablet was put on the tissue paper and allowed to completely wet. The wetted tablet was then weighted. Water absorption ratio, R was determined using following equation.

\[ R = \frac{(Wa - Wb)}{Wa} \times 100 \]

Where, \( Wa \) = Weight of tablet after water absorption
\( Wb \) = Weight of tablet before water absorption

**IN-VITRO DISINTEGRATION TIME:**
Disintegration times for sublingual tablets were determined using USP tablet disintegration apparatus with saline phosphate buffer of pH 6.8 as medium. Maintain the medium temp at 37± 2°C. The time in minute taken for complete disintegration of the tablets with no palatable mass remaining in the apparatus was measured.

**IN-VITRO DRUG RELEASE STUDY:**
In-vitro release rate of felodipine sublingual tablets was carried out using United State Pharmacopoeia (USP) dissolution testing apparatus (Paddle method). The dissolution test was carried out using 300 ml of 6.8 pH saline phosphate buffer, at 37 ± 2°C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at 2, 4, 6, 8, 10, 15 and 30min. The samples were replaced with fresh dissolution medium of same quantity. The samples were filtered through Whatman filter paper No 40 and analyzed by UV spectrophotometer at 364nm. The percentage drug release was calculated using an equation obtained from the calibration curve.

Standard graph of felodipine in pH 6.8 Phosphate buffer (\( \lambda_{max} 364 \) nm).

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Concentration (mcg/ ml)</th>
<th>Absorbance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>00</td>
<td>0.000</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>0.214</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>0.428</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>0.626</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td>0.814</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>0.998</td>
</tr>
</tbody>
</table>

**Table 4: Standard graph of felodipine in pH 6.8 Phosphate buffer**

![Graph of felodipine absorption](image1)

![Graph of felodipine concentration](image2)

**Fig.2: Standard graph of Felodipine in pH 6.8 Phosphate Buffer (\( \lambda_{max} 364 \) nm)**
Pre-compressional evaluation of tablets

Table 5: Pre-compression parameters of formulations prepared by direct compression Method

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Formulation code</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>Angle of repose</td>
<td>29.41</td>
</tr>
<tr>
<td>Bulk density (gm/cc)</td>
<td>0.458</td>
</tr>
<tr>
<td>Tapped density (gm/cc)</td>
<td>0.529</td>
</tr>
<tr>
<td>Carr's Index (%)</td>
<td>15.50</td>
</tr>
<tr>
<td>Hausner's ratio</td>
<td>1.180</td>
</tr>
</tbody>
</table>

The lubricated powder blend for all the formulations containing various concentrations of super disintegrant (crospovidone) except one formulation containing sodium starch glycollate as super disintegrant and direct compressible material such as microcrystalline cellulose were used. The lubricated blend for direct compression was evaluated for pre-compression parameters like angle of repose, B.D, T.D, Carr's Index (%) and Hausner's ratio. All these values were indicated that the "good flow" behavior of the lubricated blend.

Post-compressional evaluation of tablets

Table 6: Post compression parameters of formulations prepared by direct compression method

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Formulation code</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>Hardness (kg/cm²)± SD</td>
<td>3.53±0.09</td>
</tr>
<tr>
<td>Thickness (mm)</td>
<td>3.10</td>
</tr>
<tr>
<td>Friability (%)</td>
<td>0.529</td>
</tr>
<tr>
<td>Disintegration time (sec), avg</td>
<td>15.20</td>
</tr>
<tr>
<td>Wetting time (sec), avg</td>
<td>14.42</td>
</tr>
<tr>
<td>Water absorption ratio (%), avg</td>
<td>55.25</td>
</tr>
<tr>
<td>Drug content (%) ±SD</td>
<td>101.19±0.27</td>
</tr>
<tr>
<td>Weight variation</td>
<td>190-210 mg</td>
</tr>
</tbody>
</table>

The felodipine sublingual tablets were prepared by direct compression method using single punch tablet punching machine. The tablets were evaluated for weight variation, hardness, thickness, friability, drug content, water absorption ratio, wetting time, In-vitro disintegration time and In-vitro dissolution rate. It was observed that all the tablets from each formulation passed the test for weight variation, as the percentage of weight variation was within the pharmacopoeia limits. The weight variation in all formulations (F1 to F5) was found to be in the range of 190 mg to 210 mg, which was within the acceptable limits. The prepared tablets in all formulations possessed good mechanical strength with sufficient hardness in the range of 3.20 to 4.05 kg/sq.cm with an ability to withstand physical and mechanical stress conditions while handling. The tablet mean thickness was almost uniform in all formulations. The thickness varies between 3.1-3.31 mm. The friability varies between 0.423 to 0.529%. In all the formulations, friability value was found to be less than 1.00%.
than 1%. The friability values between 0-1% were an indication of good mechanical resistance of tablets. The drug content in all formulations (F1toF5) was highly uniform and in the range of 102 to 98 % of the expected Felodipine content, which was within the acceptable limits. The wetting time was found to be in the range of 9 sec to 15 sec. The water absorption ratio in all formulations (F1toF5) was found to be in the range of 55-76 %. It was observed that wetting time and water absorption ratio increased as the concentration of crospovidone increased. The disintegration time in all formulations were observed within few seconds. The disintegration time in all formulations (F1toF5) was found to be in the range 6-16 sec. The disintegration time was decreased with increase in the concentration of crospovidone. The in-vitro dissolution studies of all formulations (F1to F5) were conducted in phosphate buffer of pH 6.8 and the results are shown in Table 7 and Figure 6.

In-vitro dissolution study:

**Table 7: In-vitro dissolution data of Felodipine sublingual tablets in pH 6.8 phosphate buffer (mean±SD)**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Cumulative Percent Drug Released</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>2</td>
<td>42.49±0.62</td>
</tr>
<tr>
<td>4</td>
<td>60.98±0.78</td>
</tr>
<tr>
<td>6</td>
<td>71.29±0.98</td>
</tr>
<tr>
<td>8</td>
<td>78.12±0.79</td>
</tr>
<tr>
<td>10</td>
<td>83.62±0.21</td>
</tr>
<tr>
<td>15</td>
<td>87.21±0.74</td>
</tr>
<tr>
<td>30</td>
<td>91.22±1.09</td>
</tr>
</tbody>
</table>

**Fig. 3: Dissolution Profile of Cumulative % Drug Release.**
From the above data it is evident that among the promising formulations, more than 40% of the drug released within 2 min and more than 80% of the drug in the 10 min. The formulation F5 showed the 99.29% of drug release in 10 min. It was observed that the rate of release of the drug from the formulation is proportional to the concentration of crospovidone. It was also observed that the drug release was faster from F2 than F3.

CONCLUSION:
1) Different formulations coded as F1, F2, F3, F4 and F5 were prepared using increasing concentrations of crospovidone as super disintegrant except the formulation F3 in which sodium starch glycollate was used as super disintegrant.
2) The lubricated blend for direct compression was evaluated for pre-compression parameters like angle of repose, B.D, T.D, Carr's Index (%) and Hausner's ratio. All these values were indicated that the “good flow” behavior of the lubricated blend.
3) All the sublingual tablets of felodipine were subjected to weight variation, drug content-uniformity, hardness, friability, water absorption ratio, wetting time, in vitro disintegration time and in vitro dissolution. Based on the above studies, following conclusions can be drawn:
4) Tablets prepared by direct compression technique were found to be good without any chipping, capping and sticking.
5) The hardness of the prepared tablets was found to be good.
6) The friability values of the prepared batches of tablets were found to be less than 1%.
7) The low values of standard deviation for average weight and drug content of the prepared tablets indicate weight and drug content uniformity within the batches prepared.
8) The in vitro disintegration time of felodipine tablets found to be in the range of 6-16 s.
9) Based on the in vitro disintegration time, wetting time, water absorption ratio and in vitro dissolution test, the formulation coded as F5, in which 16mg of crospovidone was added as super disintegrant was found to be the best formulation for development of sublingual tablets of felodipine.

REFERENCES:
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