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Research Article

Formulation and Enhancement of *In vitro* Dissolution Rate of Nevirapine as Immediate Release Tablets

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ABSTRACT

The present investigation involves formulation and assessment of Nevirapine immediate release tablets with a view to release the drug immediately to maintain the consistency into the plasma. Nevirapine is an anti -HIV drug belongs to BCS class-II in order to increase the solubility and dissolution rate of Nevirapine, the solid dispersion technique was employed by using the carriers like HPMC, Xanthan gum, Starch and sodium starch glycollate at different concentrations. Solid dispersions were prepared by solvent evaporation and surface adsorption method. The prepared solid dispersions were blended with microcrystalline cellulose, Cross carmellose sodium, Magnesium stearate and talc, then compressed into tablets. The formulated tablets complied for all official tests for the tablets. *In vitro* dissolution studies were carried out for all formulations using 0.1N HCl for 45 minutes at 37±0.5 °C. In vitro dissolution studies showed that F9 formulation containing sodium starch glycollate (1%) showed improved dissolution rate of 99.05% of drug release within 45 minutes compared to pure drug.

Keywords: Nevirapine; Sodium starch glycollate; Solid dispersions; Solvent evaporation; Surface adsorption.

INTRODUCTION

Oral route of administration is the most frequent and chosen route of delivery due to expediency and ease of intake. From a patient's scene, swallowing a dosage form is a easy for taking medication. As a result, patient fulfillment is more proficient with orally administered medications as compared to other routes of administration, for example, parenteral route (Dharna Allawadi, Neelam Singh *et al* 2013). Even though the oral route of administration is preferred, in case of many drugs it can be a challenging and ineffective form of delivery for a number of reasons. Inadequate drug absorption follow-on to poor bioavailability is amid the potential problems that can be defeat while delivering an active agent via the oral route (Sameer Singh *et al* 2011).

After administering a drug orally, it initially dissolves in gastric media and then diffused to the GI tract membrane and reach systemic circulation. Consequently, a drug with poor aqueous solubility will characteristically show dissolution rate limited absorption, and a drug which are having poor membrane permeability will normally exhibit permeation rate limited absorption. Thus, pharmaceutical researches that focus on the oral bioavailability of drugs include (Ahire B. R *et al*, 2010)

- Improving solubility and dissolution rate of poorly water-soluble drugs
- Improving permeability of poorly permeable drugs.

Solid dispersions

Solid dispersion technology is the science in which one or more drugs are dispersed in an inert matrix in the solid stage in order to obtain increased dissolution rate, sustained release of drugs, altered solid state properties, enhanced drug release from ointment and suppository bases, and improved solubility and stability (Patil RM, et al, 2011).

Selection of a carrier

A carrier should have the fallowing characteristics

- Carrier should be freely water-soluble.
- They are non-toxic and pharmacologically inert.
- They should be thermo stable and it should have fewer melting points.
- It should be soluble in all of solvents and easily evaporate in solvent evaporation for the solvent method.
- Mainly it should increase the aqueous solubility of the drug.

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- It should be chemically compatible with the drugs.

Generally used carrires for solid dispersions are cellulose derivatives like HPMC, Methylcellulose, Hydroxypropylcellulose, Cyclodextrins and Surface active self-emulsifying carriers like Poloxamer 408, Tween 80, Gelucire 44/141.

Selection of Solvents

Solvents used for the solid dispersion should have following characteristics

- Both drug and carrier must be dissolved in the solvent.
- Ethanol can be used as a solvent, as it is less toxic.
- Water based systems are preferred.
- Surfactants are used as carrier and they can reduce glass transition temperature, so care should be taken in to account (Dau K and Sharma VK, 2009), (Chiou WL and Riegelman S, 1971).

Solid dispersions can be prepared by following methods Fusion method, Solvent evaporation method, Supercritical fluid methods, Co-precipitation method, Melt agglomeration method, Hot Melt Extrusion method, Spray-drying, Freeze-drying and Surface Solid Dispersion Technology (Cilurzo F, *et al*, 2002)(Geetha Rao CG *et al,*.2010).

The drug Nevirapine, non-nucleoside reverse transcriptase inhibitors used to treat AIDS. Nevirapine is BCS classes II drug (low solubility and high permeability) so there is a necessity enhance the solubility of the drug. The solubility was enhanced by preparing the drug into solid dispersion. Solid dispersion prepared by solvent evaporation and surface adsorption methods and they were compared with the pure drug's solubility (Sekiguchi K and Obi N, 1961).

MATERIALS AND METHODS

Materials used

Raw materials supplied by Nevirapine procured from Micro labs Pvt Ltd. HPMCE5LV obtained Molychem Xanthan gum and Starch were procured MERK pvt Ltd. Sodium starch glycolate taken as gift sample from NR Chem. Micro crystalline cellulose and Cross coramellose sodium were obtained from Yellow chem. Magnesium stearate and Talc were procured from SD fine chem Ltd.

Methods

Preformulation studies

Standard calibration curve for Nevirapine at 313nm in 0.1N HCl by Labindia (UV-2201) UV visible spectrophotometer Standard calibration curve of Nevirapine was obtained by plotting absorbance vs concentration. From the stock solution, appropriate aliquots were pipetted into different volumetric flasks and volumes were made up to 10ml with 0.1N HCl, so as to get drug concentration of 2,4,6,8,10µg/ml. the curve is found to linear in the beers range between 10-100mcg/ml at 313nm. The absorbance of standard concentrations were shown in table 1 and the calibration curve was shown in figure 1.

Drug compatibility studies

Compatibility studies were carried out by mixing definite properties of drug and excipient and kept in glass vials, which are stored at temperature conditions like 55^{oC} (2weeks). The samples were withdrawn at periodic intervals and given to analytical development for analysis of following parameters (Singh MC, *et al*, 2010).

FT-IR studies

FT-IR spectra of IR spectrum of pure Nevirapine, HPMC, sodium alginate, xanthan gum and combination were recorded. The instrument was operated under dry air purge and the scans were collected at scanning speeds 2mm/sec with resolution of $4cm^{-1}$ over the region 4000-400cm^{-1}. The scans were identified in the presence of principal peaks of drug, shifting and masking of peaks due to presence of excipients.

Formulation and evaluation of Nevirapine solid dispersions

The solid dispersions of Nevirapine were prepared by three polymers with the different concentrations. The solid dispersions are prepared by surface adsorption method and solvent evaporation method (Leuner C and Dressman J, 2000). The combination of the polymers used to prepare solid dispersion and formulation chart were shown in table 2 and 3.

Solvent evaporation method

- The drug and carrier weighed accurately.
- The drug and carrier were dissolved chloroform which is evaporated at low temperature.
- After evaporation of the solvent the resulted film is dried under hot air oven. The mixture was passed through the sieve no 18.
- This prepared Nevirapine solid dispersions were compressed into tablet dosage form by using 10 station rotary tablet press.
- To this solid dispersions add the required amount of excipients by mixing diluents, distergrant, glidant and lubricant and compress them into tablets by using a single rotary tablet press (Tiwari R, Tiwari G, *et al*, 2009).

Surface adsorption method

- The drug and carrier weighed accurately.
- The carrier was dissolved in methanol (15ml).
- Then the drug was dissolved for the above mixture.

- The entire mixture was kept under the electronic stirrer at room temperature.
- This process is continued until the solvent is evaporated.
- The prepared mixture was dried in hot air oven. The mixture was sieved through sieve no: 18.
- This prepared Nevirapine solid dispersions were compressed into tablet dosage form by using 10 station rotary tablet press.
- To this solid dispersions add the required amount of excipients by mixing diluents, distergrant, glidant and lubricant and compress them into tablets by using a single rotary tablet press (Patidar K, *et al*, 2011).

EVALUATION STUDIES

Pre compression studies

The pre compression parameters like Angle of repose, bulk density, tapped density, carr's index, hausner's ratio were evaluated according to the standard procedures.

Post compression studies of the prepared formulations

Weight variation

Randomly twenty tablets be taken and for this twenty tablets weigh up individually in weighing balance and take the total average of the twenty tablets.

Friability

Friability test is done by use of Roche friabilator. According to the specifications randomly the tablets are taken as well as note the initial weight of the tablets and place in the drum. The drum is rotates at 25rpm for 5mins. After completing the rotation of the drum remove the tablets from drum and dedust them as well as note the final weight. Then calculate the total percentage of the tablets by applying the friability formula (T. Jyothibasu *et al*, 2011) (Rajesh Kaza, Y *et al*, 2013).

Hardness

Get arbitrarily tablets in each formulation and this be tested with using hardness tester. The break of the tablet on definite point with applying the pressure on it Average value is eminent in Kilogram per centimeter.

Disintegration test

The test is done from disintegration apparatus. Inside the tubes the tablets were placed as well as the discs are placed over the tablets. The test is runned intended time as the tablets were disintegrates entirely along with the time and the estimated be record (Ushesh S. Ingle *et al*, 2011).

***In vitro* dissolution test**

The dissolution test is done by using USP dissolution test type II apparatus. The paddles were setted in 900ml of 0.1N HCl were used as dissolution medium. The rpm of paddle was set at 50 and temperature was maintained at $37^{\circ C} \pm 0.5^{\circ C}$ temperature 5ml of the aliquots were withdrawn at regular time interval of 5, 10, 15, 25, 35 and 45minutes and 5ml of the medium was replaced for every sample is withdrawn. The samples were diluted with the dissolution medium and analyze them in UV spectrophotometer at 313nm. The percent drug release was calculated.

RESULTS AND DISSCUSSION

Preformulation studies

Drug compatibility studies

The drug excipient interaction study was carried out using FTIR studies. The spectral data obtained showed that all the excipients are compatible with Nevirapine used in the formulation and no physical and chemical interaction with the active ingredient was observed. The FTIR spectrums were shown in figure 2 and 3 and they were interpreted in table 4.

Pre compression parameters

Angle of repose was carried out funnel method. Based on the angle of repose it was observed that formulations form F6 to F9 showed excellent flow property, while other showed good flow property.

Bulk density of all formulations from F1 to F9 was in the range of 0.503±0.005 to 0.551±0.01 g/cc.

Tapped density of all the formulations varied from F1 to F9 was in the range of 0.580 ± 0.01 to 0.67±0.05g/cc. The results of tapped density of all formulations were found that within the limits.

Carr's index of all the formulations varied from F1 to F9 was in the range of 13 ± 0.01 to 16.16±0.05. The results of tapped density of all formulations were found that within the limits. The results of carr's index of all formulations were represented in the table no 17.

Hausner's ratio of all the formulations varied from F1 to F9 was in the range of 1.02±0.02 to 1.16±0.03. The results of hausner's ratio of all formulations were found that within the limits. All the results were tabulated in table 5.

Post compression parameters

The percentage weight variations for all formulations were found to be within the limit.

The formulations showed hardness in the range of 3.40±0.01 to 3.65±0.03 Kg/cm^2. The results of all formulations were represented in the table no 21.

Table 1: Standard calibration curve for Nevirapine

S. no	Concentration (µg/ml)	Absorbance (at 313nm)
1	0	0.00
2	2	0.215
3	4	0.400
4	6	0.642
5	8	0.854
6	10	0.988

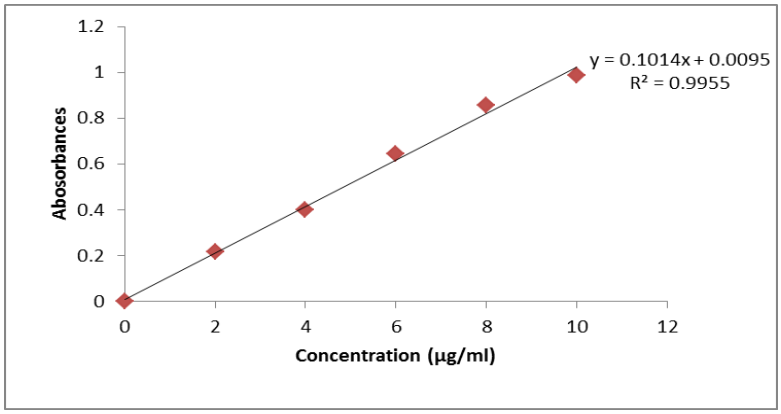

Figure 1: Standard calibration curve for Nevirapine

Table 2: Formulation of solid dispersions of Nevirapine

Formulation code	Drug	Carrier	Drug: carrier	
F1	Nevirapine	--	--	--
F2	Nevirapine	HPMC	1:0.5	Solvent evaporation method
F3	Nevirapine	HPMC	1:1	
F4	Nevirapine	Xanthan gum	1:0.5	
F5	Nevirapine	Xanthan gum	1:1	
F6	Nevirapine	Starch anhydrous	1:0.5	Surface adsorption method
F7	Nevirapine	Starch anhydrous	1:1	
F8	Nevirapine	Sodium starch glycolate	1:0.5	
F9	Nevirapine	Sodium starch glycolate	1:1	

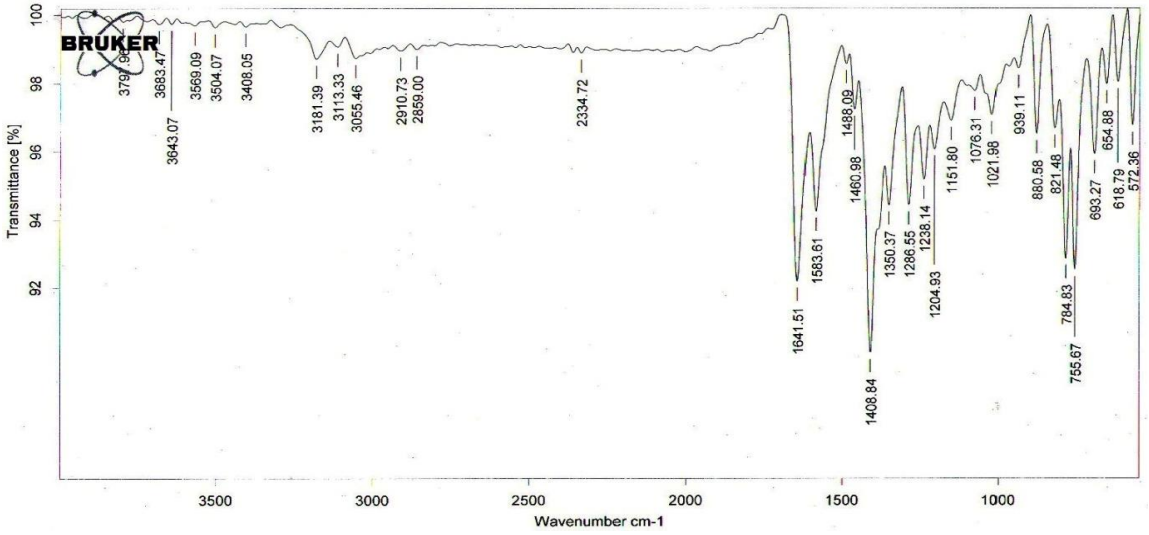

Figure 2: FTIR spectra of drug Nevirapine

Friability of all formulations varied from F1 to F9 which were in the range of 0.43 to 0.65% and all formulations possesses good mechanical strength

All the formulations have different disintegration time profiles that confirms within 5mins. All the results of post compression parameters were shown in table 6.

Table 3: Formulation of Nevirapine immediate release tablets

Ingredients		Solvent evaporation method (All the weight are in mg)				Surface adsorption method (All the weight are in mg)			
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	200	--	--	--	--	--	--	--	--
Drug+HPMC	--	300	400	--	--	--	--	--	--
Drug+xantham gum	--	--	--	300	400	--	--	--	--
Drug+starch	--	--	--	--	--	300	400	--	--
Drug+SSG	--	--	--	--	--	--	--	300	400
Micro crystalline cellulose	209	159	59	159	59	159	59	159	59
Cross carmellose sodium	36	36	36	36	36	36	36	36	36
Mg. stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total tablet weight	500	500	500	500	500	500	500	500	500

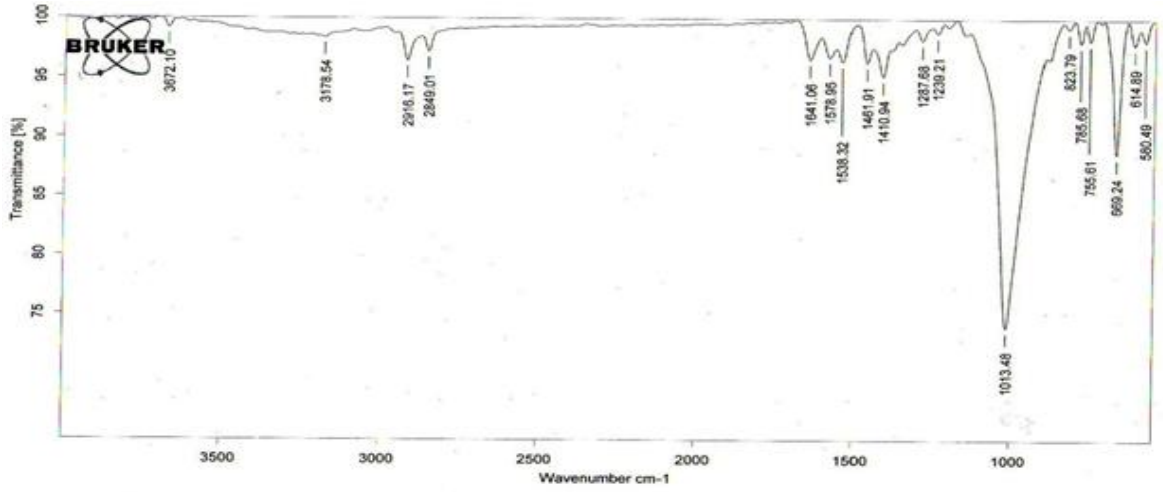

Figure 3: FTIR spectra of drug Nevirapine and all excipients

Table 4: Characteristic peaks of Nevirapine

Sl. No	Type of bond	Actual frequency (cm^{-1})	Observed frequency (cm^{-1})	Observed frequency (cm^{-1})	Confirmation
1	C=N	1630 to 1690	1583	1583	Amide
2	C-H	3100 to 3500	3181	3178	Aromatic
3	C=C	1450 to 1600	1410	1408	Aromatic
4	N-H	1650 TO 1700	1641	1641	1^0 Amine

Table 5: Results of pre compression parameters

Formulation code	Angle of repose Avg±SD (n=3)	Bulk density Avg ± SD (n=3)	Tapped density Avg ± SD (n=3)	Carr's index Avg ± SD (n=3)	Hausner's ratio Avg ± SD (n=3)
F1	23.61±2.25	0.503±0.01	0.60±0.00	16.16±0.12	1.15±0.01
F2	20.7±1.25	0.521±0.03	0.62±0.02	15.96±0.25	1.1±0.02
F3	21.6±1.60	0.513±0.01	0.586±0.04	13±0.12	1.12±0.03
F4	20.51±0.21	0.551±0.02	0.626±0.02	12.45±0.1	1.15±0.02
F5	22.14±1.65	0.551±0.02	0.586±0.02	13.65±0.35	1.02±0.02
F6	20.54±1.03	0.506±0.01	0.613±0.01	14.56±0.14	1.16±0.03
F7	19.02±1.04	0.521±0.03	0.626±0.02	15.12±0.21	1.15±0.01
F8	19.54±0.23	0.533±0.02	0.601±0.01	13.20±0.32	1.10±0.01
F9	19.12±0.22	0.513±0.01	0.613±0.02	12.0±0.11	1.11±0.01

***In vitro* dissolution study**

In-Vitro dissolution studies of the prepared immediate release tablets of Nevirapine were found that theF1 formulation was found to be released slowly due to its low solubility character (BCS class-II). From F2 to F5 the drug release was found to be increased gradually on increasing the carrier by solvent evaporation method. From the formulation F6 to F9 the drug release was

Table 6: Post compression parameters of all formulations

Formulation code	Weight variation(mg) Avg±SD (n=20)	Friability (%) Avg±SD (n=3)	Hardness (Kg/cm²) Avg±SD (n=3)	Disintegrating time (mins) Avg±SD (n=3)
F1	501±0.15	0.52±0.02	4.42±0.12	5.55±0.02
F2	507±0.03	0.60±0.03	4.40±0.1	3.27±0.23
F3	503±0.05	0.45±0.02	4.65±0.21	3.15±0.02
F4	506±0.04	0.65±0.02	4.55±0.07	4.05±0.07
F5	503±0.06	0.55±0.13	4.44±0.14	3.56±0.025
F6	501±0.05	0.43±0.11	4.47±0.13	3.32±0.11
F7	506±0.03	0.54±0.3	4.39±0.09	3.25±0.02
F8	507±0.04	0.60±0.05	4.40±0.11	3.15±0.01
F9	505±0.06	0.51±0.02	4.42±0.09	3.05±0.012

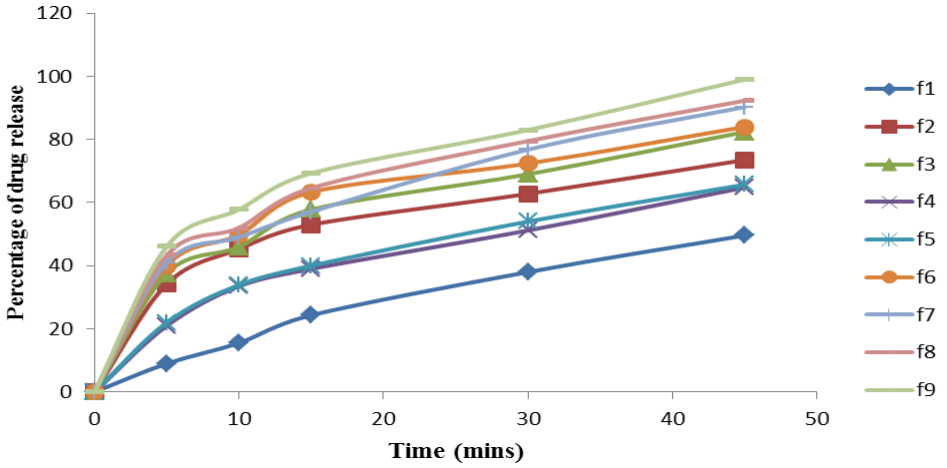

Figure 4: Cumulative percentage (%) drug release for all formulations

Table 7: Percentage drug release from F1-F9

Cumulative % drug release Avg ±SD (n=6)	Time in minutes				
	5	10	15	30	45
F1	9.05±0.31	15.35±0.29	24.24±0.56	38.85±0.71	49.65±0.01
F2	32.29±0.54	45.37±0.31	53.01±0.40	62.81±0.32	73.52±0.03
F3	37.50±0.05	46.01±0.03	57.8±0.06	69.05±0.04	82.49±0.07
F4	21.05±0.05	33.59±0.04	39.04±0.07	51.23 ±0.06	64.8±0.05
F5	22.01±0.06	33.90±0.04	40.81±0.06	54.04±0.03	65.70±0.05
F6	40.09±0.21	49.81±0.40	63.34±0.15	72.45±0.36	84.09±0.22
F7	41.05±0.05	49.05±0.07	57.18±0.03	76.81±0.02	90.35±0.04
F8	45.31±0.54	52.01±0.23	64.66±0.33	79.57±0.12	92.35±0.22
F9	46.15±0.05	57.81±0.06	69.32±0.04	83.09±0.05	99.05±0.03

extensively enhanced due to surface adsorption of the drug to the carrier starch and sodium starch glycollate. The drug release was enhanced gradually on increasing amount of carrier upto 1:1 ration of dug and carrier respectively. The percentages of drug release of all formulation were shown in table 7 and the dissolution profiles were shown in figure 4.

CONCLUSION

Form the present work formulations and In-Vitro evaluation of Nevirapine immediate release tablets. Drug-excipient compatibility studies were proved by FTIR. The solid dispersions of Nevirapine were prepared by surface adsorption method and solvent evaporation method. The prepared solid dispersions were compressed into tablets. The formulated tablets complied for all official and un-official tests for tablets. From the dissolution studies concluded that the solid dispersion technique is better choice for enhancement of dissolution rate by surface adsorption method and solvent evaporation method. From the dissolution studies concluded that the sodium starch glycolate was good carrier for enhancing the solubility of poorly water soluble drug of Nevirapine.

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