www.ThePharmaJournal.com

The Pharma Innovation

ISSN: 2277- 7695
TPI 2015; 4(10): 76-82

www.thepharmajournal.com
Received: 10-10-2015
Accepted: 12-11-2015

**Prathusha P**
Browns College of Pharmacy
Ammapalem Konijerla (mdl),
Khammam-507305, India.

**Bhargavi L**
Browns College of Pharmacy
Ammapalem Konijerla (mdl),
Khammam-507305, India.

**Belsen David J**
Browns College of Pharmacy
Ammapalem Konijerla (mdl),
Khammam-507305, India.

**Yogesh Choudhary**
Grace Davision Chemical
India pvt ltd, Turkapally,
Hyderabad- 500078. India.

**Upendra Reddy K**
Grace Davision Chemical
India pvt ltd, Turkapally,
Hyderabad- 500078. India.

**Ajith Patil**
Grace Davision Chemical
India pvt ltd, Turkapally,
Hyderabad- 500078. India.

**Fred Monsuur**
Grace Davision Chemical
India pvt ltd, Turkapally,
Hyderabad- 500078. India.

**Correspondence:**
**Prathusha P**
Browns College of pharmacy
Ammapalem Konijerla (mdl),
Khammam-507305, India.

# Formulation development and *in-vitro* evaluation of Nifedipine sublingual tablets using mesoporous silica

**Prathusha P, Bhargavi L, Belsen David J, Yogesh Choudhary, Upendra Reddy K, Ajith Patil, Fred Monsuur**

**Abstract**
The objective of the study was to develop and optimize sublingual tablets of Nifedipine for the treatment of angina and hypertension. The solubility of Nifedipine was improved by solid dispersion. FTIR studies confirmed the absence of drug-excipients interactions. Eight formulations (F1-F8) of sublingual tablets were prepared by direct compression method using various concentrations of superdisintegrant and diluents. The formulated tablets were evaluated for hardness, thickness, weight variation, friability, wetting time; *in-vitro* dispersion time, water absorption ratio, drug content, disintegration time and the results were within USP limits. Formulation F8 showed shorter wetting time 22 sec, *in-vitro* dispersion time of 41 sec and disintegration time 1 min 45 sec and so it was selected as the optimized formulation. F8 showed 88 folds increase in solubility and *in vitro*-dissolution at 10 min compared to pure Nifedipine and 10 fold increase compared to marketed oral Nifedipine tablets. The drug releases from the sublingual tablets follow Higuchi release kinetics and diffusion was the main mechanism for drug release. Optimized formulation (F8) was found to be stable from stability studies.

**Keywords:** Nifedipine, sublingual, solid dispersion, Mesoporous silica, angina and hyper tension.

## Introduction
Sublingual administration (SL) of the drug means placement of the drug under the tongue and drug reaches directly into the blood stream through the ventral surface of the tongue and floor of the mouth [1]. Passive diffusion is the main mechanism for the absorption of the drug in to oral mucosa. The absorption of the drug through the sublingual route is 3 to 10 times greater than oral route [2]. Systemic drug delivery through sublingual mucosa is one of the best known methods to bypass hepatic first pass metabolism as drugs are not exposed to the metabolic enzymes of the liver [3]. Nifedipine is a calcium channel blocker antihypertensive drug. Nifedipine is a class II compound, which has poor water solubility and dissolution rate and limited absorption through the sublingual mucosa [4]. The dissolution rate can be improved by the use of surfactants, solid dispersion and complexation with cyclodextrin [5]. Solid dispersion of Nifedipine prepared with different grades of Mesoporous silica (MPS) by solvent loading method proved that MPS enhances dissolution and bioavailability of poorly soluble drugs. The formation of crystals is prevented by the confined space of the pores, which are slightly larger than the drug molecules that entrap the drug in its amorphous form. High surface area and hydrophilicity of MPS enhances wettability resulting in faster dissolution. It is also reported that MPS can help improve permeability of large hydrophilic molecules in presence of permeation enhancers [6]. Direct compression requires incorporation of a Superdisintegrant into the formulation, or the use of highly water soluble excipients to achieve fast tablet disintegration [7].

## Materials and Methods
### Materials
Nifedipine was received as a gift sample from Suchem laboratories, Ahmadabad**.** Cross povidone Pearlitol and Ludiflash were purchased from Signet Chemical Corporation Pvt. Ltd, Mumbai. Silsol 6035, Syloid XDP 3050, Syloid 72 FP and Syloid 244FP were purchased from Grace Davison Chemical India Pvt. Ltd, Hyderabad. Lactose monohydrate was purchased from Meggle Group Wasserburg, Germany. Citric acid was purchased from Merck specialities Pvt. Ltd, Mumbai, India. Sodium saccharine was purchased from Sun Pharma, Mumbai. Magnesium stearate was purchased from avian international Ltd, Mumbai. All the chemicals and solvents used were of analytical grade.

## Methods

### Preparation of Nifedipine solid dispersion by Solvent loading method [8]

In this method drug was dissolved in Acetone and this drug solution was filled into burette and loaded onto different grades of silica (Silsol 6035, Syloid XDP3050and Syloid 72FP) in varying percentages like 10%, 20%and 30% by adding drop by drop drug solution with continues stirring.

### Pre-compressional Evaluation of Tablets [9]

All the powder blends for Nifedipine tablets (F1 to F8) were subjected to pre-formulation studies like bulk density, Tapped density, Angle of repose, Carr's index and Hausner's ratio. The results are presented in Table 2.

### Compatibility studies

### Fourier transform infrared spectroscopy (FTIR) [10]

FTIR spectra of Nifedipine, solid dispersion of Nifedipine with Silsol 6035, and other excipients was compared with Nifedipine reference standard using FTIR spectrophotometer (Jasco, 6600) by KBr pellet method. The scanning was in between 400 to 4000 cm–1 and with 1 cm–1 resolution. The results are shown in Figures 2.3 and 4.

### Preparation of Nifedipine sublingual tablets [11]

Nifedipine sublingual tablets were prepared by direct compression method. The composition of batches F1 to F8 are shown in Table 3. All the ingredients except Magnesium stearate were passed through mesh # 40, and transferred into a polyethylene bag and mixed for 5 min. Magnesium stearate was passed through #60 and added to the above blend then further mixed for additional 2 min. The mixed blend was compressed into tablets of the 300mg using 9mm punches on a Rotary Tablet Compression Machine (Eliza press 200).

### Analytical method development

### Preparation of Standard

A standard solution of Nifedipine was prepared by dissolving accurately weighed 1.32 mg of pure drug in 1:1 ratio of methanol and HPLC water and sonicated for 10 min. Standard curve was obtained by making 100 dilutions to the above solution with methanol and HPLC water to give the concentration of 132 µg/ml. The prepared standard solution was scanned using HPLC Agilent, 1260 infinity). Nifedipine showed maximum absorbance (λ max) at 238 nm. Thus 238 nm is selected as a wavelength for further analysis.

### HPLC Analysis

The amount of Nifedipine dissolved was determined by HPLC analysis (Agilent, 1260 infinity). The mobile phase consisted of methanol and HPLC water in a volume ratio of 1:1 and the flow rate was maintained at 1ml/min in HPLC column (Rocket HL 53mm*7mm*4.6mm, 3µ) at 40 °C. The detection wavelength was set to 238 nm. The injection volume was 20 µl with pressure 20 bars and run time of 5min**.**

### Post-compressional Evaluation of Tablets

### Hardness [12]

The hardness of the tablets was determined by a hardness tester (Electrolab). Ten individual tablets from each batch were selected and hardness was determined. The results are presented in Table 4.

### Thickness [13]

The thicknesses of tablets were determined by using a digital Verniercallipers. Ten individual tablets from each batch were selected and the average thickness was calculated. The results are presented in Table 4.

### Weight variation [14]

Weight variation was calculated as described in USP. 20 whole tablets were individually weighed their average weight noted. The requirements are met if the weights of not more than 2 of the tablets differ from the average weight by more than the percentage listed in the accompanying table and no tablet differs in weight by more than the double that percentage. The results are presented in Table 4.

$$\% \text{ Weight variation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 10$$

**Table 1:** Weight Variation Tolerances for Uncoated tablets and coated tablets (other than Film coated tablets)

| Average Weight of Tablet, mg | Percentage difference |
|---|---|
| 130 or less | 10 |
| From 130 through 324 | 7.5 |
| More than 324 | 5 |

### Friability [15]

The friability values of the tablets were determined as per USP. For tablets with a unit weight equal to or less than 650 mg, take a sample of whole tablets *n* corresponding as near as possible to 6.5 g. For tablets with a unit weight of more than 650 mg, take a sample of 10 whole tablets. The tablets should be carefully dedusted prior to testing. Accurately weigh the tablet sample, and place the tablets in the drum. Rotate the drum 100 times, and remove the tablets. Remove any loose dust from the tablets as before and accurately weigh. The test should be repeated three times and the mean of the three tests determined. A maximum weight loss (obtained from a single test or from the mean of three tests) of not more than 1.0% is considered acceptable for most products. The results are presented in Table 4.

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

### Drug content

Tablets ($n$ = 6) were weighed individually, and the drug was extracted in Methanol: water solution (1:1), and the solution was filtered. One ml of the filtrate was suitably diluted and Nifedipine content was estimated at 238 nm using Agilent analytical HPLC. The results are presented in Table 5.

### Wetting time [16]

The tablet was placed at the centre of two layers of absorbent paper fitted into a petridish. After the paper was thoroughly wetted with distilled water, 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. The results are presented in Table 5.

### Water absorption ratio [17]

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. 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. The results are presented in Table 5.

R = 100 × Wa –Wb/Wa
Where, Wa = Weight of tablet after water absorption
Wb = Weight of tablet before water absorption

***In-vitro* disintegration test** [18]
According to USP disintegration test for sublingual tablets, the disintegration apparatus for oral tablets is used without the covering plastic disks, and 2 min is specified as the acceptable time limit for tablet disintegration fulfilling the official requirements (<2 min) for the sublingual dosage form. The test was carried out using a tablet disintegration apparatus (LABINDIA). Distilled water was used as the disintegrating medium at 37 ± 2 °C. The time required to obtain complete disintegration of all the tablets was noted. The results are presented in Table5.

***In-vitro* drug release study** [19]
Dissolution study was conducted for all formulations using USP dissolution test apparatus type II (DS8000, LABINDIA). Five hundred millilitres of phosphate buffer (pH 6.8) was taken in a dissolution apparatus, which was maintained at 37 °C ±0.5 °C at 50 r.p.m. Two millilitres aliquots were periodically withdrawn and the sample volume was replaced with an equal volume of fresh dissolution medium. Samples were collected at predetermined time intervals and filtered by whatman filter paper. The samples were analyzed by HPLC at 238 nm. The results are presented in Table 7.

**Kinetic Studies** [20, 21]
The dissolution data of F8 formulation (conducted in 500ml phosphate buffer (pH 6.8) was fitted into various mathematical models (Zero order, First order, Higuchi, Korsmeyer- peppas model) to know which mathematical model will best fit for the drug release profile. The results are presented in Table 6.

**Stability studies** [22]
The stability studies were carried out on the optimized formulation F8 as per ICH guidelines Q1C. Tablets were sealed in aluminum foil and kept in a humidity chamber maintained at 40 ± 2 °C/75 ± 5 % relative humidity (RH) for 1 month. At the end of the studies, the samples were analyzed for % drug release and drug content. The results are presented in Table 8.

**Results and Discussion**
The Nifedipine sublingual tablets were prepared by direct compression method using Eliza press 200 tablet punching machine.

**Table 2:** Evaluation of pre compression parameters of Formulation F1 to F8

| Formulation code | Bulk density (gm/cm3) | Tap density (gm/cm3) | Carr's Index (%) | Hausner's ratio | Angle of repose |
|---|---|---|---|---|---|
| F1 | 0.32±0.02 | 0.46±0.05 | 27.92±2.10 | 1.38±0.04 | 36.27±0.62 |
| F2 | 0.46±0.01 | 0.62±0.02 | 22.81±0.34 | 1.32±0.03 | 33.64±2.15 |
| F3 | 0.44±0.01 | 0.58±0.09 | 23.80±0.36 | 1.40±0.11 | 35.19±2.27 |
| F4 | 0.40±0.01 | 0.54±0.02 | 26.41±0.54 | 1.36±0.02 | 38.37±2.31 |
| F5 | 0.33±0.04 | 0.47±0.06 | 28.92±2.2 | 1.39±0.05 | 37.28±0.73 |
| F6 | 0.45±0.02 | 0.53±0.03 | 21.82±0.33 | 1.30±0.02 | 32.51±2.01 |
| F7 | 0.42±0.02 | 0.56±0.05 | 21.80±0.21 | 1.20±0.01 | 32.19±1.27 |
| F8 | 0.44 ±0.01 | 0.58±0.09 | 22.81±0.34 | 1.32 ±0.03 | 33.64±2.15 |

*Data represents Mean ± SD (n=3)

**Table 3:** Formulation Composition of Nifedipine sublingual tablets

| Ingredients(mg) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
|---|---|---|---|---|---|---|---|---|
| Nifedipine SD (A1) | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| MCC102 | 66.5 | - | 106.5 | 88.25 | - | 83.25 | - | - |
| Lactose monohydrate | 60 | - | 60 | - | - | - | - | - |
| Pearlitol | - | 156.5 | - | - | - | - | - | - |
| Ludiflash | - | - | - | 88.2 | 176.5 | 83.2 | 166.5 | 156.5 |
| Crospovidone : Syloid244 FP | 60 | - | 20 | 10 | 10 | 20 | 20 | - |
| Crospovidone | - | 30 | - | - | - | - | - | 30 |
| Sodium saccharine | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Citric acid | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| Syloid 244FP | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Magnesium stearate | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| Total | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 300 |

*Crospovidone: Syloid244FP mixture was prepared in 1:1 ratio by co milling for 10 min.
**Note:** Capping was observed for F1, F2, F3 and F6 batches.

**Table4:** Weight variation, Hardness, Thickness, and Friability of Nifedipine sublingual tablets

| Formulation code | Weight variation | Hardness (Kg/cm$^2$) | Thickness (mm) | Friability (%) |
|---|---|---|---|---|
| F4 | 298±1.11 | 4.6±2.71 | 5.6±0.03 | 0.12 |
| F5 | 301±0.98 | 4.5±1.22 | 5.5±0.04 | 0.08 |
| F7 | 299±1.26 | 2.5±2.21 | 5.7±0.03 | 0.06 |
| F8 | 299 ±2.11 | 6.5±1.74 | 5.6±0.02 | 0.07 |

The tablets were evaluated for hardness, thickness, weight variation, friability, drug content, water absorption ratio, wetting time, *In-vitro* disintegration time, and *In-vitro* dissolution rate. The prepared tablets in all formulations possessed good mechanical strength with sufficient hardness in the range of 4.6 to 6.5 Kg/cm$^2$. The tablet mean thickness was

almost uniform in all formulations. The thickness varies between 5.6 to 5.7 mm. 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 (F1toF8) was found to be in the range of 299 mg to 300 mg, which was within the acceptable limits. The friability varies between 0.07to 0.12 %. The friability values between 1% were an indication of good mechanical resistance of tablets.

**Table 5:** Water absorption ratio, Wetting Time, Disintegration time and Drug content of Nifedipine sublingual tablets

| Formulation code | Water absorption ratio (%) | Wetting time(Sec) | Disintegration time (Sec) | Drug content (%) |
|---|---|---|---|---|
| F4 | 35±0.99 | 58.12±1.52 | 185.11±2.12 | 97.6±0.85 |
| F5 | 41±1.21 | 65.22±0.66 | 183.22±5.12 | 97.9±0.88 |
| F7 | 39±1.48 | 55.21±1.22 | 180.24±2.14 | 98.6±0.95 |
| F8 | 53±1.52 | 22.21 ±2.11 | 105.12±2.21 | 98.9 ±0.95 |

The drug content in all formulations (F1 to F8) was highly uniform and in the range of 97 to 98 %. The wetting time was found to be in the range of 22 sec. The water absorption ratio in all formulations (F1 to F8) was found to be in the range of 41-53 %. The disintegration time in all formulations were observed within fraction of minute. The disintegration time in all formulations (F1 to F8) was found to be in the range 2-3 min. Formulation F8 showed faster disintegration and wetting as compared with other formulations.

**Table6:** Regression analysis of Nifedipine sublingual tablets

| S. No | Formulation | Release Kinetics | | | |
|---|---|---|---|---|---|
| | | Zero- order | First -order | Higuchi | Korsmeyer Pappas |
| 1 | F4 | 0.986 | 0.859 | 0.996 | 0.974 |
| 2 | F5 | 0.978 | 0.895 | 0.976 | 0.899 |
| 3 | F7 | 0.997 | 0.861 | 0.947 | 0.916 |
| 4 | F8 | 0.984 | 0.854 | 0.982 | 0.956 |

From release kinetic parameters it is clearly indicated that highest regression coefficient value ($r^2$) the best fit model for optimised formulation (F8) was Higuchi model, indicating that the release of drug follows the Higuchi release kinetics and diffusion is the dominating mechanism for drug release.

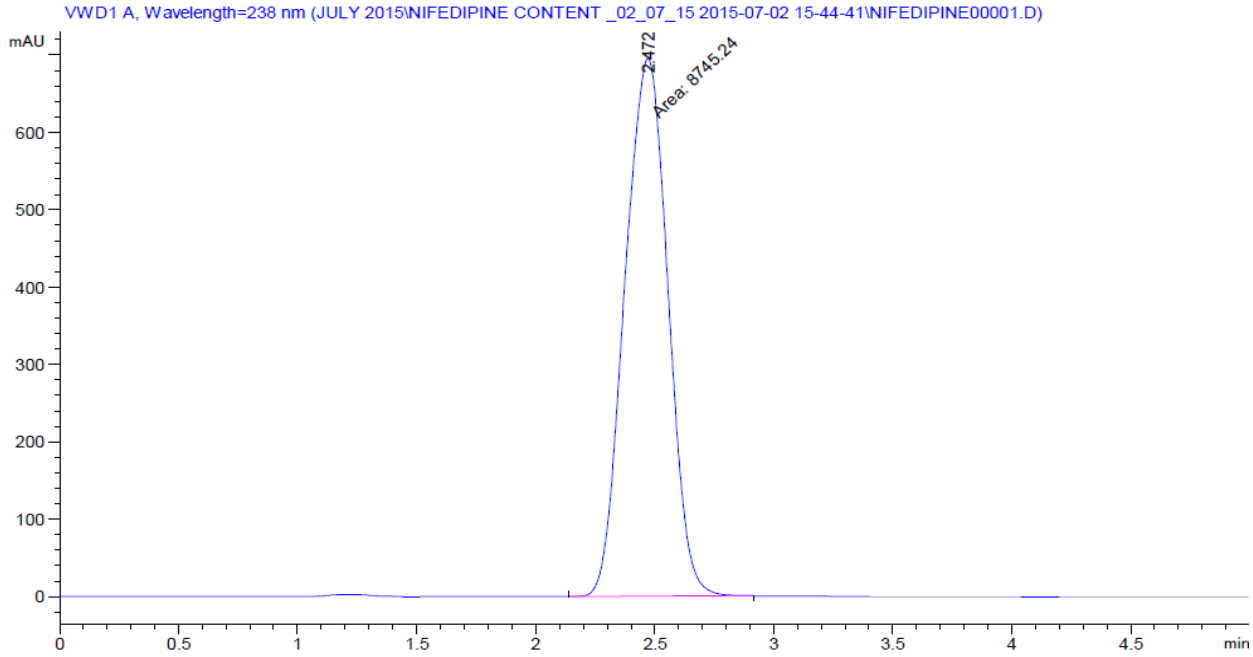


**Fig 1:** Standard Graph of Nifedipine

Nifedipine standard solution was prepared as mentioned in the Methods. The λ max was found to be 238nm.

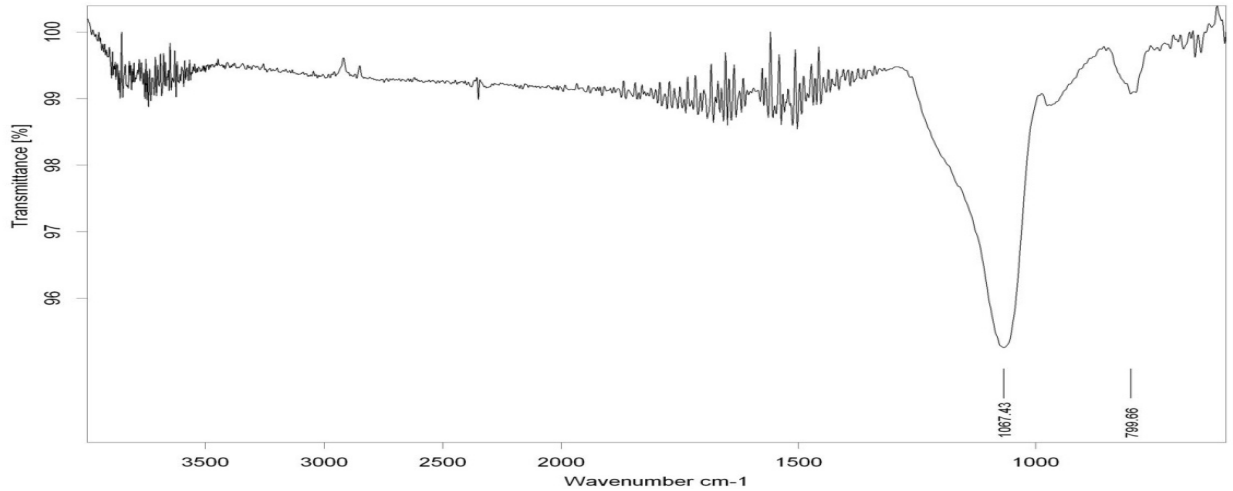


**Fig 2:** FTIR of Silsol 6035

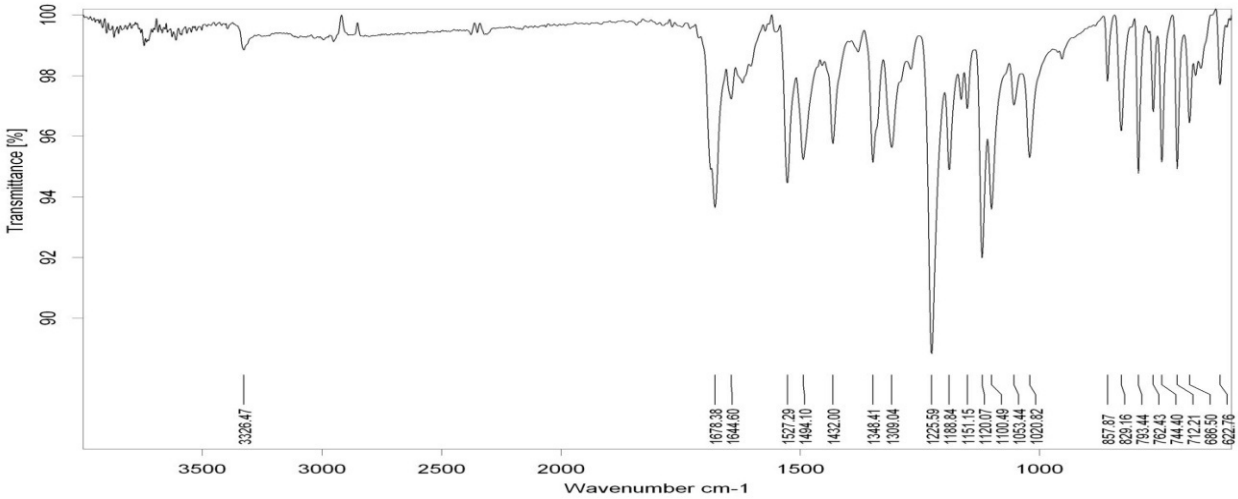


**Fig 3:** FTIR of Nifedipine pure drug

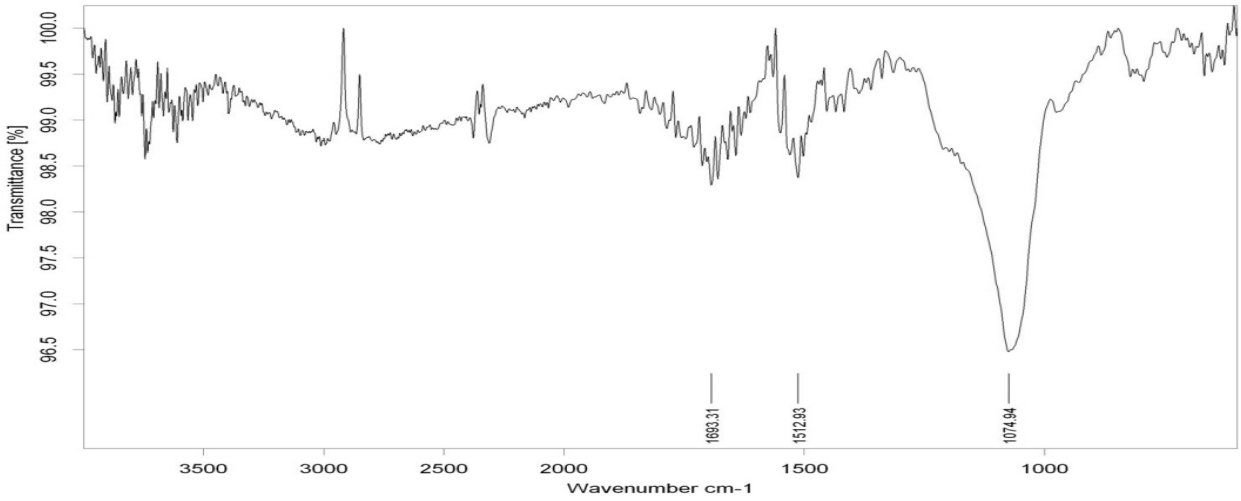


**Fig 4:** FTIR of Optimised formulation blend (F8)

The results from FTIR showed that Nifedipine exhibits a peak due to C=O stretching at 1678.35 $cm^{-1}$, N-O stretching at 1527.29 $cm^{-1}$, and C-N stretch at 1053.44, C-H stretch at 793.44. Optimized formulation F8 blend gave respective peaks at 1693.31 $cm^{-1}$, 1512.93 $cm^{-1}$, 1074.94 $cm^{-1}$ (figure 25,26). Silsol 6035 showed peaks at 1067.43 $cm^{-1}$ due to C-N stretching, 799.66 due to C-H stretching (figure 23). It was observed that there was no change in these main peaks in the FTIR spectra of a mixture of drug, carrier and excipients. Hence it was concluded that no physical or chemical interactions of Nifedipine with silica and other excipients were found.

**Table 7:** Comparison of Dissolution profile of formulation F8 with Marketed oral tablet and Nifedipine pure drug

| Time(min) | Nifedipine (milled)Powder | F8 formulation | Nifedipine marketed oral tablet |
|---|---|---|---|
| 0 | 0.00 | 0 | 0 |
| 2.5 | 0.00 | 6.51±3.33 | 0.39±0.14 |
| 5 | 0.17±1.22 | 14.16±3.69 | 1.06±0.38 |
| 10 | 0.24±1.16 | 21.20±2.16 | 2.68±0.86 |
| 15 | 0.45±1.43 | 30.60±3.42 | 4.92±1.42 |
| 30 | 1.09±1.58 | 32.93±3.17 | 11.71±2.49 |
| 45 | 1.93±1.35 | 57.34±3.67 | 19.82±2.97 |
| 60 | 2.86±1.60 | 68.86±3.12 | 29.83±3.22 |

*Data represents Mean ± SD (n=3)

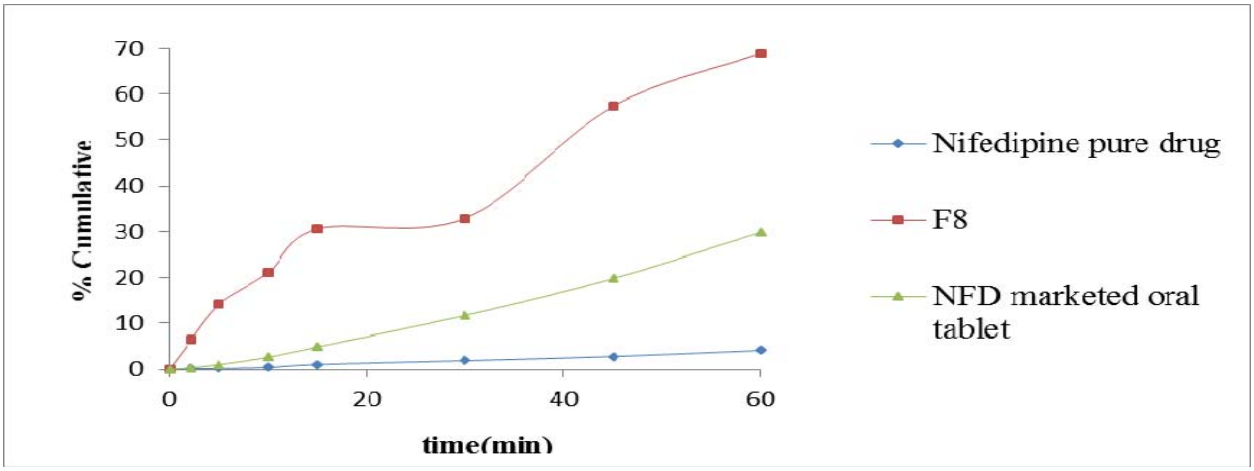


**Fig 5:** Comparison of Dissolution profile of formulation F8 with marketed oral tablet and Nifedipine pure drug)

The optimized formulation F8 was further evaluated for *in-vitro* drug release studies and the results are shown in Table 6. At 10 min time point it showed 88folds increase in solubility and dissolution compared with Nifedipine pure drug and 10 folds compared with marketed oral tablet, which indicates that F8 is the optimized formulation.

**Stability Studies**

**Table 8:** Stability testing data of optimized formulation (F8) kept for stability at 40°C /75%RH

| Time (min) | F8 Initial | F8 1Month |
|---|---|---|
| 0 | 0 | 0 |
| 5 | 5.93±0.55 | 5.61±0.75 |
| 10 | 10.45±1.08 | 10.66±0.27 |
| 15 | 14.11±2.11 | 16.15±1.11 |
| 20 | 18.05±2.39 | 18.92±0.91 |
| 30 | 22.55±2.64 | 22.72±1.52 |
| 45 | 29.62±2.69 | 27.76±1.80 |
| 60 | 37.12±2.48 | 32.66±1.45 |

*Data represents Mean ± SD (n=3)

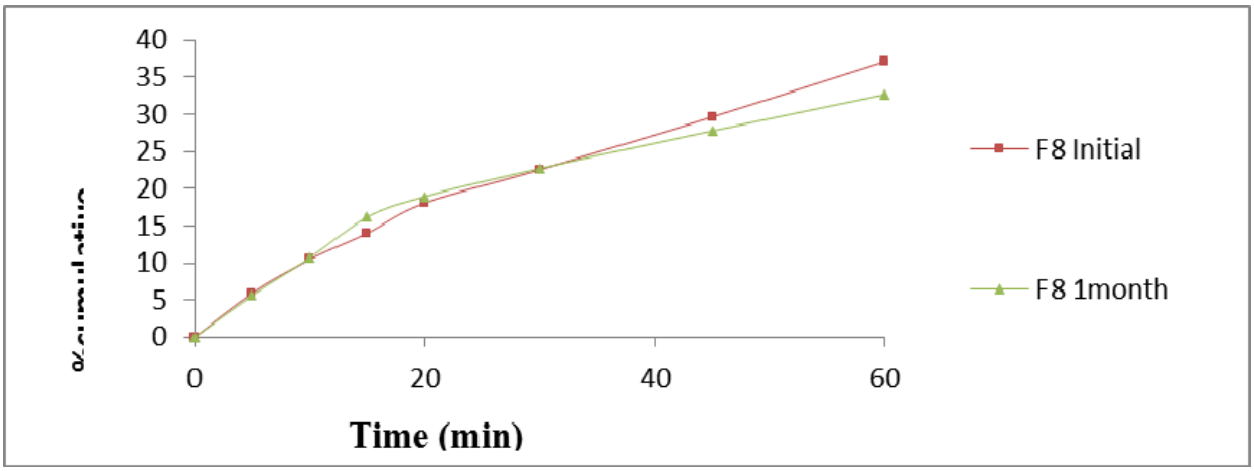


**Fig 6:** Comparison of dissolution profiles of pure drug, Initial and 1 Month samples of Formulation F8

**Table 9:** Nifedipine content study for stability samples

| Formulation code | Actual amount (%) present in the tablet after 1 month storage |
|---|---|
| F8 | 98.20±0.92 |

The stability testing of optimized formulation F8 was carried out as per the ICH guidelines. The optimized formulation was subjected to stability studies at 40 °C and 75 % RH for a period of one month. The physical stability was assessed by the physical appearance and there was no change in the colour, and the chemical stability by change in the % drug release and drug content. The drug content was found to be 9.8 mg after 1month stability study, it was found to be similar to the initial results. So, it was clear that drug and formulation were thermally stable as well as not affected by high humidity at 40 ± 2 °C/75 ± 5 % RH. The results of the stability tests are shown in Table 8 and 9.

## Conclusion

A satisfactory attempt was made to develop Nifedipine sublingual tablets by direct compression method using different excipients (Ludiflash, crospovidone, sodium saccharine, citric acid, Syloid 244 FP, magnesium stearate). The Preformulation properties i.e. Angle of repose, Bulk density, Tap density, Carr's Index, Hausner's ratio, were found to be acceptable according to USP limits. The sublingual tablets of Nifedipine were prepared by direct compression method (F1 to F8). The prepared tablets were evaluated for Hardness, Wetting time and *in- vitro* dispersion time, disintegration time, on the basis of these results formulation F8 was selected as an optimized formulation. From the dissolution profile at 10min time point (Table 7) formulation F8 showed 88 folds increase in solubility and dissolution compared with pure Nifedipine drug and 10 folds compared with marketed oral Nifedipine tablet, the drug release follows Higuchi release kinetics. Diffusion is the main mechanism for drug release. Accelerated stability studies, proved that the formulation is quite stable. Optimized sublingual tablet of Nifedipine was prepared for the treatment of angina and hypertension.

## Acknowledgement

The author wishes to give thanks to Grace Davison Chemical India Pvt. Ltd, Hyderabad for providing suitable research laboratory and Browns College of pharmacy, Khammam for support and guidance to carry out this project work. And my deep gratitude to Suchem laboratories, Ahmadabad for providing Nifedipine gift sample.

## References

1. Neha Narang, Jyoti Sharma. Sublingual mucosa as a route for systemic drug delivery, International Journal of Pharmacy and Pharmaceutical Sciences. 2011; 3(2):18-22.
2. Priyank Patel, Sandip Makwana, Urvish Jobanputra, Mihir Ravat, Ankit Ajmera, Mandev Patel. Sublingual route for the systemic delivery of Ondansetron, Int. J Drug Dev Res. 2011; 3(4):36-44.
3. Harris D, Robinson JR. Drug delivery via the mucous membranes of the oral cavity. J Pharm Sci. 1992; 81:1-10. doi:10.1002/jps.2600810102
4. Mahesh Kumar, Kataria1, Anil Bhandari. Formulation and Evaluation of Solid dispersion for Dissolution Enhancement of Nifedipine. World Journal of Pharmaceutical Sciences. ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
5. Liu C, Zhu SJ, Zhou Y, Wei YP, Pei YY. Enhancement of dissolution of cyclosporine A using solid dispersions with polyoxyethylene (40) stearate. Pharmazie. 2006; 61(1):681-684.
6. Foraker AB, Walczak RJ, Cohen MH, Boiarski TA, Grove CF, Swaan PW. Micro fabricated porous silicon particles enhance par cellular delivery of insulin across intestinal Caco -2 cell mono layers. Pharm Res. 2003; 20(1):110-116.
7. Allen LV. Rapid-dissolve technology: an interview Int J Pharm Technol 2003; 7:449-450.
8. Yogesh Choudhari, Hans Hoefer, Cristian Libanati, Monsuur and William McCarthy. Mesoporous Silica Drug Delivery Systems. Chapter ID 23, 2014.
9. http://www.drugfuture.com/pharmacopoeia/usp32/pub/data/v32270/usp32nf27s0_c1174.html
10. Shailesh T Prajapati, Manoj V Patel, and Chhaganbhai N Patel.Preparation and evaluation of sublingual tablets of zolmitriptan. Int J Pharm Investig. 2014; 4(1):27-31.
11. Naimish A, Sarkhejiya Krupaj K, Khachar Vipul Patel P. Formulation development and evaluation of sublingual tablets of Risperidone.Resaerch J Pharm. And Tech. 2013, 6(4).
12. Mutaliksrinivas, Hiremath doddaya, Formulation and evaluation of chitosan matrix tablets of nifedipine, The Eastern Pharmacist 2000; 2:137-139.
13. http://www.usp.org/sites/default/files/usp_pdf/EN/dietarySupp/c2091.pdf
14. Lachman l, Liberman A, King JL, Tablets: The thory and practice of industrial pharmacy.Varghese publishing house.1987; 3rded:296-300
15. http://www.pharmacopeia.cn/v29240/usp29nf24s0_c1216.html
16. Sunada H, Bi Y. Preparation, evaluation and optimization of rapidly disintegrating tablets. Powder Technology. 2002; 122:188-198. doi:10.1016/S0032-5910(01)00415-6
17. Sanada H, Yonezawa Y, Danjo K. Preparation and evaluation of compressed tablet rapidly disintegrating in the oral cavity. Chemistry Pharma Bulletin. 1996; 44(1):2121-2127.
18. Bayrak Z, Tas C, Tasdemir U, Erol H, Ozkan CK, Savaser A *et al.* Formulation of zolmitriptan sublingual tablets prepared by direct compression with different polymers: *In vitro* and *in vivo* evaluation.Eur J Pharm Biopharm. 2011; 78:499-505. [PubMed: 21352916]
19. Noushin Bolourtchian*a b***, Naghmeh Hadidi*a*, Seyed Mohsen Foroutan*a b,* Bijan Shafaghi*a.* Formulation and Optimization of Captopril. Sublingual Tablet Using D-Optimal Design. Iranian Journal of Pharmaceutical Research. 2008; 7(4):259-267.
20. Dash S, Padala NM, Lilakanta N, Chowdhury P. Kinetic modeling on drug release from controlled drug delivery systems. Acta Poloniae Pharmaceutica n Drug Research. 2010; 67(3):217-23.
21. Noushin BB, Naghmeh H, Seyed MF, Bijan S. Formulation and optimization of Captopril sublingual tablet using D-Optimal Design. Iran J Pharm Res. 2008; 7(4):259-67.
22. Note for guidance on stability testing. Stability testing of new drug substances and products.
23. http://www.ich.org/products/guidelines/quality/article/qualityguidelines. html.