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FORMULATION AND EVALUATION OF FAST DISINTEGRATING TABLET OF NEVIRAPINE BY MELT SONO CRYSTALIZATION TECHNIQUE

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ABSTRACT

Oral drug delivery is the most preferred route of drug delivery of pharmaceuticals and convenient option as the oral route provides maximum active surface area among all drug delivery system for administration of various drugs. A revolutionary particle manufacturing process called melt sonocrystallization involves applying ultrasonic (Ultrasonic) energy to a soft or viscous molten mass that is spread in an immiscible liquid. Fast-disintegrating tablet of Nevirapine were prepared by direct compression method using different concentration of superdisintegrant. The prepared fast-disintegrating tablet of Nevirapine were evaluated for hardness, thickness, weight variation, friability, disintegration time, wetting time and In-vitro release study and the results found to be satisfactory. Batch no F9 were selected as optimized formulation and it was subjected to kinetic study and it was appeared to occur in the pattern case II transport. Optimized formulation was then subjected to stability studies for 3 months with at specific temperature and relative humidity.

KEYWORDS: Nevirapine, Drug delivery, Ultrasonic, Melt sonocrystallization, Crospovidone.

1. INTRODUCTION

Oral drug delivery is the most preferred route of drug delivery of pharmaceuticals and convenient option as the oral route provides maximum active surface area among all drug delivery system for administration of various drugs. In the pharmaceutical industry, it has been the most preferred drug delivery system due to its many potential benefits, which include a well-established delivery system, patient friendliness, convenience, cost effectiveness, and non-invasiveness. The bioavailability of a medicine, and ultimately its solubility and absorption, determine its therapeutic effectiveness. About 40% of drugs with market approval and nearly 90% of molecules in the drug discovery pipeline are poorly water soluble. The solubility issues can affect the oral delivery of the new drugs and also the delivery of many existing drugs. As a result, a medicine with poor water solubility would usually exhibit limited absorption due to dissolving rate, and a drug with poor membrane permeability will usually exhibit limited absorption due to penetration rate. To improve a low dissolving rate, a number of techniques have been used, including salt creation, solid dispersion, complexation, size reduction, and liquisolid technique.[1-4]

A revolutionary particle manufacturing process called melt sonocrystallization involves applying ultrasonic (Ultrasonic) energy to a soft or viscous molten mass that is spread in an immiscible liquid. Under the impact of ultrasonic energy, emulsified melt is solidified or crystallised. The process, which was first applied to the production of sintered crystals and a porous glassy bead, extends the US energy received by the melt while it is still emulsified and controls the properties of the resulting particles, which depend on the input and frequency of Ultrasonic energy as well as the melt's rate of solidification. This final factor in turn is influenced by the material's and the medium's glass transition temperatures. Ultrasonic use at temperatures above the transition temperature is advantageous. Ultrasonic processing at temperatures above the transition temperature encourages crystallisation, whilst processing at temperatures below the transition temperature produces an amorphous state. Sintered crystals or porous beads are produced as a result of the mechanical stress caused by ultrasonication. The porous structure and potential for manufacturing both crystalline and amorphous particles provide the technology versatility and are thought to improve the solubility of medications that aren't very soluble.[5-9]

2. MATERIALS AND METHODS

1) Materials

Nevirapine was obtained from Yarrow chem products Mumbai. Crospovidone, Croscarmellose, Magnesium Stearate, Talc, Sodium saccharine and Dicalcium phosphate obtained from Thermosil fine chem industrie, Charholi.

2) Method[10-18]

- **Solubility determination**

Solubility is expressed in terms of milligrams of solvent in which 1g of solid is soluble. Solubility of the drug in different solvents like Distilled water 0.095mg/ml, Methanol 50mg/ml, Phosphate Buffer 6.8 0.055mg/ml and 0.1 N HCL 2.22 mg/ml were determined at 20°c.

- **Melting point determination**

Melting point of drug sample was determined by capillary tube method. The identification test was performed to find out thermo stability of the drug sample.

- **Compatibility studies between Nevirapine and Polymers**

The compatibility between Nevirapine and the excipients used was examined using FTIR spectroscopy. In the FTIR spectroscopy technique, significant changes in the shape and position of the absorbance bands are analyzed. It analyzes significant changes in the shape and position of the absorbance bands to show the assumption of different functional groups of present and subsequent molecules.

- **Preparation of calibration curve for nevirapine**

An accurately weighed quantity of 100mg of Nevirapine, pure drug, was taken in 100ml of volumetric flask and is dissolved with small portion of methanol and made up to the volume with water to form 1000µg/ml. 1ml from the stock solution was pipetted out into a 10 ml volumetric flask and volume was made up to the mark with water to form 100µg/ml. Pipetted out 1, 2, 3, 4 and 5 ml from working standard and transfer to separate 10ml volumetric flasks and volume was made up to 10ml with water to yield 10, 20, 30, 40 and 50µg/ml solutions respectively.

- **Preparation of melt sonocrystallized nevirapine**

1gm of Nevirapine were melted in a test tube of 10ml capacity by placing it on a heavy liquid paraffin oil bath material is heated until it becomes a molten liquid. The molten mass was poured into deionized water maintained at a temperature of 50°C. The suspension was sonocrystallized using a probe tip sonicator at a frequency of 33±3 kHz and amplitude of 80% for 20 min. After sonication, the content is filtered off using Whatman filter paper. The filtrate is dried for several hours to obtain a room temperature.

❖ **Pre-compression parameters of nevirapine**

a. The angle of repose

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane. Angle of repose was determined by using fixed funnel method. The fixed funnel method employs a funnel that was secured with its tip at a given height (2cm), above the graph paper that was placed on a flat horizontal surface. Granules or tablet blend were carefully poured through the funnel until the apex of the conical pile just touches the tip of the funnel. Thus, with r being the radius of the base of the conical pile.

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

Where,

h= height of pile.

r= radius of the base of pile

θ= angle of repose.

b. Determination of bulk Density and Tapped density

It refers to a measurement to describe packing of particles and also used to determine the amount of drug that occupies the volume in mg/ml before tapping and after tapping. The graduated cylinder was filled with the powder in an amount that was precisely weighed, the volume (Vo) was measured, the graduated cylinder was then sealed with a lid, and it was placed inside the density measurement device. After 500 taps, the volume (Vf) was measured and the density apparatus kept running until the two successive readings were equal. The following formula was used to determine the bulk density and the tapped density:

Bulk density = W / Vo

Tapped density = W / Vf

Where,

W = weight of the powder

Vo = initial volume

Vf = final volume

c. Carr's compressibility index

Compressibility is the ability of powder to decrease in volume under pressure using bulk density and tapped density the percentage compressibility of powder were determined, which is given as carr's compressibility index. It is indirectly related to the relative flow rate.

Carr's compressibility index was determined by the given formula.

$$CI = \frac{TD - BD}{TD} \times 100$$

Where,

TD – Tapped density

BD – Bulk density

d. Hausner's ratio

The Hausner's ratio is a number that is correlated to the flow ability of a powder or granular material. It indicates the flow property of the powder and measured by the ratio of tapped density to bulk density.

Hausner's ratio= Tapped density / Bulk density

❖ **Preparation of melt sonocrystallized nevirapine tablet**

Fast disintegrating tablets of Nevirapine were prepared by direct compression method according to the 3 2 full factorial design and batch given in Table No. 1. Weighed quantity of Nevirapine along with different concentration of superdisintegrant and binder along with excipients were mixed in geometric progression in a dry and clean mortar. Then the blend were passed through sieve number 60 for direct compression. The powder blend were then compressed into tablets using 8 mm punch in multipunch tablet compression machine.

Table No. 01: Formulation table as per 3^2 full factorial design.

Ingredients (mg)	Batches								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Nevirapine	50	50	50	50	50	50	50	50	50
Crospovidone	5	8.75	12.5	5	8.75	12.5	5	8.75	12.5
Croscarmellose sodium	1.25	1.25	1.25	6.87	6.87	6.87	12.5	12.5	12.5
Dicalcium phosphate	177.2	173.5	169.7	171.6	167.8	164.1	166	162.2	158.5

Magnesium stearate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2
Sodium saccharine	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5

❖ **Evaluation of nevirapine tablet by melt sonocrystallization techniqe**

- **Weight uniformity**

The weight variation test would be a satisfactory method for determining drug content uniformity of drug. In this test is performed by taking 20 tablets, from a batch. 20 tablets are weighed individually and the average weight was determined and percentage deviations were calculated. The tablets meet the USP test if not more than 2 tablets are outside the percentage limits and if no tablets differ by more than 2 times the percentage limit.

Formula for weight variation:

$$\textbf{Deviation } \% = \frac{\textbf{weight of each tablet } - \textbf{ average weight of tablets}}{\textbf{average weight of tablet}} \times \mathbf{100}$$

- **Hardness**

ODT has a significant strength that is challenging to create because of the complex manufacturing procedures and ingredients. The ODT's maximum allowable hardness is typically kept in the lower range to encourage early dissolution in the mouth. The hardness of the tablet were measured by using monsanto hardness testers.

- **Friability**

To achieve % friability within limits for an ODT is a challenge for a formulator since all methods of manufacturing of ODT are responsible for increasing the % friability values. The procedure for a standard tablet friability test applicable to manufactured tablets is outlined in USP 24/NF19.Individual weight of ten tablets from each batch was taken. Then each group of tablets was placed in a friabilator. The tablets were rotated for 1 minute at 100 rotations per minute. After rotation was complete, the tablets were collected and weighed again. The friability was calculated for each batch of tablets by using the following equation.

$$\% \, \boldsymbol{Friability} = \frac{\boldsymbol{W1 - W2}}{\boldsymbol{W1}} \times \mathbf{100}$$

Where,

W1= Weight of tablet before test

W2 = Weight of tablet after test

- **Wetting time**

The wetting time is evaluated by a piece of tissue paper (10.75×12 mm), fold it twice and place it in a culture dish (d= 6.5 cm) containing 6 ml of water. Put a tablet on the paper and record the time required for complete wetting.

- **In-Vivo disintegration test**

The test was conducted on six tablets using the apparatus described in buffer solution 6.8 at 37°C 2°C was used as a disintegration media and the time in seconds is taken for full disintegration of the tablet with no palpable mass remaining in the apparatus.

- **Content uniformity**

Tablets were crushed and the amount equivalent to 20 mg of Nevirapine was weighed accurately and dissolved in 100 ml of methanol in a volumetric flask. The solution is filtered, diluted suitably with methanol and drug content is analyzed at 282 nm by UV spectrophotometer.

- **In vitro dissolution study**

Using the paddle method and the USP dissolving testing apparatus-2, the release of specially prepared fast disintegrating tablets was evaluated. 500 mL of phosphate buffer solution, pH 6.8, 37 0.5 C, and 50 rpm were used for the dissolving test. At predetermined intervals, a sample (5 mL) of the solution was taken out of the dissolution equipment and replaced with new dissolution media. Whatman filter paper was used to filter the samples. These solutions' 282 nm absorbance was determined using a UV spectrophotometer.

- **Kinetic study**

To analyze the mechanism for the drug release and release rate kinetics of the dosage form, the data obtained from in vitro drug release studies was fitted in to zero order, first order, Higuchi's and Peppa's model.

1) Zero order equation

$Qt = Qo + Kot$

Where,

Qt is the amount of the drug release at time t,

Qo is the initial amount of drug in the solution (most time Qo = 0) and

Ko is the zero order release constant.

2) First order equation

Ln Qt = In Qo + K1t

Where,

Qt is the amount of drug release at time t,

Qo is the initial amount of drug in the solution and

K1 is the first order release constant.

3) Higuchi's equation

Qt = KHt 1/2

Where,

Qt is the amount of drug release at time t, and

KH is the Higuchi diffusion rate constant.

4) Krosmeyer peppa's equation

Mt / M∞ = K tn

Where the Mt is the amount of drug released at time t, M∞ is the amount of drug released after infinite time, K is the kinetic constant incorporating structural and geometric characteristics and n is the diffusional exponent indicative of the drug released mechanism.

For n=0.5 indicate pure Fickian diffusion-controlled drug release and n =1 indicated swelling controlled drug release or case II transport. Other values for n indicated anomalous transport kinetics, i.e., a combined mechanism of pure diffusion and case II transport. The special case with n = 0.5 in above equation represents the Higuchi model.

- **Stability studies of optimized formulation**

Stability of a pharmaceutical preparation can be defined as "the capability of a particular formulation in a specific container/closure system to remain within its physical, chemical, microbiological, therapeutic and toxicological specifications throughout its shelf life." The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under influence of a variety of environmental factors such as temperature, humidity and light, and enables recommended storage conditions, re-test periods and shelf-lives to be established. ICH specifications for stability study

- Long term testing: 25°C ± 2°C /60% RH ± 5% RH for 12 months.
- Accelerated testing: 40°C ± 2°C /75% RH ± 5% RH for 6 months.

Procedure

In the present study, stability studies were carried out at room temperature 40 ± 20C and 75 ± 5% RH for a specific time period up to 3 Months for selected formulations. For stability study, the tablets were sealed in aluminium packaging coated inside with polyethylene. These sample containers were placed in Stability chamber maintained at 60% RH.

3. RESULTS AND DISCUSSIONS

1) Solubility profile

Solubility of Nevirapine in different solvents was determined and they are as follows.

Table No. 02: Solubility profile.

Sr. no.	Solvent	Solubility (mg/ml)
1	Distilled water	0.095
2	Methanol	50
3	Phosphate buffer 6.8	0.055
4	0.1N HCL	2.22

2) Melting point determination

Melting point of drug sample was determined by capillary Method and found to be 246-248 ℃.

3) Compatibility studies between Nevirapine and Excipients

- **FT-IR Spectrum**

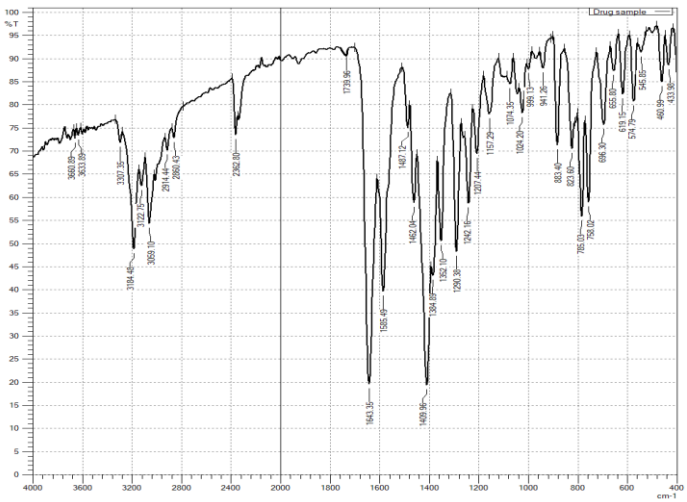

Fig. No. 01: FTIR spectrum of nevirapine.

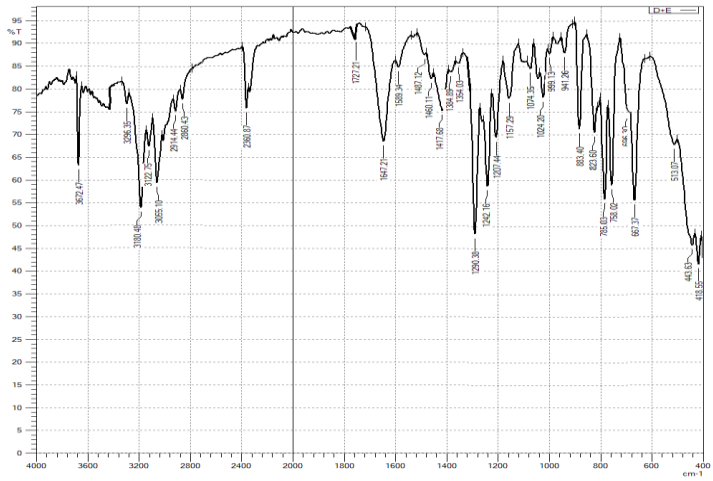

Fig. No. 02: FTIR spectrum of nevirapine with excipients.

Table No. 03: Interpretation of IR spectra of Blend.

Functional group	Observed peak (cm^{-1})
N-H Stretching	3296.35 (cm^{-1})
C=C Stretching	1647.21 (cm^{-1})
C=O Stretching	1727.21 (cm^{-1})
C-H Stretching	3065.10 (cm^{-1})

FT-IR of drug and excipients blend shows bands at 3296.35 (cm^{-1}), 1647.21 (cm^{-1}), 1727.21 (cm^{-1}), 3065.10 (cm^{-1}), of N-H, C=C, C=O, C-H, which are in the range of pure drug band ranges. The FT-IR spectrum of drug and excipients blend revealed no interaction. (fig 1 and fig 2) and the interpretation is shown in table no.11. From the above interpretation it is understood that there is no major shifting in the frequencies of above said functional groups. Hence these drug and excipients are compatible with each other.

4) Callibration curve of niverapine

Table No. 03: Callibration curve of niverapine.

Sr. no.	Concentration (µgm/ml)	Absorbance (nm)
1	10	0.221
2	20	0.418
3	30	0.617
4	40	0.833
5	50	1.024

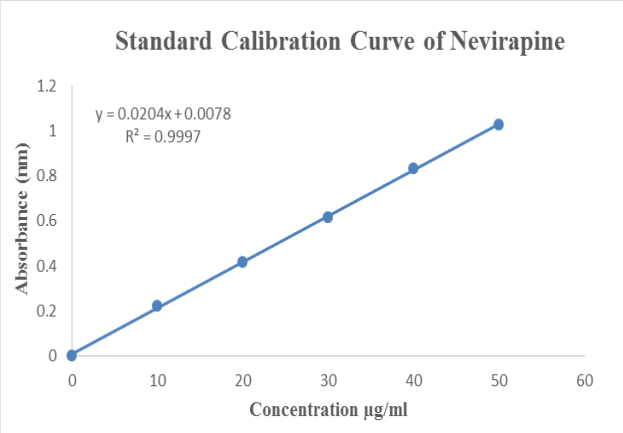

Fig. No. 03: Calibration curve of nevirapine.

5) Angle of repose

The angles of repose of all the formulations were found from 25 to 300. Hence, they all comply pharmacopeial standard.

6) Bulk Density and Tapped density

The bulk density of all the batches of Nevirapine were found from 0.57g/cm3 to 0.77g/cm3 and the tapped density of the entire powder blend batch was found from 0.68g/cm3 to 86 g/cm3 which have been used for further calculation of carr‟s index and Hausner‟s ratio.

7) Carr's index

The measurement of free-flowing powder can also be done by Carr‟s index. The Carr‟s indexes of all the powder blend batches were found to be 13.09% to 17.79%.

8) Hausner's ratio

The Hausner‟s ratio of formulation blend was done as per procedure. The hausner‟s ratio of the of formulation blend were found between 1.15 to 1.21

Table No. 04: Precompression evaluation.

Batch No.	Bulk Density (g/cm3)	Tapped density (g/cm3)	Carr's Index (%)	Angle of Repose (θ)	Hausner's Ratio
F1	0.57	0.68	13.09	26.32	1.15
F2	0.63	0.71	15.2	26.54	1.18
F3	0.73	0.84	17.27	28.32	1.19
F4	0.58	0.69	13.81	29.42	1.21
F5	0.68	0.71	14.66	27.16	1.14
F6	0.75	0.83	16.05	29.18	1.19
F7	0.64	0.76	15.11	28.12	1.17

F8	0.72	0.84	14.96	28.23	1.16
F9	0.77	0.86	17.79	29.91	1.19

9) Weight uniformity

The weight of different tablets were found to be varying. weight was found to be in the range of 229 ± 0.75 mg to 264 ± 0.35 mg shown in table no 5. The average % deviation of all formulation was found to be with in the limit the weight of tablet depend on the amount of diluent added in the formulation. The amount of diluent increase also the weight of tablet increases.

10) Hardness

The hardness for tablets varied between 3.0±0.05 and 3.8±0.09 kg/cm2 shown in table no 5. Hardness depend on the compression force of of the force punching machine high compression force resulting hardness of the tablet.

11) Friability test

All the batches were found under 1% which is within limit as shown in table no 5.

12) Disintegration time

All prepared batches showed good disintegration. Disintegration time varied between 30 - 61 sec. (showed in table no 5). Batch no F9 showed disintegration time of 30 sec, it was because of concentration disintegrant, lower the amounts of disintegrant Higher the disintegration time.

13) Wetting time

All prepared batches showed good wetting time. wetting time varied between 34 to 46 sec. (showed in table no 5).

14) Content uniformity

Nevirapine tablets were tested for their drug content and all the formulation showed drug content 87.2% to 100.2%, shown in table no 5. batch no. F3 and F7 showed less drug content while batch F9 have higher drug content.

Table No. 05: Post compression evaluations.

Batch No.	Weight variation (%) ± S.D	Hardness (kg/cm2)	Friability (%)	Disintegration Time (sec)	Wetting time (sec)	% Drug content
F1	237±0.24	3.0±0.05	0.26±0.05	61	36	97.56±0.15
F2	255±0.30	3.1±0.05	0.24±0.05	49	34	97.36±0.25
F3	258±0.25	3.2±0.04	0.36±0.20	37	35	89.23±0.36
F4	264±0.35	3.3±0.08	0.54±0.25	57	35	98.69±0.28
F5	229±0.75	3.8±0.06	0.41±0.25	46	38	91.33±0.12
F6	232±0.46	3.6±0.09	0.71±0.05	37	37	96.01±0.45
F7	232±0.25	3.8±0.09	0.74±0.75	53	46	87.21±0.50
F8	259±0.30	3.7±0.07	0.8±0.25	42	38	97.87±0.36
F9	262±0.50	3.2±0.05	0.6±0.05	30	34	100.2±0.11

15) In vitro dissolution study

Cumulative percent drug released for all the nine batches were shown in the table no.6. Batch no. 9 was selected as optimized batch because it shoes highest drug release of 99.9%and have been selected for further studies.

Table No. 06: Drug release profiles.

Time in min.	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	8.49	9.08	9.18	10.7	9.48	10.0	12.0	9.18	9.58
10	18.5	19.2	20.7	23.7	24.0	28.1	24.0	19.8	23.0
15	37.7	35.8	36.6	36.6	39.6	43.4	38.9	35.0	38.0
20	56.4	52.3	52.9	58.8	59.9	57.4	58.0	50.9	56.5
25	76.4	74.1	78.6	78.8	77.3	75.1	72.9	70.5	76.1
30	88.1	90.1	93.6	91.3	92.7	94.8	91.4	97.0	99.9

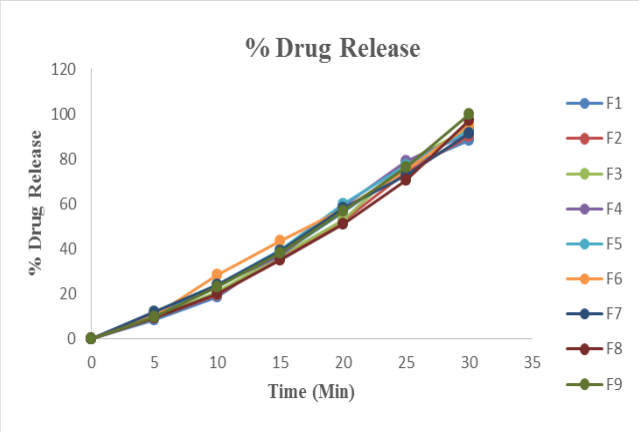

Fig. No. 04: Cumulative percent drug release.

16) Kinetic studies

Batch no.9 was selected for kinetics studies. The slope n was computed to know whether the release was Fickian or Non-Fickian. For Non-Fickian release the n values falls between 0.5 and 1.0, while for Fickian diffusion n is less than or equal to 0.5. The slope values are tabulated in below chart The values of n were more than 1 for all formulations.

- **Diffusional n values**

In is the Diffusional exponent and is also an important indicator of transport of drug through the dosage form.

Table No. 07: Diffusional n values.

N	Mechanism
0.5	Fickian diffusion
0.5<n<1	Non-Fickian diffusion
1	Case II transport

Table No. 08: Kinetic drug release of batch F9.

Batch No	Zero order R2values	First order R2 values	Higuchi R2values	Korsmeyer-PeppasR2 values	'n' value
F9	0.982	0.562	0.542	0.999	1.341

- **Zero order drug release kinetics**

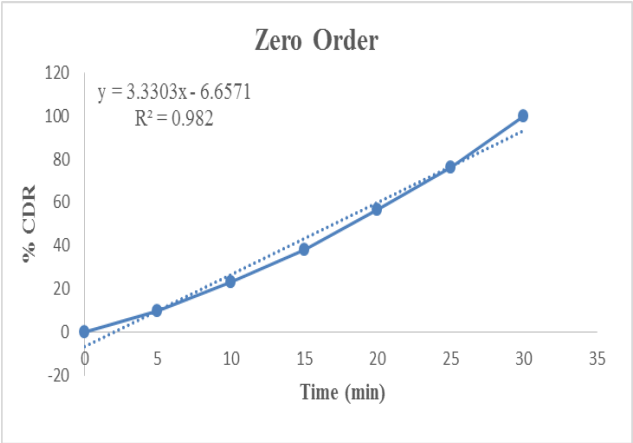

Fig. No. 05: Zero order drug release kinetics.

- **First order drug release kinetics**

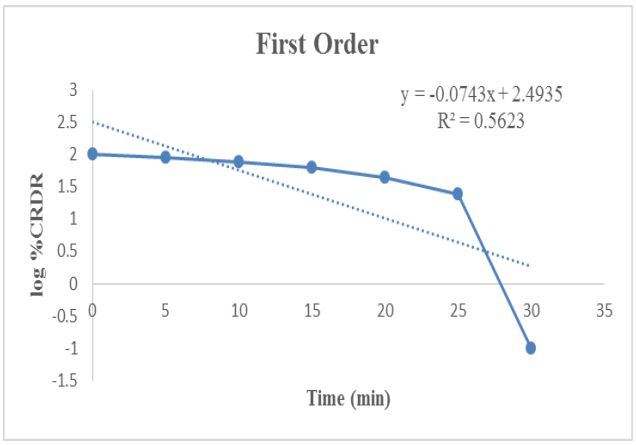

Fig. No. 06: First order drug release kinetics.

- **Higuchi's drug release kinetics**

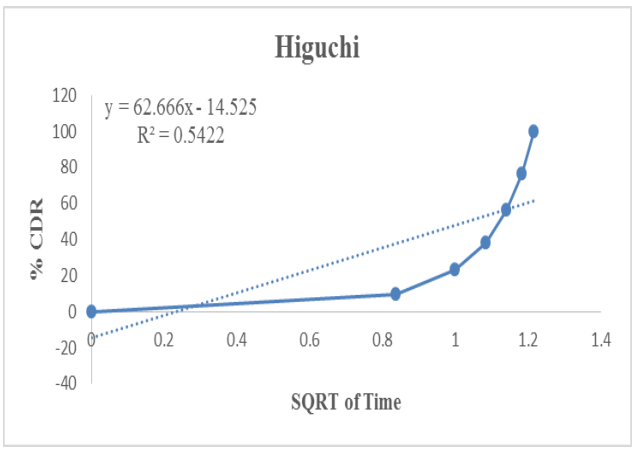

Fig. No. 07: Higuchi's drug release kinetics.

- **Korsmeyer-Peppa's drug release kinetics**

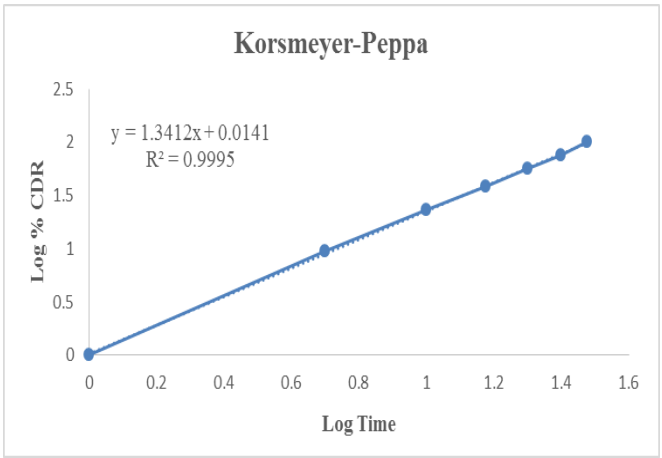

Fig. No. 08: Korsmeyer peppa's drug release kinetics.

➢ **Stability study**

Final optimized formulation F9 was subjected to aggravated conditions of temperature and relative humidity the tablets were kept in stability chamber, at 40 ± 20C temperature and 75 ± 5% RH for 3 months. After 3 months the tablets were tested for different evaluation parameters. The results of evaluation parameters shown in table no. 9.

Table No. 18: Stability study.

Evaluation Parameters	Observation			
	Initial	1 Month	2 Month	3 Month
Weight variation	262±0.50	262±0.45	261±0.25	260±0.25
Hardness (kg/cm^2)	3.2±0.05	3.2±0.1	3.1±0.05	3.0±0.1
Friability (%)	0.6±0.05	0.6±0.05	0.6±0.04	0.5±0.04
Disintegration time (sec)	30	30	29	29
Content Uniformity (%)	100.2±0.11	100±0.05	99.9±0.05	99.8±0.1
Dissolution study (%)	99.9	99.7	99.5	99.2

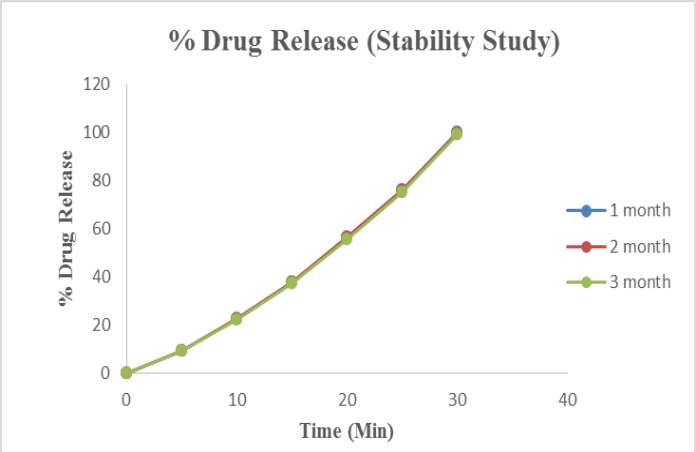

Fig. No. 09: Drug release after stability study.

CONCLISION

Since all the formulation procedure were simple, inexpensive and less time consuming because of the tablets were made by direct compression method. From the results obtained, following conclusion can be made; Preformulation parameters for identification of drug such as melting point, solubility determination and UV spectrum were evaluated. The results found to be satisfactory and all the values obtained comply within pharmacopeial limits. FTIR Spectrum of drug was carried out. In that all the characteristic's peaks of Nevirapine were present at their respective wavelength. Melt sono crystalized nevirapine were prepared and

evaluated for preformulation studies. Compatibility studies were performed using FTIR, and there is no interactions were found between drug and excipients. Fast-disintegrating tablet of Nevirapine were prepared by direct compression method using different concentration of superdisintegrant. The prepared fast-disintegrating tablet of Nevirapine were evaluated for hardness, thickness, weight variation, friability, disintegration time, wetting time and In-vitro release study and the results found to be satisfactory. Batch no F9 were selected as optimized formulation and it was subjected to kinetic study and it was appeared to occur in the pattern case II transport. Optimized formulation was then subjected to stability studies for 3 months with at specific temperature and relative humidity.

From the above studies it is concluded that fast-disintegrating tablet of Nevirapine can be formulated by using melt sonocrystallization technique by using various superdisintegrant, which not only increases the solubility but also increases the oral bioavailability of Nevirapine.

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