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# NIFEDIPINE SUBLINGUAL TABLETS: FABRICATION USING SUPER DISINTEGRANTS AND THEIR EVALUATION

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## ABSTRACT

The aim of present research was to develop sublingual tablets of nifedipine (a calcium channel blocker used as an antianginal and antihypertensive drug) by complexing with β-cyclodextrin and drug-carrier solid dispersion to improve its solubility and bioavailability. Sublingual route is most widely used method to improve the bioavailability, by enhancing drug to completely disintegrate. Thus it delivers the drug particles from the dosage form directly into the systemic circulation by avoiding the first pass metabolism. Sublingual tablets of nifedipine (23 batches) using polymers like CP, SSG, CCS at different concentration and combination were prepared by direct compression and wet granulation techniques. To improve the solubility, drug was complexed with β-cyclodextrin and drug -solid dispersion using PVP-K30/PEG4000.The results of pre-compression parameters were in acceptable range as per specifications given in the IP. Prepared tablets were evaluated for thickness, uniformity of weight, hardness, friability and the results are within the IP limits. Out of 23 formulations tablets contained 5% of CP and 3% of SSG(NF9) showed low wetting time 17sec, low *in vitro* disintegration time 15sec, high water absorption ratio 37.94% and high drug release profile 92.7%. Further complexation of NF9 at 1:4 drug: β-cyclodextrin ratio had shown improved wetting, *in vitro* disintegration and water absorption which enhances the *in vitro* release (NF 19). The stability studies were done for optimized batch F9 and F19 by storing at $40^0C \pm 2^0C$ / 75% ±5% RH up to 90 days. After 90days there was no significant changes in the tablets was observed.

**KEYWORDS:** Nifedipine, Superdisintegrant, β-cyclodextrin, PVP-K 30, PEG-4000, Sublingual tablets.

## INTRODUCTION

Hypertension and angina are the major risk factors in the development of cardiovascular diseases (CVD). Reduced functional ability and extreme restlessness were seen in patients with high blood pressure and angina attack, hence rapid onset of action is required.[4,10]

Sublingual administration provides a rapid onset of action which bypasses the hepatic first pass metabolism and drug is directly absorbed into the systemic circulation by simple diffusion. For these formulations, the small volume of saliva is usually sufficient to result in tablet disintegration in the oral cavity. The sublingual route is suitable for the drugs which are inactivated by the first pass-intestinal or hepatic metabolism.[4,10]

Nifedipine a calcium channel blocker used as an antianginal and antihypertensive agent. Nifedipine is rapidly and almost completely absorbed from the gastrointestinal tract, but under goes extensive hepatic first pass metabolism. Nifedipine has low aqueous solubility and it is classified BCS class II drug.[1-3] Nifedipine acts by blocking the transport of calcium into the smooth muscle cells which lines coronary arteries and other arteries of body. By blocking the calcium transport artery muscle relaxes and dilates arteries of the body including coronary arteries. By this relaxation, nifedipine helps in treating and preventing chest pain (angina) resulting from coronary artery spasm. Relaxation of muscles lining arteries of rest of the body lowers blood pressure, which reduces the burden on heart as it pumps blood to the body. Reducing heart burden lessens the heart muscle's demand for oxygen and further helps to prevent angina in patients with coronary artery disease.

Nifedipine is extensively metabolized in liver by cytochrome P450 (CYP) and about 60-80% of the dose (inactive metabolites) is excreted mainly in urine and remaining is excreted in the feces. Total plasma clearance is 308ml/min and the elimination half-life is about 2-2.5hrs.[7-8]

Since nifedipine is poorly soluble super disintegrants are added. These are the agents added to tablet formulations to promote its breakup into smaller fragments in an aqueous environment there by increasing the available surface area for promoting a more rapid release of drug

substance. The choice of a suitable type and an optimal amount of disintegrant is paramount for ensuring a high disintegration rate. There are three mechanisms by which superdisintegrants works they are Swelling, porosity and capillary action (wicking), and deformation.[9-10] Thus the aim of research was to develop nifedipine sublingual tablets using three different superdisintegrants.

## MATERIALS AND METHODS

### Materials

Nifedipine was gifted by alembic Pharma Ltd (Vadora, India), and other materials were purchased as follows: crospovidone from sigma-aldrich corporation (Bengaluru), croscarmellose sodium from Micro Labs (Bengaluru,India), sodium starch glycolate, β-cyclodextrin, PEG-4000 and PVP-K30 were procured from Sisco research laboratories (Mumbai,India), micro crystalline cellulose from S.D.Fine chemical Ltd (Mumbai, India), Lactose from qualigens fine chemicals (Mumbai, India), Mannitol from Roquette Pharma (Bengaluru,India), starch, sodium saccharine, citric acid, talc, magnesium stearate, sodium hydroxide pellets from S.D.Fine chemical Ltd(Mumbai,India), potassium dihydrogen ortho phosphate from Sisco research laboratories (Mumbai,India), potassium bromide (IR grade) from Merck (Mumbai,India).

### Method

#### Determination of λmax

Nifedipine was dissolved in a small quantity of methanol and further diluted with distilled water to 100 ml. The drug solution was scanned for maximum absorbance in UV-visible double beam spectrophotometer (Shimadzu 1800) in the range from 200 to 400 nm. The λ max was found to be 238nm.

#### Preparation of standard curve of nifedipine in phosphate buffer pH 6.8

10 mg of the drug was weighed and dissolved in 10 ml of phosphate buffer solution to make stock solution S1 (1mg/ml). 1ml solution was withdrawn from S1 and volume was made up to 50ml (20mcg/ml) with phosphate buffer solution. From this secondary stock solution, aliquots of 1ml to 5ml were transferred into a series of 10ml volumetric flasks and final volume was made up with buffer to give concentration in range of 2-10mcg/ml. The absorbance of these solutions was measured against a phosphate buffer pH 6.8 as blank in UV/visible spectrophotometer at 238nm. Average of three determinations was taken.

### Compatibility studies

#### Fourier transfer infrared spectroscopy

FTIR spectra were performed on drug physical mixture and other excipients by KBr pellet method. It was compared with nifedipine. The spectrum was scanned over a frequency range 4000-1000 $cm^{-1}$ with a resolution of 4 $cm^{-1}$

### Preparation of sublingual tablets of nifedipine by direct compression technique

#### Method

Sublingual tablets were prepared by direct compression technique using 3 different superdisintegrants (CP, CCS,SSG) at 2 different concentration (5% & 8%) i.e. NF1 to NF6(Table 1).

In order to evaluate the effect of combination of superdisintegrants 6 formulations (NF7 to NF12) were developed using 2 different superdisintegrants at 5% & 3%.

Tablets containing 5% CP & 3% SSG prepared by direct compression (i.e., NF9) was selected to evaluate the effect of processing method & mode of addition of Superdisintegrants (NF13 to NF15- table 2).

As a method to improve solubility of the drug, complexation using β-CD or solid dispersion using carriers such as PVP K30 or PEG 4000 were employed (table 3).

**Preparation of complex**: Drug was dissolved in methanol & stirred intensively, β-CD (1:1, 1:2, 1:3 & 1:4 ratio) was added & thick slurry was kneaded for 45min & dried at $40^0$C. Dried mass was pulverized & sieved through a (# 100) mesh. (NF 16 to NF 19).

**Preparation of solid dispersion:** Nifedipine was dissolved in methanol & stirred intensively, polymers like PVP-k30 (1:1, 1:3 ratio) / PEG- 4000 (1:1, 1:3 ratio) was added. Later solvent was rapidly evaporated at $50^0$C. Dried mass was pulverized & sieved through a (# 100) mesh. (NF 20 to NF 23).

**Table 1: Effect of concentration of superdisintegrants(direct compression method).**

| Ingredients | NF1 CP 5% w/w | NF2 CP 8% w/w | NF3 CCS 5% w/w | NF4 CCS 8% w/w | NF5 SSG 5% w/w | NF6 SSG 8% w/w |
|---|---|---|---|---|---|---|
| **Weight in mg** | | | | | | |
| **Nifedipine** | 10 | 10 | 10 | 10 | 10 | 10 |
| **Micro crystalline cellulose** | 64 | 52 | 64 | 52 | 64 | 52 |
| **Mannitol** | 57 | 45 | 57 | 45 | 57 | 45 |
| **Lactose** | 47 | 65 | 47 | 65 | 47 | 65 |
| **Magnesium stearate** | 5 | 5 | 5 | 5 | 5 | 5 |
| **Talc** | 3 | 3 | 3 | 3 | 3 | 3 |
| **Citric acid** | 1 | 1 | 1 | 1 | 1 | 1 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Sodium saccharin** | 3 | 3 | 3 | 3 | 3 | 3 |
| **Crospovidone** | 10 | 16 | - | - | - | - |
| **Croscarmellose** | - | - | 10 | 16 | - | - |
| **Sodium starch glycolate** | - | - | - | - | 10 | 16 |
| **Total weight** | **200mg** | **200mg** | **200mg** | **200mg** | **200mg** | **200mg** |

**Table 2: Effect of combination (direct compression), processing method and mode of addition of super disintegrants.**

| **Ingredients** | **NF7 CP 3% & CCS 5% w/w** | **NF8 CCS 3% & SSG 5% w/w** | **NF9 CP 5% & SSG 3% w/w** | **NF10 CCS 5% & SSG 3% w/w** | **NF11 CP 3% & SSG 5% w/w** | **NF12 CP 5% & CCS 3% w/w** | **NF13 (IG)** | **NF14 (EG)** | **NF15 (50% IG & 50% EG)** |
|---|---|---|---|---|---|---|---|---|---|
| **Weight in mg** | | | | | | | | | |
| **Nifedipine** | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **Microcrystalline Cellulose** | 62 | 52 | 62 | 52 | 62 | 52 | 62 | 62 | 62 |
| **Mannitol** | 55 | 45 | 55 | 45 | 55 | 45 | 55 | 55 | 55 |
| **Lactose** | 45 | 65 | 45 | 65 | 45 | 65 | 45 | 45 | 45 |
| **Magnesium Stearate** | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| **Talc** | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| **Citric acid** | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **Sodium Saccharine** | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| **Crospovidone** | 6 | - | 10 | - | 6 | 10 | 10 | 10 | 10 |
| **Croscarmellose sodium** | 10 | 6 | - | 10 | - | 6 | - | - | - |
| **Sodium starch glycolate** | - | 10 | 6 | 6 | 10 | - | 6 | 6 | 6 |
| **Total weight** | **200mg** | **200mg** | **200mg** | **200mg** | **200mg** | **200mg** | **200mg** | **200mg** | **200mg** |

**Table 3: Improvement of solubility and bioavailability of nifedipine by encapsulating the drug in β-CD and by preparing drug solid dispersion using carriers PVP-K 30, PEG-4000.**

| **Ingredients** | **NF 16 1: 1 (D:β-cd) w/w** | **NF 17 1: 2 (D:β-cd) w/w** | **NF 18 1: 3 (D:β-cd) w/w** | **NF 19 1: 4 (D:β-cd) w/w** | **NF 20 1: 1 (D: PVPK30) w/w** | **NF 21 1: 3 (D: PVPK30) w/w** | **NF 22 1: 1 (D: PEG 4000) w/w** | **NF 23 1: 3 (D: PEG 4000) w/w** |
|---|---|---|---|---|---|---|---|---|
| **Weight In mg** | | | | | | | | |
| **Drug** | 10 | 10 | 10 | 10 | - | - | - | - |
| **β-cyclodextrin** | 33 | 66 | 99 | 132 | - | - | - | - |
| **Drug + Carrier** | - | - | - | - | 20 | 40 | 20 | 40 |
| **Microcrystalline Cellulose** | 51 | 40 | 29 | 12 | 58 | 50 | 58 | 50 |
| **Mannitol** | 44 | 33 | 22 | 9 | 52 | 46 | 52 | 46 |
| **Lactose** | 34 | 23 | 12 | 9 | 42 | 36 | 42 | 36 |
| **Magnesium Stearate** | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| **Talc** | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| **Citric acid** | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **Sodium Saccharine** | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| **Crospovidone** | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **Sodium starch glycolate** | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| **Total weight** | **200mg** | **200mg** | **200mg** | **200mg** | **200mg** | **200mg** | **200mg** | **200mg** |

**Tablets were evaluated for pre compression and post compression parameters as per the standards Pre compression evaluation**

The powder blend was evaluated for

1. Bulk density
2. Tapped density
3. Compressibility Index(Carr's index)
4. Hausner's ratio
5. Angle of repose

**Post compression evaluation**

The prepared tablets were evaluated for

1. Thickness
2. Hardness
3. Friability

4. Weight variation
5. Wetting time
6. Water absorption ratio
7. *In-vitro* disintegration time
8. Drug content
9. *In-vitro* dissolution studies

**Accelerated stability studies**

The optimized formulations were packed suitably and kept in stability chamber under following conditions 40 ± $1^0$C and RH 75% ± 5% for a period as prescribed by ICH guidelines. The samples were analyzed at 30, 60 and 90 days intervals for different physiochemical and *in vitro* drug release profile.

## RESULTS

**Standard curve for Nifedipine in phosphate buffer pH 6.8**

**Table 4: Standard curve of Nifedipine in 6.8 Phosphate buffer.**

| Concentration (mcg/ml) | Absorbance |
|---|---|
| 0 | 0 |
| 2 | 0.116 |
| 4 | 0.225 |
| 6 | 0.346 |
| 8 | 0.439 |
| 10 | 0.538 |

**Standard curve of Nifedipine in phosphate buffer of pH 6.8.**

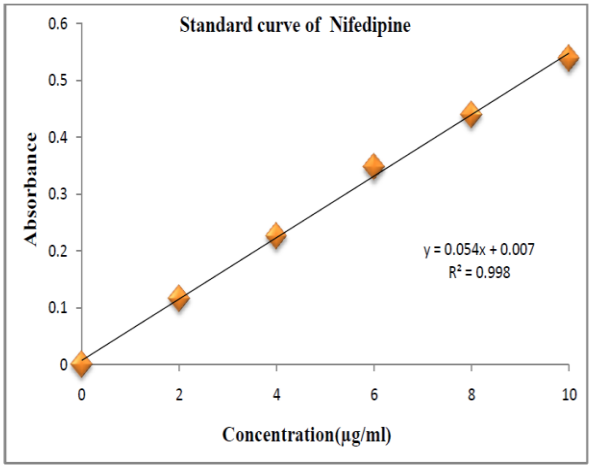



**Figure 1: calibration curve of nifedipine in 6.8 phosphate buffer**

**Compatibility studies**

Compatibility studies were carried out as per procedure mentioned in the methodology. Following spectra shows the results

Drug & excipient compatibility study for Nifedipine FTIR spectra of pure drug and formulation NF19. (Blue line – Nifedipine, Red line - Formulation NF19)

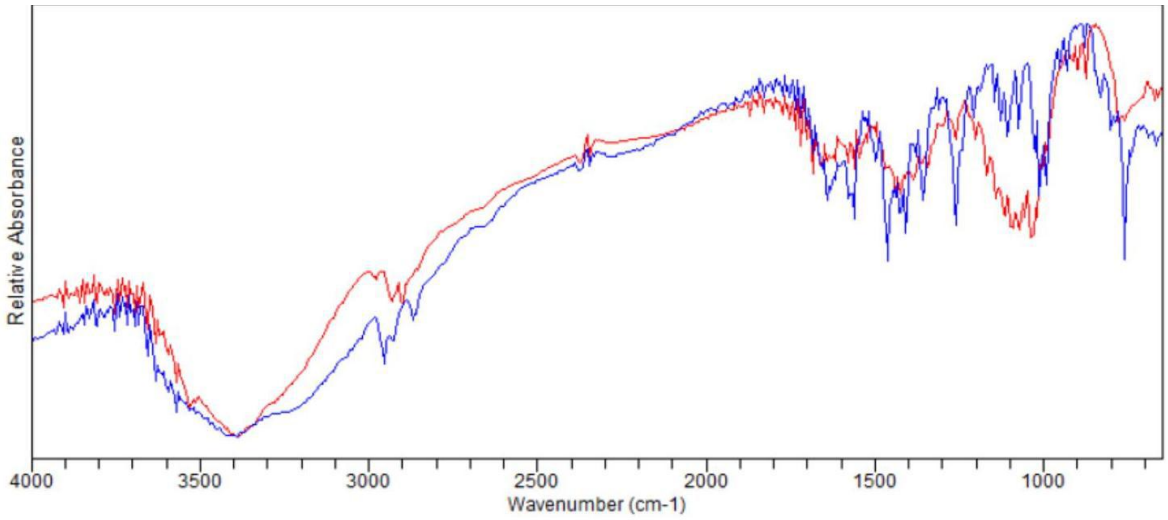



**Figure 2: FTIR spectra of pure drug and formulation NF19. (Blue line – Nifedipine, Red line - Formulation NF19).**

Drug excipient compatibility studies were performed using FTIR spectrophotometer. Characteristics peaks obtained for the pure drug was correlated well with that of the formulation peaks.

Granules of all the formulation were showed Carr's index and angle of repose within the range of 15.78% - 17.85 % and 18°.44'to 18°.48'respectively. Tablet hardness and friability of all formulations were in the range of 3.0±0.05 to 3.8±0.03 kg/cm$^2$ and 0.09% respectively. Average thickness was found to be 3.5±0.05 to 3.8 ±0.02mm.

Wetting time decreased with increase in concentration of superdisintegrant, however % water absorption increased with increase in concentration with CSS & CP except in SSG where % water absorption decreased with increase in concentration.

Tablets with CP disintegrated rapidly whereas SSG tablets took more time for disintegration (i.e., CP> CSS> SSG). Again with CP & CSS increase in concentration has resulted in faster tablet disintegration, with SSG disintegration time further increased with increase in concentration (further delayed).

Superdisintegrants when used in combination i.e., (CP with SSG) exhibited higher release than when they were used alone. NF9 formulation with high CP & low SSG (5% & 3% w/w) gave maximum release.

Tablets prepared by direct compression method gave rapid dissolution of contained drug (92.7%) with in 30min. In case of wet granulation method tablets gave relatively low dissolution (74.61%) within 30 mins.

Superdisintegrants when added extra granularly yielded higher cumulative drug release from the tablets than intra granular or 50% intra granular and 50% extra granular addition. Also in comparison to wet granulated tablets, directly compressed tablets showed faster wetting and disintegration with maximum water absorption.

Upon complexing with β-cyclodextrin dissolution rate has increased and almost 100% of drug was released from the tablet containing β-cyclodextrin at the ratio of 1:4 with respect to drug. Preparation of drug-solid dispersion using carriers like pvp k-30, peg 4000 has enhanced the drug release. Further, increase in their concentration has increased in drug release. PEG 4000 was more efficient than PVP K-30 in drug release.

**Table 5: Wetting time, water absorption ratio and disintegration time of formulations NF 9 and NF 19.**

| Sl. No. | Formulations | Wetting time (seconds) | Water absorption ratio (%) | Disintegration Time(seconds) |
|---|---|---|---|---|
| 1 | NF 9 | 17 | 42.94 | 15 |
| 2 | NF 19 | 13 | 44 | 18 |

**Table 6: In vitro release studies of formulations NF 9 and NF 19.**

| Sl. No. | Formulations | 5 min | 10 min | 15 min | 20 min | 25 min | 30 min |
|---|---|---|---|---|---|---|---|
| 1 | NF 9 | 38.34 | 46.08 | 61.2 | 72.72 | 86.22 | 92.7 |
| 2 | NF 19 | 47.41 | 68.32 | 89.89 | 97.28 | 99.34 | 99.89 |

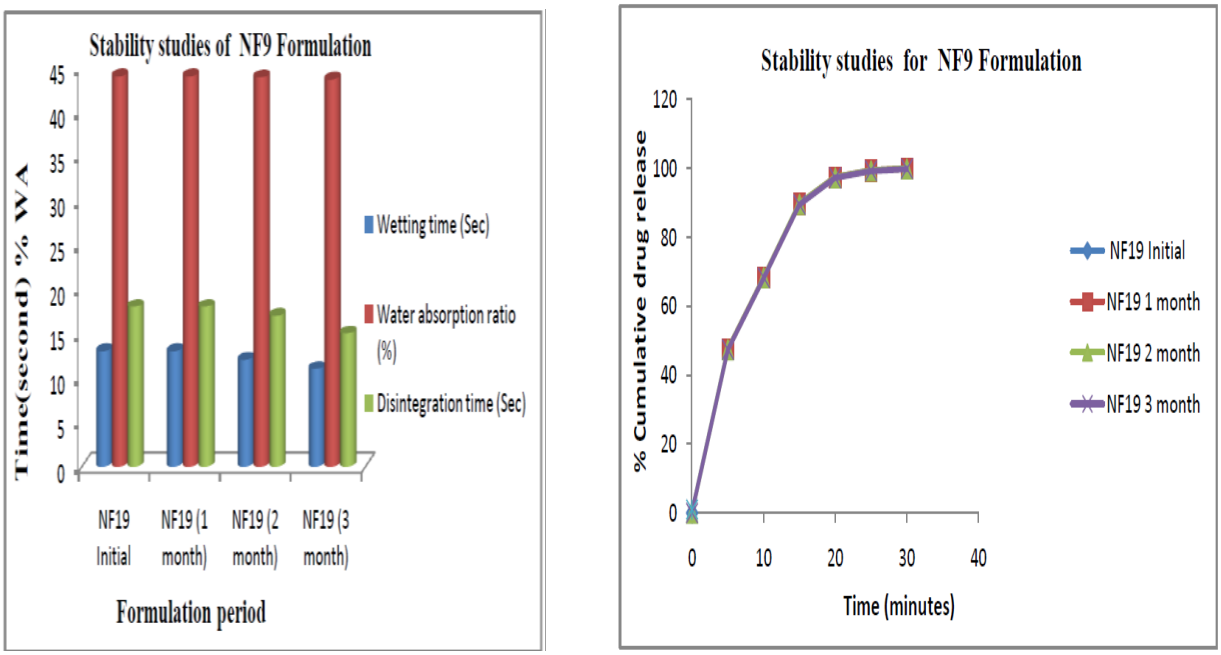
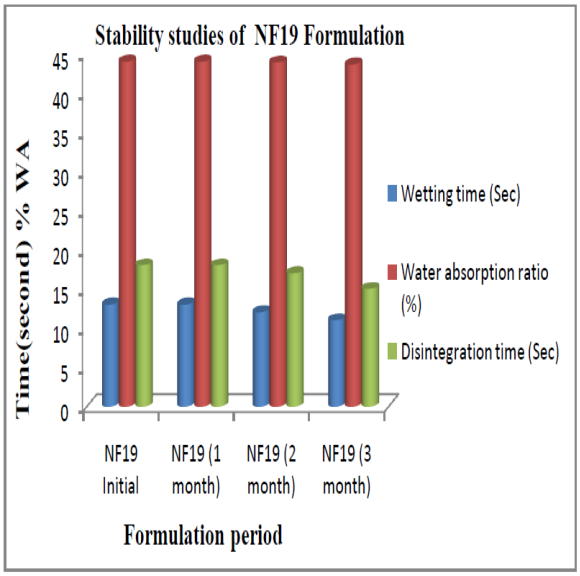



**Figure 3: Wetting time, Water absorption ratio and Disintegration time stability studies, *In vitro* release stability studies of Formulations NF9.**



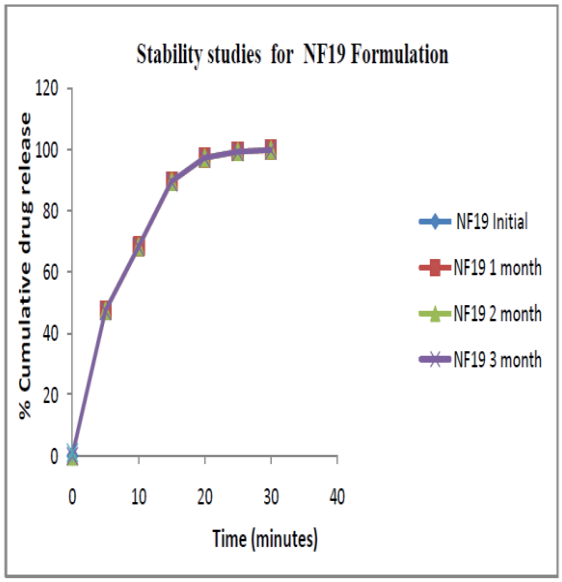




**Figure 4: Wetting time, Water absorption ratio and Disintegration time stability Studies, *In vitro* release stability studies of Formulations NF19.**

## DICUSSION

In the present work, study was made to enhance solubility of Nifedipine by preparing solid dispersion (PVP K-30, PEG 4000) and complexation with beta-cyclodextrin. Superdisintegrants (CP, CSS, SSG) were used to formulate sublingual tablets of Nifedipine by different techniques. The tablets were subjected to pre and post-compression evaluation in order to determine the effect of formulation ingredients and process variables on properties of tablets including *in vitro* release profile.

### Absorption maximum and calibration curve

Nifedipine was scanned in the UV wavelength region of 200-800 nm for maximum absorption (λmax) and the λmax was found to be at 237.18 nm that was almost same as reported value (238nm). Standard curve of the drug prepared in Phosphate Buffer pH 6.8(Table 4, figure 1) showed a linear relationship between concentration and absorbance values in the range of 2 – 10µg/ml. $R^2$ value was found to be 0.998.

### FTIR Spectroscopy studies

Drug excipient compatibility studies were performed using FTIR spectrophotometer. Characteristics peaks (figure 2) obtained for pure drug correlated well with that of formulation peaks. This indicated that drug was Compatible with formulation components.

### Evaluation of Pre-compression parameters[5-6]

Bulk density and tapped density of all prepared formulations was found in the range of 0.46 to 0.48gm/cc and 0.56 to 0.58 gm/cc respectively, which indicates that powder was loosely packed. Carr's index, Hausner's ratio and angle of repose were within the range of 15.78% - 17.85 %, 1.17 -1.21 and 18°.44'to 18°.48' respectively indicating good flowability of powder.

### Evaluation of Post-compression parameters[5-6]

### Weight variation, thickness

All the prepared Sublingual tablets of Nifedipine (200 mg) were evaluated for weight variation and found that all tablets were within permitted limit of ±7.5% as per IP whereas thickness was found to be within the range of 3.5±0.05 to 3.8 ±0.02mm. Thickness was almost uniform for all tablets.

### Hardness

Average hardness of all tablet formulations NF1 to NF23 was in the range of 3.0±0.05 to 3.8±0.03 kg/cm$^2$. Wet granulation process in which starch paste was used as binder yielded harder tablets than direct compression process. From the result, it is clear that increased concentration of CP & CCS has decreased tablet hardness, whereas tablet hardness increased with increase in concentration of SSG. Lesser the value of hardness, lesser will be tablets wetting time which ultimately affects dissolution that is prerequisite for Sublingual tablets.

### Friability

Calculated percent loss in weight checked by Roche Friabilator tester, it was in permitted range as given in IP (1%). Lower values of percent loss ensure that tablets were mechanically stable which determines of durability of tablets at the time of production.

NF9 (CP & SSG at 5 & 3% w/w) had lower value for friability (0.09%) & disintegrated quickly (15sec). Based on these results it was decided as optimized formulation for further evaluation.

### Wetting time

Average wetting time of all tablet formulations (NF1 to NF23) was in the range of 11 to 28 sec. It is clear from

the results that formulation containing SSG had shown more wetting time than CCS and CP. This concludes that wetting is associated to inner structure of the tablets and hydrophobicity of components. Higher the value of wetting time, greater the time for tablet to disintegrate.

**Water absorption ratio (WAR)**

The water absorption ratios for the tablets were computed using formula:

$$R = \frac{Wa - Wb}{Wb} \times 100$$

Results indicated that WAR varied between 31 to 46.22% for all formulations. Water content was observed maximum for NF2 formulation (CP at 8% w/w) 46.22% and minimum for NF6 formulation (SSG 8% w/w) 32.09%. It was noticed that water absorption ratio increased with increased concentration of superdisintegrant. Augmentation of water absorption ratio may lead to decreased wetting time as well as disintegration time, thus decreasing the absorption time of the drug from the formulation.

**In vitro disintegration time**

Average *in-vitro* disintegration time of all tablet formulations was in the range of 14 to 35 sec. Tablets prepared using 8% of CP showed rapid disintegration in 14 sec. From the result it was indicated that disintegration time of the tablets decrease with increase in the concentration of CCS and CP. Whereas disintegration time increased with increase in the concentration of SSG, reason may be due to blockage of capillary pores in tablet mass as result of formation of viscous plugs by SSG, which subsequently prevented free access of fluid into tablet.

**Drug content uniformity**

The percentage drug content of tablet formulations was found to be in the range of 91.16 % to 99.65 % indicating drug was present uniformly in the tablets.

**In vitro Dissolution Studies**

*In vitro* dissolution studies of prepared Sublingual tablets were performed in phosphate buffer pH 6.8. Cumulative % drug release was higher for CP, CCS than SSG. The dissolution was found to be increased with increasing concentration of superdisintegrant except in SSG, where increase in concentration has decreased drug release. Superdisintegrants when used in combination i.e., NF9 (CP 5% & SSG 3%) exhibited higher release 92.7% at the end of 30 min than when they were used alone. (table 5, 6 figure 3 & 4).

- Direct compression tablets exhibited faster wetting & disintegration with maximum absorption & drug release compared to wet granulation. Among wet granulation extra granulation addition was better than any other mode of addition of superdisintegrants.
- Drug β-CD complex prepared in 1:4 ratio (NF19) by Kneading method showed an improvement in dissolution compared to drug & superdisintegrant alone (NF9). This might be due to improved wettability & solubility of inclusion complexation.
- Poorly soluble drug nifedipine was dispersed in a highly soluble solid hydrophilic matrix (PVP K-30, PEG 4000) to enhance the dissolution of drug. An increased dissolution rate was observed which may be due to reduction in particle size to sub-micron level or solubilization effect by carrier or increased wettability and dispersibility of carriers or formation of meta stable dispersion with reduced lattice energy for faster dissolution.

**Stability studies**

Since formulations NF9 and NF19 showed best disintegration time and *In vitro* drug release they were selected as optimized formulations and further charged for stability. Tablets were stored at 40±2 °C/75±5%RH to assess their long term stability as per ICH guidelines Q1C. At the end of 30, 60 and 90 days, samples were evaluated for post compression parameters. Stability results showed that there were no prominent changes in the post compression parameters for both formulations NF9 and NF19.

## CONCLUSION

- Bioavailability of nifedipine can be improved by complexation with β-cyclodextrin or by preparing solid dispersion using PVP K-30 or PEG 4000. Sublingual tablets of Nifedipine were prepared by direct compression method using CP & SSG in combination at a concentration of 5 & 3% w/w respectively.
- Post-compression studies of the prepared tablets were subjected to different evaluation parameters such as hardness, friability, and weight variation, drug content uniformity, wetting time, water absorption ratio, *in vitro* dissolution studies and accelerated stability studies.
- The percent loss in weight checked by Roche Friabilator was in permitted range as given in IP (1%). The lower values of percent loss ensure that tablets were mechanically stable which determines the durability of tablets at the time of production.

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