

## FORMULATION DEVELOPMENT AND CHARACTERIZATION OF NISOLDIPINE FAST DISSOLVING TABLET

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### ABSTRACT

**Objective:** The objective of this study was formulation, development and characterization of nisoldipine fast dissolving tablets. This study was aimed to formulate nisoldipine fast dissolving tablets to increase its bioavailability.

**Methods:** Nisoldipine FDT's were prepared by direct compression method using different ratios of super-disintegrants and effervescent agents. The prepared tablets were subjected to both pre and post evaluation parameters including FTIR, micromeritics properties, Hardness, weight variation, friability, Disintegration time, wetting time analysis and *in-vitro* dissolution studies.

**Results:** FTIR studies indicate that the drug and excipients were compatible. The micromeritics study indicates that all formulations were of acceptable to good flow ability. Tablet hardness and friability indicated that the prepared formulations were having good mechanical strength. The formulation F5 which was prepared by using the combination of super-disintegrants like Sodium starch glycolate and Crosspovidone gave the good results for tablet disintegration, wetting time and *in-vitro* dissolution.

**Conclusion:** It can be concluded that the formulation F5 (6% combined SSG and CP) showed faster disintegration, dissolution profile and increased onset of action compared to conventional dosage form.

**Keywords:** Nisoldipine FDT's, Effervescent agents, Super-disintegrants, FTIR.

### INTRODUCTION

The most popular route of administration is an oral route of administration which is very safest, more convenient and patient compliance. But most of the patients show difficulty in swallowing tablets and capsules which results in non-compliance and ineffective therapy. To eradicate these defects formulation scientists have developed novel oral dosage form known as fast dissolving tablets. [1-4]

The US Food and drug administration defines fast dissolving tablet as "a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue". [5, 6]

Nisoldipine is a dihydropyridine derivative belongs to calcium channel blocker, primarily used to treat hypertension.[7] Nisoldipine blocks the inward movement of calcium by binding to the L- type calcium channel in the heart and in smooth muscle of the peripheral vasculature, which prevents calcium dependent smooth muscle contraction and subsequent vasoconstriction. It also used to treat heart stroke, angina pectoris and mild diuresis. [8, 9]

As it is poorly soluble drug, it is categorized as class II compound as per BCS classification system. In the process of absorption, dissolution is the rate limiting step which in turn dependent on drug disintegration. Dissolution is increased by incorporating the drug in fast dissolving dosage form.

The poor bioavailability of Nisoldipine after oral administration may be due to low aqueous solubility, poor permeability, poor wettability and rapid first pass hepatic metabolism. Developing a unique formulation that modifies solubility and dissolution will produce higher concentration of Nisoldipine in solution at the absorption site and may conquered the first pass effect mediated low bioavailability. [10, 11]

The dissolution and bioavailability parameters of poorly soluble drug in a solid dosage form mainly depend upon excipients added to the formulation and their characteristics. According to these parameters the present study was proposed to formulate oral drug delivery dosage form in the form of fast dissolving tablet of nisoldipine to increase its bioavailability. In the present

investigation FDTs were prepared by direct compression method by using two approaches namely superdisintegrants and effervescent agent. The prepared tablets were subjected to both pre and post-compression parameters. [12]. The main intention of present study was to prepare fast dissolving tablet of Nisoldipine using superdisintegrants and effervescent agent is to enhance the onset of action, improve dissolution and bioavailability. [13]

### MATERIALS AND METHODS

Nisoldipine was procured as a gift sample from Mylan laboratories limited, India. Sodium starch glycolate was acquired from signet chemicals, Mumbai. Crosspovidone and croscarmellose sodium was obtained from Torrent pharmaceuticals Ltd, Ahmadabad. Other chemicals and reagent used in this study were of analytical grade.

#### Preparation of fast dissolving tablets by direct compression technique

Total eleven formulations were prepared in which one is conventional and remaining six formulations prepared by using different concentration of superdisintegrants namely SSG and CCS (4.5, 6, 7.5% w/w.), SSG and CP (4.5, 6, 7.5% w/w.) and remaining formulations by using effervescent agents. All formulations are given in table 1. In all formulations 10mg of drug is taken in each 200mg of tablet. All the ingredients except magnesium stearate were passed into 60 mesh sieve.

Magnesium stearate was added and then the blend was thoroughly mixed and compressed with 8mm flat surface punches using 16 station rotary machines (Cadmach CMD4). In effervescent formulations, sodium bicarbonate and citric acid was preheated to 80°C to remove residual moisture and then directly compressed. The compressed FDT were evaluated for pre and post-compression parameters. [14, 15]

#### Physico-Chemical Evaluation of FDT of Nisoldipine

##### FTIR Study

IR spectra for pure drug and for best formulation (F5) were recorded on FTIR spectrophotometer to find out if any possible drug-excipients interaction. The scanning range for IR was 500 to 4000 cm<sup>-1</sup>. [16]

**Micromeritics analysis: [17, 18]****Angle of repose ( $\theta$ )**

Angle of repose measures the frictional force of a powder blend, which indicates the flow properties of the blend. Angle of repose can be expressed by an equation.

$$\theta = \tan^{-1} (h/r)$$

Where:  $\theta$  is angle of repose, h is height of pile and r is radius of base of pile.

**Bulk density**

Bulk density was derived by introducing the blend into a 100ml graduated cylinder.

The bulk volume ( $V_0$ ) and weight of powder ( $M$ ) was determined. Bulk density was calculated by using the formula.

$$P_0 = M / V_0$$

Where,  $P_0$  - Bulk density

$V_0$  - Bulk volume

$M$  - Weight of powder blend.

**Tapped density**

The known amount of mixed blend present in a 100ml measuring cylinder was tapped from a height of 2.5cm at 2sec interval. Tapped density can be calculated by using the formula.

$$P_t = M / V_t$$

Where,  $P_t$  - Tapped density

$V_t$  - Tapped volume

$M$  - Weight of powder blend.

**Carr's index and Hausner ratio**

Carr's index or compressibility index of a powder blend was expressed in percentage. It is an indicative of flow properties of a blend. It is determined by using the following formula.

$$I = \frac{P_0 - P_t}{P_0} \times 100$$

Where,  $P_t$  - Tapped density

$P_0$  - Bulk density

$I$  - Compressibility index

Hausner ratio was determined by using the formula

$$\text{Hausner ratio} = P_t / P_0$$

**Table 1: Formulations of fast dissolving tablets of nisoldipine**

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Nisoldipine	10	10	10	10	10	10	10	10	10	10	10
Sodium starch Glycolate	-	4.5	4.5	6	6	7.5	7.5	-	-	-	-
Cross Carmellose sodium	-	4.5	-	6	-	7.5	-	-	-	-	-
Cross Povidone	-	-	4.5	-	6	-	7.5	-	-	-	-
Sodium bicarbonate	-	-	-	-	-	-	-	20	26.5	30	37.5
Citric acid	-	-	-	-	-	-	-	10	11	15	16.5
Aspartame	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Mannitol	187	178	178	175	175	172	172	157	149.5	142	133
Total weight	200	200	200	200	200	200	200	200	200	200	200

**Evaluation of post compression parameters**

**Hardness:** Hardness of the tablet is the force required to break a tablet in a diametric compression force. Monsanto hardness tester was used in this study. Five tablets were chosen randomly and tested for hardness and the average was calculated. [19]

**Friability:** Roche friabilator (lab India) was used in this study to determine the friability of a 20 tablets. Pre weighed tablets were rotated at 25rpm for 4min. at the end of the test tablets were dedusted, reweighed and the percentage of loss in the weight was calculated. [20]

$$F = \left\{ 1 - \frac{W_0}{W} \right\} \times 100$$

Where,

$W_0$  - Weight of tablet before test.

$W$  - Weight of tablet after test.

**Weight variation:** 20 tablets were randomly selected from each formulation and weighed individually. Calculating the average weight and comparing the individual tablet weight to the average weight. [21]

**Wetting time:** wetting time of a dosage form can be measured by using simple method. A piece of filter paper (12cm X 10.75cm) folded twice was placed in a petri dish with 10cm diameter containing 6ml of Sorenson's buffer pH 6.8.

Tablet was carefully. placed on the paper and the time for complete wetting was noted. Three trials for each formulation were performed. [22]

**In-vitro disintegration time:** six tablets was placed in disintegration test apparatus containing distilled water at  $37 \pm 2^\circ\text{C}$  and the time for complete disintegration of tablet was noted. [23]

**In-vitro dissolution study:** *In-vitro* dissolution of nisoldipine FDT was carried out in USP type-II apparatus (USP XXIII dissolution test apparatus) at 50 rpm in 900 ml of 6.8 pH phosphate buffer at  $37 \pm 2^\circ\text{C}$  as dissolution medium. Aliquots of 5ml dissolution medium were withdrawn at specific time intervals (5, 10, 15, 30, 45, 60 and 90 mins) and equal volume of fresh medium was replaced.

The aliquots withdrawn were spectrophotometrically analyzed for drug content at  $\lambda_{\text{max}}$  238 nm. Dissolution studies were carried out in triplicate. [24]

**RESULTS AND DISCUSSION**

Nisoldipine FDTs were prepared by simplest and economic technique i.e., by direct compression method. Two approaches namely superdisintegrants and effervescent agent. Mannitol was used as diluents as it shows good aqueous solubility and wetting properties which facilitates tablet breakdown as well as it gives cooling effect into the mouth. SSG, CP and CCS were used as superdisintegrants. All the excipients used in the formulation were hydrophilic to obtain fast dissolving tablet of fast dissolution rate.

**FTIR of nisoldipine FDT**

IR of pure drug physical mixture of drug and excipients of best formulation was determined by using FTIR spectra. All the principle peaks of nisoldipine are present in their original position which denotes the absence of drug-excipients interaction shown in fig.1a and 1b.

### Pre-compression parameters

#### Micromeritics study

Angle of repose is an indicative of the flow ability of the powder. All the formulation F1-F11 showed good flow properties in the range of  $26.47^{\circ} \pm 0.15$  to  $29.69^{\circ} \pm 0.19$ . Bulk density and tapped density showed values in the range of 0.422 to 0.437 and 0.468 to 0.486 respectively. It denotes these formulations were of acceptable to good flowability. Carr's index and Hausner ratio of the powder blend of all the formulations are within the stated limits (Table 2).

#### Post-compression parameters

Hardness of nisoldipine FDTs vary from 2.55 to 4.0 Kg/cm<sup>2</sup>. Percentage friability was in the range of 0.28 to 0.79 and shows good mechanical characteristics to withstand the loss of surface powder while handling of tablets.

Weight variation of all the FDT formulations were ranged from  $196 \pm 0.08$  to  $202.02 \pm 0.02$  which denotes that weight variations are within the pharmacopial limits. The decreased in wetting time of all formulations is due to the presence of superdisintegrants, which absorbs water and swells causing the breakdown of the tablets. By increasing the concentration from 4.5% to 6% the wetting time was decreased from 72 to 15 sec. Similar results were obtained for F10 and F11 prepared by using effervescent agent. Disintegration time is very important for fast dissolving tablet, which should be less than a minute. All the formulation batches showed disintegration time within a stated limit. Disintegration time decreases as the amount of superdisintegrants added. *In-vitro* disintegration was less for the formulation F5 (SSG 3% and CP 3%). The same results were obtained for formulations F8, F9, F10 and F11 prepared by using effervescent agent (Table 3). It was also observed that the Wetting time and *in-vitro* Disintegration of all formulations was decreased compared to control formulation

Table 2: Micromeritics analysis of nisoldipine FDTs

FC	Bulk Density * (gm/cm <sup>3</sup> )	Tapped Density * (gm/cm <sup>3</sup> )	Carr's Index*	Hausner Ratio*	Angle of Repose *(θ)
F1	0.436±0.07	0.480±0.05	09.514±0.02	0.86±0.08	26.64±0.06
F2	0.428±0.02	0.486±0.02	10.714±0.08	0.89±0.03	28.89±0.14
F3	0.499±0.03	0.468±0.05	10.49±0.06	0.89±0.05	27.12±0.12
F4	0.425 ±0.06	0.476±0.08	10.634±0.09	0.89±0.06	29.14±0.08
F5	0.428±0.04	0.465±0.02	07.857±0.02	0.92±0.08	26.77±0.16
F6	0.422±0.02	0.476±0.05	11.26±0.04	0.88±0.02	28.55±0.17
F7	0.422±0.07	0.472±0.04	10.56±0.05	0.89±0.07	28.63±0.12
F8	0.428±0.08	0.476±0.01	10.01±0.07	0.90±0.05	29.69±0.19
F9	0.434±0.06	0.482±0.09	9.42±0.03	0.90±0.03	26.47±0.15
F10	0.437±0.07	0.483±0.06	8.75±0.05	0.89±0.05	27.12±0.12
F11	0.431±0.02	0.483±0.01	10.79±0.04	0.89±0.08	28.46±0.02

FC: Formulation code. \* Mean ± SD, n= 3.

Table 3: Post-Compressional properties of FDT of Nisoldipine tablets

FC	Weight variation* (mg)	Hardness (kg/cm <sup>2</sup> )	Friability* (%)	Disintegrati-on time (sec)	Wetting time* (sec)
F1	197.26	3.4±0.03	0.46±0.016	58±2.08	62±2.08
F2	198.68	3.5±0.02	0.52±0.013	42±2.00	48±1.53
F3	198.85	3.2±0.03	0.34±0.029	22±2.52	25±1.53
F4	196.01	3.5±0.03	0.48±0.051	38±1.15	36±2.08
F5	198.04	4.0±0.02	0.28±0.035	12±2.08	18±1.52
F6	202.00	3.6±0.05	0.29±0.042	26±2.52	24±2.51
F7	199.16	3.4±0.06	0.30±0.056	18±1.53	28±2.52
F8	197.54	3.5±0.02	0.44±0.098	28±2.08	25±2.00
F9	198.11	3.6±0.05	0.48±0.067	22±1.03	26±3.00
F10	201.46	3.4±0.03	0.69±0.068	22±1.22	25±1.53
F11	199.69	3.1±0.05	0.79±0.056	16±1.06	22±1.34

FC: Formulation code. \* Mean ± SD, n=3.

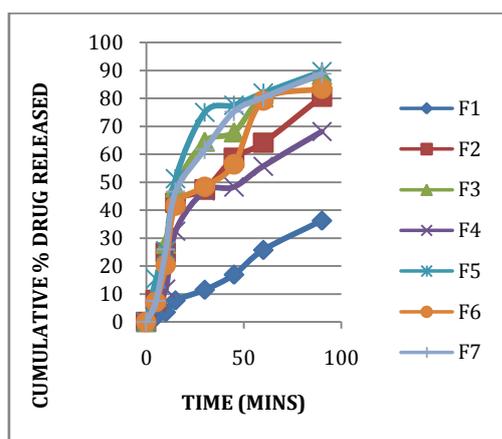


Fig.1: *In-vitro* dissolution profile of nisoldipine FDT of F2-F7 formulations compared to control F1.

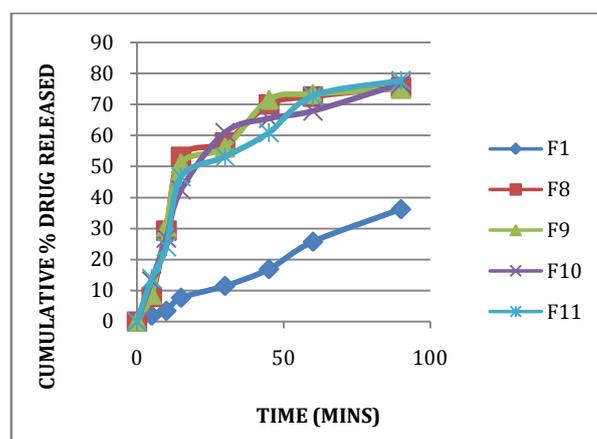


Fig 2: *In-vitro* dissolution profile of nisoldipine FDT of F8-F11 formulations compared to control F1.

**In-vitro dissolution study**

Results of in-vitro dissolution study were shown in Fig 2 and Fig 3. Eleven formulations were formulated by using direct compression method. F1 represent the conventional formulation of Nisoldipine i.e., without superdisintegrants and effervescent agent, to which other formulations were compared. F2 to F11 were formulated by using two different approaches namely superdisintegrants and effervescent agent, which shows high dissolution rate compared to control formulation F1. In case of superdisintegrants approach, formulation F5 prepared by using Sodium starch glycolate 3% and Crosspovidone 3% shows low disintegration time and high dissolution rate of 89.54% after 90mins compared to 36.42% of control formulation F1. Tablets prepared by using effervescent agent, showed an increase in the dissolution rate compared to formulation F1.

The increase in dissolution rate of F5 might be due to combination of superdisintegrants like sodium starch glycolate and Crosspovidone 6% w/w. Crosspovidone helps in making the tablet more porous causes penetration of dissolution medium which accelerates the swelling of sodium starch glycolate. The optimized combination of both the SSG and CP gives high dissolution rate.

**CONCLUSION**

Nisoldipine FDTs can be considered convenient solid oral dosage form to increase the drug bioavailability. All the formulations were formulated based on two approaches namely superdisintegrants and effervescent agent. Superdisintegrants formulation ideally F5 using 6%w/w of combined SSG and CP superdisintegrants showed faster disintegration, dissolution profile, increased onset of action and improved bioavailability.

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