



Research Article

# DEVELOPMENT OF NEVIRAPINE TABLETS BY DIRECT COMPRESSION METHOD USING SOLID DISPERSION TECHNIQUE

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## ABSTRACT:

**Purpose:** The aim of the research is to develop Nevirapine tablets by direct compression method by improving solubility using solid dispersion technique.

**Methodology:** Nevirapine is anti-viral drug, which is used in the prevention and treatment of HIV infections. It belongs to class II drug in Bio-Pharmaceutical Classification System i.e. low solubility and high permeability. It has a biological half-life of 45 hours. One of the major problems with this drug is its low solubility in biological fluids, which results into poor bioavailability after oral administration. Here, solid dispersions of Nevirapine are prepared with different carriers such as Plasdone S-630 and Soluplus in order to increase its solubility and dissolution rate. By increasing the solubility of Nevirapine, its bioavailability can be increased. Pre-formulation studies regarding the drug-carrier interaction was carried out by fourier transform infrared spectroscopy and differential scanning calorimetry. Nevirapine solid dispersions were evaluated for solubility, drug content estimation and in vitro dissolution studies. Powder blend was evaluated for bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose.

**Findings:** The dissolution pattern of the Nevirapine from all the standard dispersions followed predominantly first order kinetics. The study reflects the vital role of polymers as a novel approach to improve the solubility of nevirapine, which could minimize the variable dissolution rate with increase in bioavailability. With the studies conducted, the percentage drug release of Nevirapine was increased by melting method with Nevirapine: Plasdone S630 in the ratio of 1:2

**Practical implications:** Nevirapine is a suitable drug to formulate into tablet by using the above mentioned carriers and may provide a better therapeutic profile than that of conventional dosage form.

**KEYWORDS:** *Nevirapine; PlasdoneS630; Solid Dispersion Technique; Soluplus.*

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## INTRODUCTION:

Nevirapine (C<sub>15</sub>H<sub>14</sub>N<sub>4</sub>O) is a potent, non-nucleoside reverse transcriptase inhibitor (NNRTI) used in combination with nucleoside analogues for treatment of Human Immunodeficiency Virus Type

1 (HIV-1) infection and AIDS. Structurally, it belongs to the dipyridodiazepinone chemical class<sup>1</sup>. (As shown in figure 1)

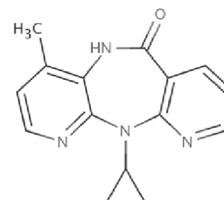


Fig.1: Chemical Structure of Nevirapine.

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Nevirapine binds directly to reverse transcriptase (RT) and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by causing a disruption of the enzyme's catalytic site.

Nevirapine belongs to class II drug in bio pharmaceutical classification system i.e. low solubility and high permeability<sup>2</sup>. One of the major problems with this drug is its low solubility in biological fluids, which results into poor bioavailability after oral administration.

Drug absorption is defined as the process of movement of unchanged drug from the site of administration to systemic circulation<sup>3</sup>. The main possibilities for improving dissolution according to Noyes – Whitney equation analysis are to increase the surface area available for dissolution by decreasing the particle size of the solid compound and/or by optimizing the wetting characteristics of the compound to decrease the boundary layer thickness, to ensure sink conditions for dissolution and to improve the apparent solubility of the drug under physiologically relevant conditions.<sup>4</sup>

The term solid dispersion is defined as a “dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent or melt-solvent method.<sup>5</sup> The solid dispersions may also be called solid - state dispersions and this technique is used for many drugs like ritonavir<sup>6</sup>.

For the development of solid dispersion films of nevirapine carriers used were Plasdone S630 & Soluplus, along with other excipients like acacia gum, croscopovidone, purified talc, magnesium stearate and prosolv.

Plasdone S630 also called as copovidone is an excellent tablet binder, matrix polymer for solid dispersions and film former for topical applications in dry granulation and direct compression tablet process. Plasdone S630 copovidone is a 60:40 linear random copolymer of N-vinyl-2-pyrrolidone and vinyl acetate. The pyrrolidone ring provides excellent solubility in water and in a range of solvents, as well as adhesive, solubilization/crystal inhibition and film forming properties. The vinyl acetate is a polymer backbone lowers the polymer's glass transition temperature. As a result Plasdone S630 copovidone is highly compressible, making it an excellent tablet binder producing more flexible

and less brittle films. The unique combination of properties allows Plasdone S630 copovidone to improve solubility and bio availability of poorly soluble drugs through the formation of melt-extruded or spray-dried solid dispersions<sup>7</sup>.

Soluplus is an innovative excipient that enables new levels of solubility and bioavailability for poorly soluble active ingredients. It has high flow ability and excellent extrudability, Soluplus shows superior performance in forming solid solutions, especially in hot melt extrusion processes. This solid solution makes the active pharmaceutical ingredient (API) available in a dissolved state, resulting in improved bioavailability once in the body.<sup>7</sup>

## **METHODOLOGY:**

### **Materials required:**

Nevirapine (Gift sample from Arene Life Sciences limited, Hyderabad), Plasdone S630 (Arihand Trading Corporation, Bengaluru), Soluplus, Acacia, Croscopovidone, talc, Magnesium Stearate & Hydrochloric Acid (S.D Fine Chemicals Limited, Mumbai) and Prosolv (Ashok Chem Pharma International, Mumbai).

### **Drug-carrier compatibility studies:**

FT-IR spectroscopy was employed to ascertain the compatibility between drug and the selected carriers. The pure drug and drug with excipients were scanned separately<sup>9</sup>.

Potassium bromide was mixed with drug and/or carrier in 9:1 ratio and the spectra was taken. FT-IR spectrum of drug was compared with FT-IR spectra of drug with carriers.

### **Differential Scanning Calorimetry (DSC):**

DSC analysis of the drug carrier solid dispersion was carried out on the samples using DSC (Mettles). Samples (5mg) were heated under nitrogen atmosphere on an aluminum pan at a rate of 10°C/m over the temperature range of 30°C and 300°C. Thermal data analysis of DSC was conducted.

### **Preparation of Solid Dispersion:**

Solid dispersions were prepared by the following methods (Formulation codes as shown in Table1)

**1. Physical mixture method:** Drug with Plasdone S630 and with Soluplus in different ratios (i.e. 1:1M, 1:2M) was mixed in a mortar for about one hour with

constant trituration, passed through sieve No. 80 and stored in desiccators over fused calcium chloride.

**2. Kneading method:** Drug with Plasdone S630 and with Soluplus in different ratios (i.e. 1:1, 1:2) was taken. Firstly the carrier is added to the mortar. A small quantity of 50% ethanol is added while triturating to get slurry like consistency. Slowly the drug is incorporated into the slurry and trituration is further continued for one hour. Slurry is then air dried at 25°C for 24 h, pulverized and passed through sieve number 80 and stored in desiccators over fused calcium chloride.

**3. Melting Method:** In melting method, accurately weighed quantities of drug and carrier were taken in a mortar and pestle and were mixed for some time. This physical mixture was transferred into a china dish and was melted on a sand bath. The fusion temperature was controlled at 165°C to 175°C. The melted mixture was immediately cooled and solidified on an ice bath with vigorous stirring. The mass obtained was scrapped, crushed, pulverized and passed through sieve number 100. The obtained product was stored in desiccators.<sup>9</sup>

**Table 1: Formulation codes for the Nevirapine solid dispersions prepared by various methods**

| Composition<br>API (NEVIRAPINE) | Methods of solid dispersions |                 |                |
|---------------------------------|------------------------------|-----------------|----------------|
|                                 | Physical mixture             | Kneading method | Melting method |
| API: PLASDONE S630-1:1          | PM-1                         | KM-1            | MM-1           |
| API: PLASDONES630-1:2           | PM-2                         | KM-2            | MM-2           |
| API: SOLUPLUS-1:1               | PM-3                         | KM-3            | MM-3           |
| API: SOLUPLUS-1:2               | PM-4                         | KM-4            | MM-4           |

## Evaluation Studies on Nevirapine Solid Dispersions

### 1. Solubility Studies:

#### Solubility in 0.1 N HCL :

Excess drug was added to 100 ml of 0.1 N HCl taken in a series of 100ml stoppered conical flasks and the mixtures were shaken for 72 h at room temperature (28°C) on a rotary flask shaker. After 72 h of shaking to achieve equilibrium, 2ml aliquots were withdrawn at 1h interval and filtered immediately using 0.45 nylon disk filters. The filtered samples were diluted suitably and assayed for Nevirapine at 282 nm against blanks prepared in the same concentration of 0.1 N HCl. Shaking was continued until three consecutive estimations were the same. The solubility experiments were conducted in triplicate.

#### Solubility in water :

Excess drug was added to 100 ml of water in a series of 100 ml stoppered conical flasks and the mixtures were shaken for 12 h at room temperature (28°C) on a rotary flask shaker and kept aside for 24 h. At the end of this period the solutions were filtered immediately using 0.45 nylon disk filters. The filtered samples were diluted suitably and the absorbance of Nevirapine was measured at 282 nm for Nevirapine content.

### 2. Drug Content Estimation :

Nevirapine solid dispersion powders were weighed, and a quantity of powder equivalent to 100 mg of nevirapine was transferred to a 100 ml volumetric flask and 10 ml methanol is added. The drug is extracted in methanol and sonicated for 15 m. Then the volume is adjusted to the mark with 0.1N HCl and the liquid is filtered. From prepared solution take 0.1ml solution in 10 ml volumetric flask and make up to mark with 0.1N HCl. The Nevirapine content was determined by measuring the absorbance at 282 nm after appropriate dilution. The drug content was calculated using the standard calibration curve. The mean percent drug content was calculated as an average of three determinations.

### 3. In vitro dissolution studies :

In vitro dissolution studies were performed using type II (paddle) dissolution apparatus at 50 rpm and 900 ml of 0.1 N Hydrochloric acid (pH 1.2) was used as a dissolution medium. Temperature of dissolution medium was maintained at 37±0.1°C. 5 ml samples were withdrawn through a filter (0.45 µ) at different intervals of time, suitably diluted and absorbance was measured at 282 nm by using UV spectrophotometer & the sample was replaced with same volume of buffer. The dissolution experiments were conducted in triplicate.<sup>10</sup>

#### Preparation of Tablets:

Direct compression method: Nevirapine tablets were prepared by direct compression method.

All the ingredients were powdered separately and passed through # 40 mesh sieved separately. The drug and directly compressible excipients were mixed by adding small portion of each at a time and blending it to get a uniform mixture and kept aside. Then the other ingredients were mixed in geometrical order in an inflated polyethylene pouch. Magnesium stearate and talc were added at last and

mixed for further 2 min. The tablets were compressed using 12 mm punches to get tablets of 850 mg weight. (As shown in table 2)

**Table 2: Formulation of Nevirapine Tablets**

| Ingredient         | F1  | F2  | F3  | F4  | F5  |
|--------------------|-----|-----|-----|-----|-----|
| Nevirapine (mg)    | 200 | 200 | 200 | 200 | 200 |
| Plasdone S630 (mg) | --  | 200 | 400 | --  | --  |
| Soluplus (mg)      | 10  | --  | --  | 200 | 400 |
| Acacia (mg)        | 25  | 10  | 10  | 10  | 10  |
| Crospovidone (mg)  | 10  | 25  | 25  | 25  | 25  |
| Talc (mg)          | 10  | 10  | 10  | 10  | 10  |
| Mg Stearate (mg)   | 10  | 10  | 10  | 10  | 10  |
| Prosolv (mg)       | 395 | 395 | 195 | 395 | 195 |
| Total (mg)         | 650 | 850 | 850 | 850 | 850 |

### Evaluation of Tablets of Nevirapine

#### Evaluation of Blend:

The powder blend was evaluated for bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose.<sup>11,12</sup>

#### Evaluation of tablets:

Weight variation: 20 tablets were weighed individually and the average weight was determined. The percentage deviation was calculated and evaluated for weight variation.<sup>10</sup>

Hardness test: This is the force required to break a tablet in diametric compression. Hardness of the tablet is determined by stock's Monsanto hardness tester which consists of a barrel with a compressible spring. The pointer moves along the gauge in the barrel fracture. The tablet hardness of 5 kg is considered as suitable for handling the tablet.<sup>13</sup>

#### Friability:

Friability of the tablets was checked by using Roche Friabilator. This test is performed to evaluate the ability of tablets to withstand abrasion in packing, handling, and transporting. Initial weight of 20 tablets is taken and these are placed in the friabilator, rotating at 25 rpm for 4min. The difference in the weight is noted and is expressed in percentage. It should be preferably between 0.5 to 1.0%.<sup>14</sup>

#### Content uniformity test:

Ten tablets were weighed and powdered. A quantity of powder equivalent to 100 mg of Nevirapine was transferred to a 100 ml volumetric flask and 10 ml methanol was added. The drug was extracted in methanol by vigorously shaking the stoppered flask for 15 min. Then the volume was adjusted to the mark with 0.1N HCl and the liquid is filtered. From prepared solution 0.1 ml of solution was taken in 10 ml volumetric flask and the volume was made up to

mark with 0.1 N HCl. The Nevirapine content was determined by measuring the absorbance at 282 nm after appropriate dilution. The drug content was calculated using the calibration curve. The mean percent drug content was calculated as an average of three determinations.

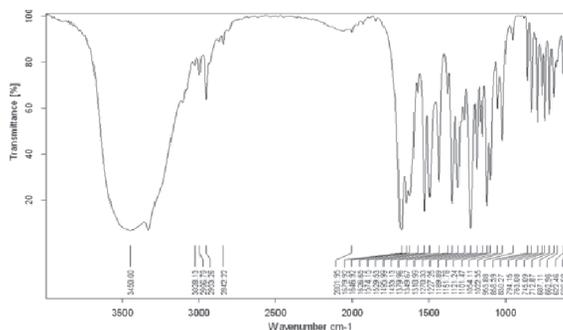
#### Dissolution studies:<sup>15</sup>

In vitro dissolution of Nevirapine tablets were performed using USP XXIII type-II dissolution apparatus employing a paddle stirrer at 50 rpm. 900 ml of 0.1N HCl was used as dissolution medium. The temperature of dissolution medium was maintained at 37 ± 0.5°C throughout the experiment. Samples from the dissolution medium (5ml) were withdrawn by means of syringe fitted with pre-filter at known intervals of time and analyzed for drug release by measuring the absorbance at 282 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Cumulative percent of Nevirapine released was calculated and plotted against time.

## RESULTS AND DISCUSSION

#### FT-IR Analysis:

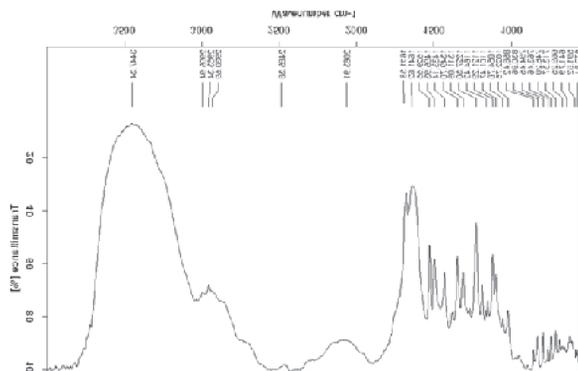
Drug and excipients absorption bands were identified and interpreted in the spectra, interpretation given in table 3. The FTIR spectra of physical mixture of drug and excipients reveal no interaction. (Fig. 2 and Fig. 3)



**Fig.2:** FTIR graph for Nevirapine pure drug

**Table 3: FTIR results analysis for Nevirapine**

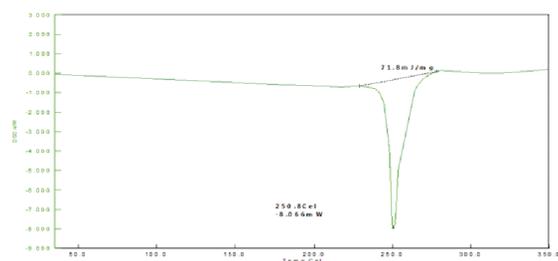
| Sample                         | NH primary stretching vibration Std - (3500-3100cm <sup>-1</sup> ) | C=C Std - (1680-1640m <sup>-1</sup> ) | C=O (KETONE group) Std - (1710-1665cm <sup>-1</sup> ) | C-H (STRETCH) Std - (3100-3000cm <sup>-1</sup> ) |
|--------------------------------|--|---------------------------------------|---|--|
| Nevirapine                     | Present (3450 cm <sup>-1</sup> )                                   | Present (1646 cm <sup>-1</sup> )      | Present (1679 cm <sup>-1</sup> )                      | Present (3028 cm <sup>-1</sup> )                 |
| Nevirapine with all excipients | Present (3447 cm <sup>-1</sup> )                                   | Present (1671 cm <sup>-1</sup> )      | Present (1671 cm <sup>-1</sup> )                      | Present (2995 cm <sup>-1</sup> )                 |



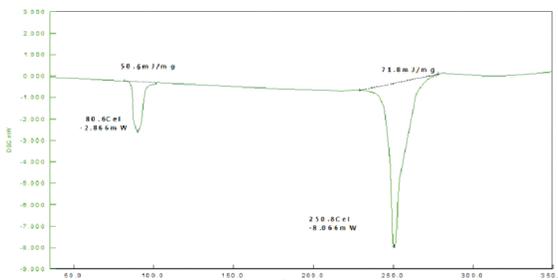
**Figure 3:** FTIR graph for Nevirapine with all excipients

### Differential Scanning Calorimetry:

DSC spectra of pure drug Nevirapine and optimized formulation F3 along with Nevirapine are shown in Fig. 13 and Fig. 14 respectively.



**Fig. 4:** DSC spectra for pure drug



**Fig. 5:** DSC spectrum for Nevirapine optimized formulation F3 and pure drug

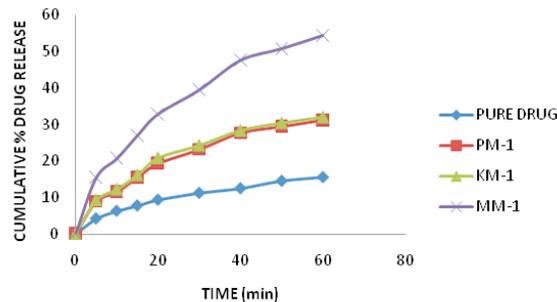
### Evaluation of Solid dispersions: Solubility Data:

Based on the solubility data, the formulation with melting method 1:2 (MM 1:2) showed an exceptional increase in solubility of Nevirapine as compared to other formulations. (Table 3)

**Table 4: Solubility data of Nevirapine in distilled water and 0.1N HCl**

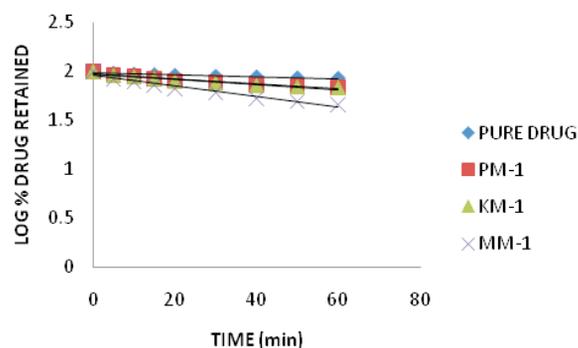
| S.No. | Formulations | Solubility in distilled water (µg/ml) | Solubility in 0.1N HCl (µg/ml) |
|-------|--------------|---------------------------------------|--------------------------------|
| 1     | Pure Drug    | 102.13±0.99                           | 123.33±1.33                    |
| 2     | PM- 1:1      | 107.73±0.86                           | 131.05±0.66                    |
| 3     | PM- 1:2      | 109.18±0.68                           | 136.54±0.59                    |
| 4     | KM- 1:1      | 121.45±0.96                           | 151.99±0.99                    |
| 5     | KM- 1:2      | 134.81±0.48                           | 160.99±1.93                    |
| 6     | MM- 1:1      | 114.46±0.83                           | 141.88±0.59                    |
| 7     | MM- 1:2      | 149.56±0.61                           | 199.90±0.24                    |

In Vitro Dissolution Studies of Nevirapine Solid Dispersions: was performed and graphs were plotted between cumulative percent drug release and time (Fig.6, Fig.8, Fig 10 and Fig.12). First order plot of Pure Nevirapine and Nevirapine: Plasdone S630 (1:1) is shown in Fig.7, Pure Nevirapine and Nevirapine: Plasdone S630 (1:2) is shown in Fig. 9, First order plot of pure Nevirapine and Nevirapine: Soluplus (1:1) in Fig. 11 and First order plot of pure Nevirapine and Nevirapine: Soluplus (1:2) is represented in Fig.13.

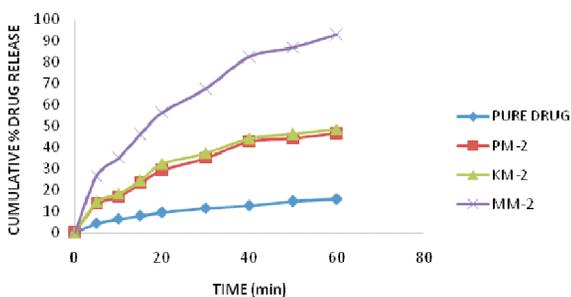


**Fig. 6:** Comparative dissolution profile of Pure Nevirapine and Nevirapine: Plasdone S630 (1:1)

From the above comparative dissolution profile of Nevirapine: Plasdone S-630(1:1) the drug release rates were higher with melting method followed by kneading method and physical mixture.

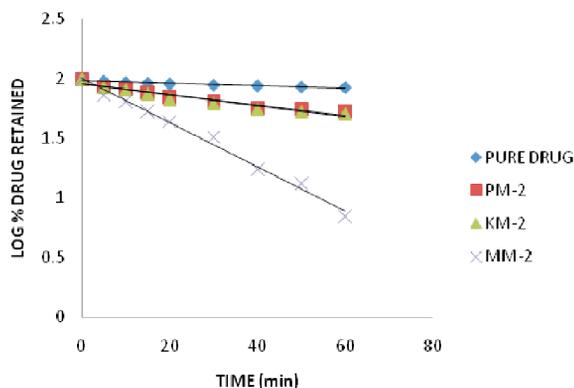


**Fig.7:** First order plot of Pure Nevirapine and Nevirapine: Plasdone S630 (1:1)

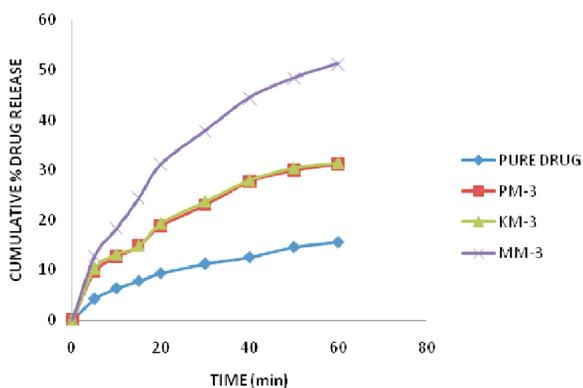


**Fig.8:** Comparative dissolution profile of pure Nevirapine and Nevirapine: Plasdone S630 (1:2)

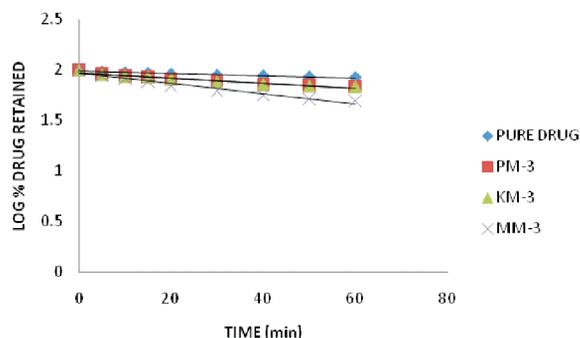
From the above comparative in vitro dissolution profile of pure Nevirapine and Nevirapine: Plasdone S630 (1:2). The percentage drug release was found to be increased by melting method.



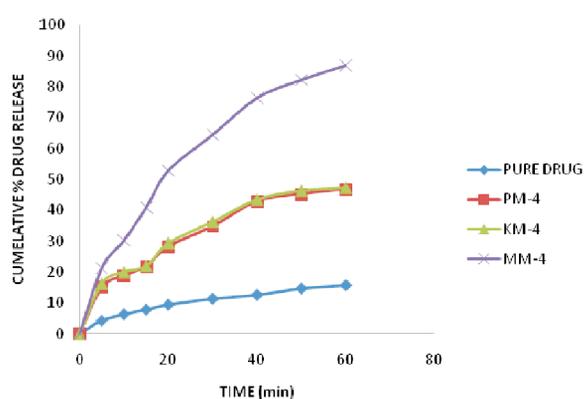
**Fig.9:** First order plot of pure Nevirapine and Nevirapine: Plasdone S630 (1:2)



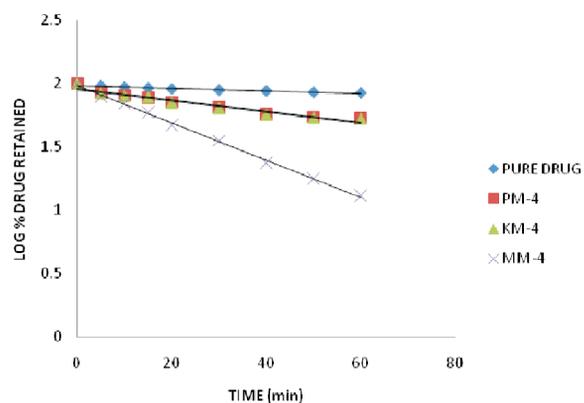
**Fig.10:** Comparative dissolution profile of pure Nevirapine and Nevirapine: Soluplus (1:1)



**Fig.11:** First order plot of pure Nevirapine and Nevirapine: Soluplus (1:1)



**Fig.12:** Comparative dissolution profile of pure Nevirapine and Nevirapine: Soluplus (1:2)



**Fig.13:** First Order Plot of pure Drug and Nevirapine: Soluplus (1:2)

### Pre Compression studies:

The prepared tablets were evaluated for their flow properties; the results for the blends of compression tablets were shown in Table 6.

**Table 5: Pre compression studies of Nevirapine tablets**

| Formulation Code | Bulk density (gm/cc) | Tapped density (gm/cm <sup>3</sup> ) | Carr's index | Hausner's ratio | Angle of repose (°) |
|------------------|----------------------|--------------------------------------|--------------|-----------------|---------------------|
| F1               | 0.40±0.05            | 0.56±0.12                            | 28.57±0.13   | 1.4±0.52        | 58.12±0.8           |
| F2               | 0.41±0.25            | 0.50±0.21                            | 13.0±0.24    | 1.5±0.04        | 25.29±0.2           |
| F3               | 0.50±0.21            | 0.58±0.44                            | 13±0.33      | 1.16±0.11       | 26.58±0.1           |
| F4               | 0.39±0.22            | 0.47±0.21                            | 17.0±0.22    | 1.56±0.31       | 26.23±0.21          |
| F5               | 0.37±0.43            | 0.41±0.22                            | 9.75±0.15    | 1.1±0.01        | 26.35±0.11          |

The bulk density and the tapped density for all formulations were found to be almost similar except F1.

The Carr's index and Hausner's ratio were found to be in the range of 18 and 1.0 to 1.56 respectively, indicating good flow and compressibility of the blends except F1.

The angle of repose for all the formulations was found to be 25.29 to 26.58 which indicating good flow (i.e. incorporation of glidant will enhance its flow) except F1.

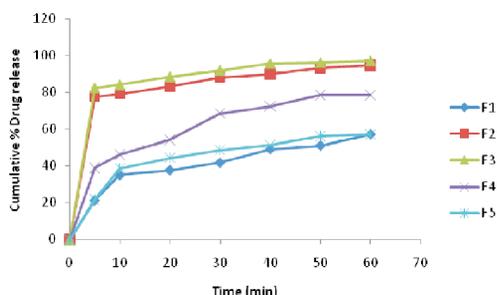
### Evaluation of Nevirapine tablets

**Table 6: Post compression studies of tablets of Nevirapine tablets**

| Formulation code | Weight variation | Hardness (kg/sq.cm) | Friability (%) | Disintegration Time (min) | Drug content (mg/tab) |
|------------------|------------------|---------------------|----------------|---------------------------|-----------------------|
| F1               | PASS             | 4.5±0.16            | 0.95±0.03      | 3.8±0.31                  | 96.3±0.3              |
| F2               | PASS             | 4.6±0.81            | 0.96±0.01      | 2.12±0.33                 | 92.87±0.5             |
| F3               | PASS             | 4.50±0.21           | 0.95±0.05      | 2.46±0.25                 | 98.62±0.2             |
| F4               | PASS             | 4.80±0.12           | 0.52±0.02      | 15.5±0.16                 | 100.02±0.1            |
| F5               | PASS             | 4.50±0.22           | 0.42±0.20      | 20.1±0.15                 | 99.15±0.1             |

The variation in weight was within the range of ±5% complying with pharmacopoeia specifications of USP. The hardness for different formulations was found to be between 4.5 to 4.8 kg/cm<sup>2</sup>, indicating satisfactory mechanical strength. The friability was < 1.0% for all the formulations, which is an indication of good mechanical resistance of the tablet. The drug content was found to be within limits. Results of Post compression studies of tablets of Nevirapine tablets is given in table 6.

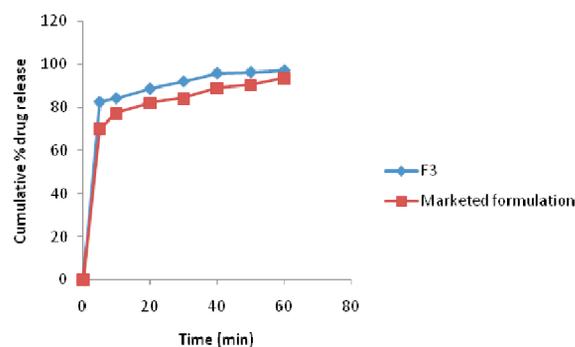
### In Vitro Dissolution Studies of Nevirapine Tablets:



**Fig. 14:** Dissolution profiles of Nevirapine tablets for F1, F2, F3, F4, F5 formulations

### Comparative Dissolution Profile of Optimized Formulation F3 and Marketed Formulation:

The Optimized formulation F3 showed better results when compared with the marketed formulation. (Fig.15). Correlation Coefficient (r<sup>2</sup>) values in the analysis of dissolution data as per Zero order and First order Models given in Table No 7.



**Fig. 15:** Comparative dissolution data of optimized formulation F3 and marketed formulation

**Table 7: Correlation Coefficient (r<sup>2</sup>) values in the analysis of dissolution data as per Zero order and First order Models**

| Formulation code | Correlation coefficient (r <sup>2</sup> ) |             |
|------------------|---|-------------|
|                  | Zero order                                | First order |
| F1               | 0.919                                     | 0.954       |
| F2               | 0.86                                      | 0.903       |
| F3               | 0.594                                     | 0.981       |
| F4               | 0.887                                     | 0.959       |
| F5               | 0.983                                     | 0.997       |

### CONCLUSION

An attempt was made to develop the solid dispersions of Nevirapine to enhance the solubility. Initially the absorption maximum of nevirapine which can be used for the dissolution studies was recorded using UV visible spectrophotometer. The incompatibility studies of the drugs with excipients indicate no interactions. Total five formulations were prepared with aim to achieve successful increase in solubility of drug by using Plasdone S-630 and Soluplus as carriers in order to dissolve the drug. Preformulation studies of blends of all formulations were performed. Post compression evaluations were done.

Optimized F3 formulation which was prepared using Plasdone S-630 in the ratio of 1:2 showed

better drug release and was compared with marketed formulation and results shows almost similar drug release profile. Hence Plasdone S-630 can be considered as good carrier to enhance the solubility of Nevirapine.

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