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FORMULATION, EVALUATION AND SOLUBILITY ENHANCEMENT OF NEVIRAPINE BY LIQUISOLID TECHNIQUE

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ABSTRACT

The aim of the research is to develop Nevirapine tablets by direct compression method by improving solubility using liquidsolid technique. Nevirapine is anti-viral drug, which is used in the prevention and treatment of HIV infections. It belongs to BCS class II drug 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 the liquidsolid compacts of Nevirapine were prepared using non volatile solvents like PEG 600 and Tween 8. The drug was dissolved in PEG 600 and Tween 80 for preparing liquid medicaments which is subsequently mixed with carrier and coating material to make free flowing compressible powder then the immediate release tablets were prepared by these liquisolid compacts using different ratios of carrier and coating material. Pre-formulation studies regarding the drug-carrier interaction was carried out by Fourier transform infrared spectroscopy and differential scanning calorimetry. Nevirapine liquisolid compact were evaluated for bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose. And the formed immediate release tablets of Nevirapine were evaluated for hardness, thickness, friability, drug uniformity, disintegration time, drug content estimation and in vitro dissolution studies. The results shown are increased solubility, increased in cumulative drug release up to 99.6%. The batch F8 was selected as optimised batch and further studies like stability studies and kinetic study.

KEYWORDS: Mg-microgram, ml-millilitres, LC- liquisolid compact.

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. Owing to its potential advantages including well established delivery system, patient friendly, convenient, cost effective, and non-invasiveness, it has been the most favored drug delivery system in the pharmaceutical field. Therapeutic efficiency of a drug is dependent on the bioavailability and eventually upon the solubility and absorption of drug molecules. 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. Therefore, a drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption. Various approaches as salt formation, solid dispersion, complexation, size reduction ,liquisolid technique have been applied to improve poor dissolution rate. The liquidsolid technique is to turn liquid in to free flowing powder apparently dry and compressible. It is one of the novel techniques which increases solubility and hence increases dissolution rate and hence increases bioavailability of poorly soluble drugs. It is first described by Spires. It is also called as "Powdered Solution Technology". During this process poorly soluble drug is mixed with non volatile solvent. This mixture is then incorporated in the suitable carrier material. Then this carrier particle having mixture of drug and solvent is saturated with former non-volatile solvent. After this saturation now the external layer is liquid. This is then coated with suitable coating material. Due to this now the external layer on particle is solid layer which gives dry, free flowing, non adherent, readily compressible powder. Such away liquid drug or drug suspension or solutions of poorly soluble drugs get transformed in to dry, non adherent, freely flowing, readily compressible powdered form.

1. MATERIALS AND METHODS

1) Materials

Nevirapine was obtained from Yarrow chem products Mumbai. Aerosil 200 was obtained from Research Lab fine chem Ltd. Mumbai. Tween 80, PEG 600, Magnesium Stearate were obtained from Thermosil fine chem industries. Charholi. Avicel ph 102 was obtained from Research Lab fine chem Ltd. Mumbai.

2) Method

- Solubility profile

Solubility analysis was done to select a suitable solvent system to dissolve the drug and to test its solubility in the dissolution medium, to select the solvent that was to be used in further work. Solubility of Nevirapine was checked in different solvents like methanol, phosphate buffer 6.8, 0.1N HCL, PEG 600, water.

- 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 amount of 10mg of Nevirapine pure drug was taken in 10ml of volumetric flask and is dissolved with small portion of methanol and made up to the volume with water to form 1000 PPM. 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 100PPM. Pipette out 0.5, 1, 1.5, 2, 2.5,3,3.5,4ml from working standard and transfer to separate 10ml volumetric flasks and make up the final volume to 10ml with water to yield 5,10,15,20,25,30,35,40µg/ml solutions respectively. The absorbance of the above solutions were measured at the wavelength of 282nm.

- Preparation of Nevirapine liquisolid Tablet:

The formulation optimization was done by central composite using design expert software as shown in table no. 1. The required quantity of the drug and non-volatile solvent and co-solvent were added in 20 ml glass beaker and heated gradually until all the drug was dissolved.The resultant warm liquid medication was incorporated into the amount of carrier and coating materials as given in table no. 5, in three steps.In the first step, the carrier and liquid medicaments were blended at an estimated mixing rate of one rotation per second for nearly one minute in order to have a uniform distribution of the liquid medication in the powder. Then coating material was added to remove moisture and make powder dry and flowable. In the second step, the liquid/powder mixture was evenly spread as a uniform layer on the surfaces of a mortar and left standing for approximately 5 min to allow the drug solution to get absorbed in the internal matrix of the powder material.In the third step, the powder is scraped off from the surface of mortar by using an aluminum spatula and then mixed with the other excipients for another 30 seconds in the same way as described in the first step.

Table 1: Formulation parameters.

Batch no.	Drug (mg)	Avicel ph 102 (mg)	Aerosol 200(mg)	PEG 600(mg)	Tween 80(mg)	Mg.stearate (mg)
F1	20	220	12	70	53	6
F2	20	220	12	60	53	6
F3	20	220	16	70	53	6
F4	20	220	16	60	53	6
F5	20	235	14	65	53	6
F6	20	235	17.3	65	53	6
F7	20	235	14	73.4	53	6
F8	20	250	10.6	65	53	6
F9	20	250	12	70	53	6
F10	20	250	12	60	53	6
F11	20	250	16	60	53	6
F12	20	250	16	70	53	6
F13	20	260	14	65	53	6

- **The Angle Of Repose**

Angle of repose was determined by using fixed funnel method. The fixed funnel method employ 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.

- Determination of bulk density and tapped density:

An accurately weighed quantity of the powder (W), was carefully poured into the graduated cylinder and the volume (Vo) was measured, then the graduated cylinder was closed with lid, set into the density determination apparatus. The density apparatus was set for 500 taps and after that, the volume (Vf) was measured and continued operation till the two consecutive readings were equal.

The bulk density and tapped density were calculated using the following formula:
Bulk density = W / V_o
Tapped density = W / V_f
Where,
W = weight of the powder
V_o = initial volume
V_f = final volume

- 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 index. It is indirectly related to the relative flow rate.

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

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

Where,
TD – Tapped density
BD – Bulk density

- 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 Nevirapine tablet

Tablets were prepared by using Direct Compression methodas summarized in Table No 1.The final mixture of liquisolid compact was compressed into tablets using multistation rotary tablet punching machine. The compression force was adjusted depending on the weight of tablet and ingredients in the formulation.25 tablets were prepared in a batch for each formulation.

- Weight Uniformity

In practice 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 differs by more than 2 times the percentage limit.

$$Deviation(\%) = \frac{\text{weight of each tablet} - \text{average weight of tablets}}{\text{average weight of tablet}} x\ 100$$

- Hardness

Hardness generally measures the tablet crushing strength**.** The crushing strength of the tablets were measured using a Monsanto hardness tester. Three tablets from each formulation batch were tested randomly and the average reading noted.

- Disintegration Time

Disintegration test was performed without disc in water at 37 ± 0.5^0C temperature using USP Disintegration apparatus. Randomly six tablets were selected from each batch. One tablet was placed in each tube and the basket rack was positioned in a 1-L beaker of simulated gastric fluid. The average disintegration time and standard deviation were calculated.

- Friability test

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.

$$\%\ Friability = \frac{W1 - W2}{W1} X\ 100$$

where,
W1= Weight of tablet before test
W2 = Weight of tablet after test

- Content Uniformity

Tablets were crushed and the amount equivalent to 20 mg of Nevirapine was weighed accurately and dissolved in 100 ml of phosphate buffer pH 6.8 in a volumetric flask. The solution is filtered, diluted suitably with same solvent and drug content is analyzed at 282 nm by UV-spectrophotometer.

- Dissolution Studies

In vitro dissolution of Nevirapine tablets were performed using USP 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±0.5^0C throughout the experiment. Samples from the dissolution medium (5ml) were withdrawn by means pipette 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.

2. RESULTS AND DISCUSSION

Solubility profile

Table 2: Solubility profile.

Sr no.	Solvent	Solubility(mg/ml)
1	Distill water	0.095
2	Phosphate buffer 6.8	0.055
3	0.1N HCL	2.22
4	PEG 600	14
5	PEG600 +TWEEN 80	350

1) Melting point determination

Melting point of drug sample was determined by capillary

Method and found to be 246-248 ^{0}C.

2) Compatibility studies between Nevirapine and polymers

FT-IR of drug and excipients blend shows bands at 3334.92 (cm^{-1}), 1645.28 (cm^{-1}), 1736.23 (cm^{-1}), 3089.96 (cm^{-1}), of N-H, C=C, C=O, C-H, which are in the range of pure drug band ranges. The FT-IR spectra of drug and excipients blend reveal no interaction. (fig 1, fig 2) and the interpretation is shown in table no.12. 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.

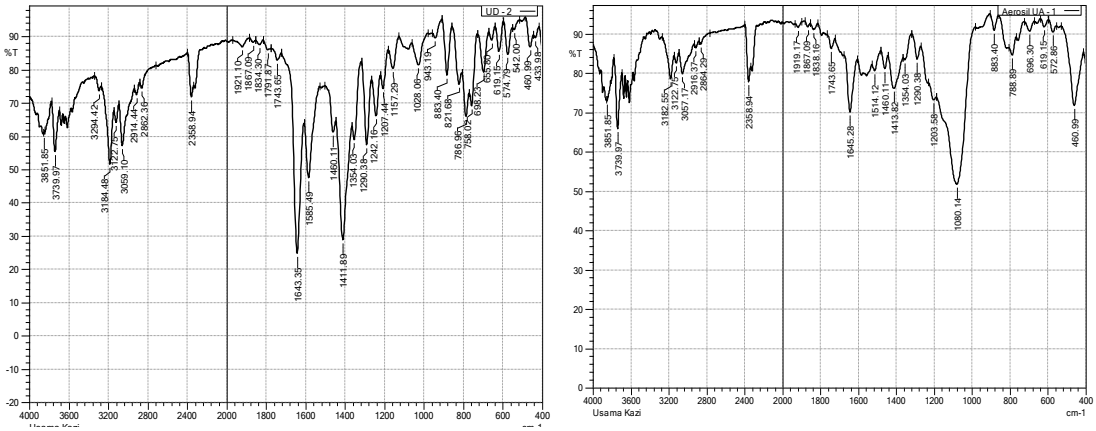


fig no. 1 FTIR of Nevirapine fig no 2 FTIR of blend

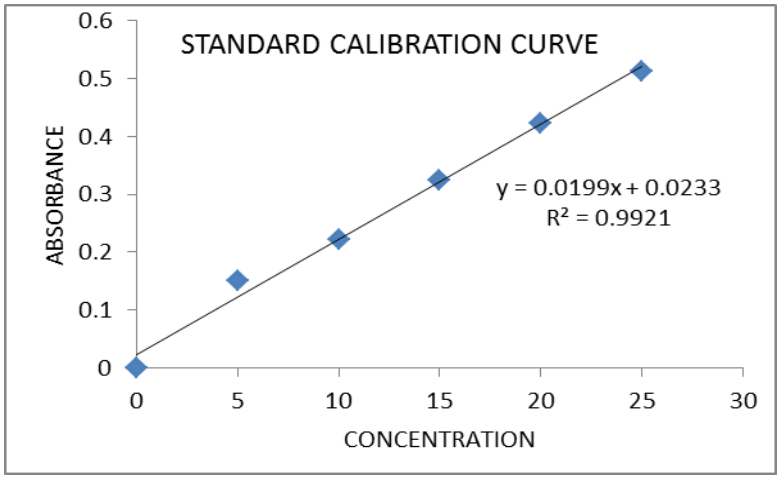
Table 3: Interpretation of IR Spectra of Blend and Nevirapine.

Functional Group	Observed Peak (cm^{-1}) Blend	Observed Peak (cm^{-1}) Nevirapine
N-H Stretching	3334.92 (cm^{-1})	3334.92 (cm^{-1})
C=C Stretching	1645.28 (cm^{-1})	1645.28 (cm^{-1})
C=O Stretching	1736.23 (cm^{-1})	1736.23 (cm^{-1})
C-H Stretching	3089.96 (cm^{-1})	3089.96 (cm^{-1})

3) **Calibration curve of Nevirapine:'**

Table 4: calibration curve of Nevirapine

Sr no.	Concentration (µgm/ml)	Absorbance (nm)
1	5	0.150
2	10	0.222
3	15	0.325
4	20	0.422
5	25	0.512



4) Angle of repose

The angles of repose of all the formulaion were found from 25 to 30^0. Hence they all comply pharmacopoeial standard.Except Batch no F7 which had highest angle of repose 33.26° because it contain highest amount of non volatile solvents.

5) Bulk Density and Tapped Density

The bulk density of all the batches of Nevirapine were found from 0.51g/cm^3 to 0.69/cm^3 and the tapped density of the entire powder blend batch was found from 0.57g/cm^3 to 0.79g/cm^3 which have been used for further calculation of carr's index and Hausner's ratio.

6) Carr's Index

The measurement of free flowing powder can also be done by Carr's index. The Carr's indexes of all the formulation batches were found to be 11.22-16 %. Exceptbatch no. F7 which have higher Carr's index of 22.36 %, because it contain highest amount of non volatile solvents which increases difference between tapped density and bulk density. which make formulation less flowable.

7) Hausner Ratio

The Hausner ratio of drug and Excipients was done as per procedure. The hausner's ratio of the of formulations were found in from 1.11 to 1.28. The batch no. F7 have higher hausner's ratio which reveals that the blend is poorly flowing. Because of this the batch no. F7 was rejected from further study.

Table 5: Results of Preformulation studies.

Batch No.	Bulk Density (g/cm^3)	Tapped density (g/cm^3)	Carr's Index (%)	Angle of Repose (θ)	Hausner Ratio
F1	0.52	0.62	16	29.28	1.19
F2	0.64	0.73	12.3	26.39	1.14
F3	0.58	0.69	15.9	26.61	1.18
F4	0.51	0.57	10.52	27.28	1.11
F5	0.69	0.79	12.65	25.61	1.14
F6	0.54	0.60	10	28.21	1.11
F7	0.59	0.76	22.36	33.26	1.28
F8	0.51	0.60	15.06	22.12	1.17
F9	0.56	0.65	13.84	27.21	1.16
F10	0.62	0.70	11.42	28.53	1.12
F11	0.59	0.68	13.23	26.32	1.15
F12	0.62	0.73	15.03	25.56	1.17
F13	0.63	0.71	11.26	28.61	1.12
F14	0.56	0.65	13.85	29.16	1.16

8) Weight uniformity

The average percentage deviation of all tablet formulations were found to be within the limit, except batch no. F6 which have values above the limits because it contains higher amount of aerosil acting as adsorbent and glidant due to that powder comes out of die during tablet punching. Remaining batches passed the test for uniformity of weight as per official requirements.

9) Hardness test

Results showed Hardness in between 3.1- 4.2 Kg/cm^2. Batches F6, F9 and F14 failed hardness test and showed very low hardness.

Batch F6 contain large amount of aerosil and Batch F9 and F14 contain large amount non volatile solvent, due to this they didn't showed considerable hardness.

10) Disintegration time

All prepared batches showed good disintegration. Disintegration time were found less than 3 min. Batch no F9 had disintegration time of 1.52 min, it was because of PEG 600 which was acted as disintegrant.

11) Friability test

All the batches were found less than 1% which is within limit as shown in table no 14.except the batch no. F6, F9 and F14 which have friability more than 1%. Because they don't had sufficient hardness.

12) Content uniformity

Nevirapine tablets were tested for their drug content and all the formulation showed drug content 70.2 to 99.2%, shown in table no 14. batch no. F6, F9, F14 were rejected for dissolution study because they failed many of evaluations tests. Batch F8 have higher drug content.

Table 14: Evaluation of Nevirapine formulations.

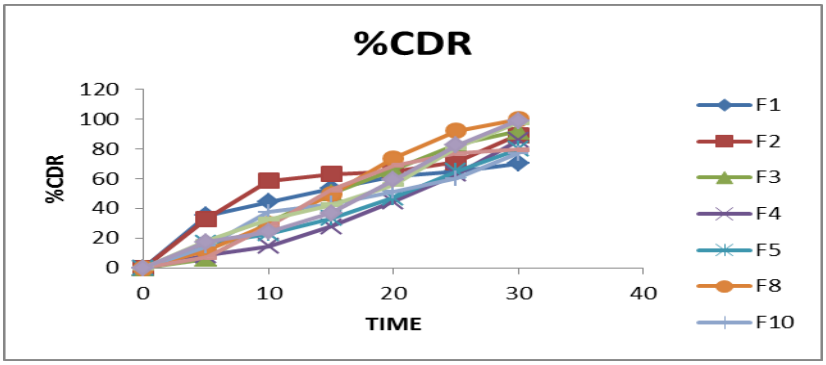
Batch No.	Hardness (kg/cm2)	Friability (%)	Weight variation Test (%) ±S.D	Uniformity of Drug Content (%) ± S.D	Thickness of Tablets (mm)	Disintegration Time (min) ± S.D
F1	3.5	0.58	415.3±15	78.5±0.25	3.9	3.50
F2	3.4	0.56	405.9±0.32	86.5±0.36	3.8	2.09
F3	3.9	0.21	419.4±0.28	95.8±0.55	3.9	3.20
F4	2.6	0.30	409.2±0.45	89.6±0.28	3.8	3.10
F5	3.3	0.20	425.2±0.53	92.4±0.62	4	3.37
F6	1.2	11.6	430.2±2.8	68.2 ±0.35	4	2.05
F8	3.2	0.39	428.9 ±0.48	100.6±0.58	4	3.08
F9	1.1	20	423.8±1.5	70.9±0.98	4	1.52
F10	3.6	0.83	446.6±0.61	82.6±0.57	4.2	3.27
F11	4	0.71	434.3±0.51	92.4±0.29	4.1	2.40
F12	4.2	0.20	437.3±0.28	96.3±0.64	4.1	3.22
F13	4.1	0.52	450±0.42	98.5±0.42	4.2	2.48
F14	0.9	22	451.4±0.56	75.2±0.75	4.2	2.56

13) Dissolution studies

Cumulative percent drug released from the batches were shown in the table no. 15. Batch no. F6, F9 and F14 were rejected because they have low drug content and did not comply all the above evaluation parameters. Batch no 8 was selected as optimized batch because It have highest drug release of 99.6.

Table 15: Cumulative percent drug release of Nevirapine.

Time in min	F1	F2	F3	F4	F5	F8	F10	F11	F12	F13
0	0	0	0	0	0	0	0	0	0	0
5	35.1	32.85	5.94	8.1	16.38	11.52	14.4	7.02	17.82	17.28
10	44.1	58.59	30.42	14.4	22.68	29.43	37.26	27.99	32.4	24.12
15	53.1	63	49.86	27.54	33.3	49.41	43.02	52.29	42.12	36.72
20	61.2	64.44	66.33	44.55	46.98	73.62	51.3	68.76	55.71	59.13
25	64.8	71.19	82.89	63	64.89	92.07	60.03	77.04	80.91	82.44
30	70.2	89.19	91.62	85.77	79.74	99.6	77.04	79.47	97.47	98.91



3. CONCLUSION

Since all the formulation procedure were simple, inexpensive and less time consuming and from the results obtained, following conclusion can be made; Preformulation parameters such as melting point, solubility determination and evaluated. The results found to be satisfactory and all the values obtained comply within pharmacopoeial limits. FTIR Spectrum of drug was carried out. In that all the characteristic's peaks of Nevirapine was present at their respective wavelength.Liquidsolid compact of Nevirapine were prepared for 14 batches and evaluated for preformulation studies, Compatability studies were performed using FTIR and DSC, and there is no interactions were found between drug and Excepients. Immediate release tablets of liquidsolid compact of Nevirapine were prepared by direct compression method without superdisintegrant. The immediate release tablet of Nevirapine liquisolid compact were evaluated for hardness, thickness, weight variation, friability, In-vitro release study. And results found to be satisfactory. From above studies it is concluded that in future solid immediate release tablet of Nevirapine can be formulated by using liquisolid technique without superdisintegrant with different polymers, which not only increases the solubility but also increases the oral bioavailability of Nevirapine.

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