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ENHANCEMENT OF SOLUBILITY OF NEVIRAPINE BY USING HPMC BY SOLID DISPERSION METHOD

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ABSTRACT

Solid dispersion has attracted considerable interest as an efficient means of improving the dissolution rate and hence bioavailability of a range of hydrophobic drug. The present study was to enhance the solubility and dissolution rate of anti-HIV drug Nevirapine (NVP) by solvent evaporation method (SEM) and physical mixture (PM) by using polymer such as HPMC E5 LV in different ratios like 1:1, 1:2, 1:3, 1:4, 1:5, 1:6. The solid dispersion in solid state was determined by solubility studies. The interaction of Nevirapine with HPMC E5LV was studied by using Fourier transform infrared spectroscopy (FTIR). Standard calibration curve and in vitro dissolution study of NVP was performed in 0.1 N HCl. Based on the solubility study, polymer HPMC E5 LV with ratio 1:4 and 1:3 by using solvent evaporation method and physical mixture respectively were selected for solid dispersion. The study shows that solubility of Nevirapine was successfully enhanced by using hydrophilic polymer such as HPMC E5LV which also increased the bioavailability of Nevirapine.

Keywords: Nevirapine, solid dispersion, HPMC E5LV, solubility, bioavailability, etc.

INTRODUCTION

Oral route of the drug administration is the common route of delivery of dosage form due convenience and the ease of ingestion. From the patients prospective swallowing of a dosage form is comfortable and familiar means of taking the medication. As a result the treatment is more effective with oral administration of dosage form as compared to other route of drug administration. Limited drug absorption resulting in poor bioavailability is paramount of the entire potential problem that can be observed when delivering an dosage form via oral route[1]. The oral bioavailability of drug is depends on its solubility and the dissolution rate, therefore the major problem can be observed with these drug are its low solubility in biological fluids which result in poor bioavailability after oral administration, A drug with poor aqueous solubility is typically shows the dissolution rate limited absorption, and drug with the poor membrane permeability shows the permeation rate limited absorption. Therefore the researchers are focus on enhancing the solubility and the permeability of poorly water soluble drug.

It has been estimated that the 40% of new chemical entities shows the poor aqueous solubility and poor permeability and hence shows the poor bioavailability after administration via oral route[2]. Solid dispersion methods are particularly promising method for enhancing the solubility and dissolution rate of BCS class-II drugs[1].

Nevirapine is the drug belonging to BCS class-II having poor water solubility and dissolution rate and hence having poor bioavailability. The Nevirapine is a potent non-nucleoside reverse transcriptase inhibitor used in combination with nucleoside analogous for the treatment of HIV-1 infection. Chemically it is 11-cyclopropyl-4-methyl-5, 11- dihydro-6*H*- dipyrido [3,2-*b*:2′,3′-*e*] [1,4]diazepin-6-one[3].

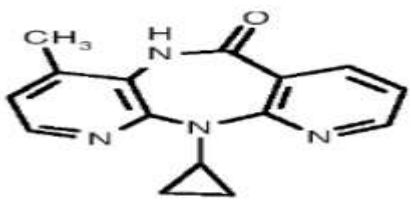

Figure 1: Chemical structure of Nevirapine

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 was having extensive first pass metabolism, and relative Elimination half-life of about 45 hrs. (extended-release) and associated with frequent dosing of conventional dosage form makes it suitable candidate for sustained release dosage form for patient compliance. The drugs with poor water solubility are challenging to develop the new dosage form. Solid dispersion method is able to enhance the solubility and dissolution rate of Nevirapine and enhancing the bioavailability ofNVP[3].
The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles[4]. Various carriers can be used for solid dispersion method which includes polyethylene glycol, poly vinyl pyrrolidone, urea, mannitol, poloxamer, cellulose derivatives etc. Solid dispersion can be prepared by various methods such as solvent evaporation method, fusion method and melt solvent method and novel methods used for preparation includes super critical fluid technology, Electrospinning, spray drying, Lyophilization and melt extrusion method, physical mixture method, kneading method[2].

The aim of present study is to enhance solubility of poorly water soluble drug by solid dispersion method. The main objective of the study is-

- To enhance solubility and dissolution of poorly water soluble drug using solid dispersion method, this is simple, feasible, cost effective and novel.
- To enhance absorption of drug.
- To enhance bioavailability of drug.
- Formulation of solid dispersion system with acceptable flow ability and compressibility.

MATERIALS

Nevirapine was received as a gift sample from cipla, Mumbai, HPMC E5LV were purchased from lova chemie, Mumbai, mannitol, starch, sodium starch glycolate purchased from Samar chem. Products, Nagpur, magnesium Sterate, talc, methanol, Hydrochloric acid purchased from yarrow chem. products, Nagpur.

METHODS

Preparation of physical mixture of Nevirapine and HPMC E5LV

The physical mixture of drug such as Nevirapine and polymer such as HPMC E5LV was prepared by simple mixing in different ratios such as 1:1 to 1:6 w/w. Simply drug and polymer in different ratios were taken in mortar. Than mixed these two ingredients with the help of mortar and pestle for 10 min. Then passes through the #40 meshes sieve and used for the further formulation.

Preparation of solid dispersion of Nevirapine:

Preparation of solid dispersion of Nevirapine by solvent evaporation method

The solid dispersion of Nevirapine and HPMC E5LV was prepared in different ratios such as 1:1 to 1:6 w/w for Nevirapine and HPMC E5LV by using solvent evaporation method. The polymer was added in the solution of methanol and water having 1:1 ratio. An appropriate amount of drug was added into a solution of polymer, methanol and water. The solution was stirred continuously until the solvent was evaporated and solid mass was formed. Then the solid mass was dried in hot air oven at 40^0C for 1 hr and, pulverized and sieved by using the #40 meshes sieve and used for the further formulation.

Evaluations of solid dispersion of Nevirapine:

Solubility study of solid dispersions containing Nevirapine[3]:

The solubility of Nevirapine, solid dispersion of Nevirapine and HPMC E5 LV by physical mixture, solid dispersion of Nevirapine with HPMC E5 LV by solvent evaporation method was determined in 0.1 N HCl. The solubility of pure drug, solid dispersion made by solvent evaporation method and physical mixture of Nevirapine and HPMC E5LV was determined by taking 100mg of solid dispersion and added them in 20 ml of 0.1 N HCl and then stirred this solution continuously by using magnetic stirrer until the solid dispersion solubilize in 0.1 N HCl. Then from that solution 1ml was taken out and diluted up to 100ml and analysed that solution by using UV-visible spectrophotometer at261nm.

Drug Excipients Interaction Study:

Drug excipients interaction study was done by using the Fourier transform infrared spectroscopy (FTIR) of optimised batches. Fourier transform infrared spectroscopy (FTIR) was employed to characterize further the possible interactions between the drug and the carrier in the solid state on a FTIR spectrophotometer by the conventional KBr pellet method. The spectra were scanned over a frequency range 4000-400cm^{-1}.

Evaluation of powder blends of solid dispersion containing Nevirapine:

The powder blend was evaluated for bulk density, tapped density, Hausner's ratio, Carr's index and angle of repose.

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Preparation of formulation of solid dispersion containing Nevirapine:

Table 1: Formula for conventional tablet and capsule of solid dispersion containing Nevirapine

Sr. No.	Name of Ingredients	Quantity For Tablet and Capsule (mg)	
		F1(tablet)	F2(Capsule)
1	Nevirapine	100	100
2	HPMC E5 LV	300	400
4	Mannitol	50	50
5	Starch	25	25
6	Sodium starch glycolate	25	25
7	Magnesium Sterate	5	5
8	Talc	5	5
	Total	**510**	**610**

Evaluation of formulated tablet and capsule of solid dispersion containing Nevirapine:

The formulation was evaluated by various parameters such as weight variation, friability, hardness, thickness, diameter, in vitro dissolution test, and in vitro disintegration test.

Dissolution test:

Dissolution test of tablets were performed using 0.1 N HCl with USP dissolution apparatus II at 50 rpm and 37^{O}C the test samples (0.5 ml) were withdrawn at particular time interval (15, 30, 45 minutes) and replaced with the fresh dissolution media maintained at 37^{O}C. The test samples were filtered and the concentration of dissolved drug was determined using UV spectrophotometer. This test was performed on three tablets and mean SD calculated.

Stability study:

The accelerated stability study of optimized batches was checked for stability at 40^{o}C/75% RH for 1 month in well wrapped aluminum foil. Then after 1 month formulations were removed and evaluated for various parameters include hardness, thickness, diameter, friability, weight variation, in vitro disintegration, in vitro dissolution test, etc. data was compared with before stability data of optimized batches.

RESULT AND DISCUSSION

Solubility study of solid dispersion containing Nevirapine:

Table 2: Physical mixture of Nevirapine with HPMC E5LV

Sr. No.	Batch no.	Ratio	% solubility
1	B1	1:1	70.763%
2	B2	1:2	94.425%
3	B3	1:3	97.146%
4	B4	1:4	94.750%
5	B5	1:5	90.231%
6	B6	1:6	88.305%

Table 3: Solid dispersion by solvent evaporation method of Nevirapine with HPMC E5LV

Sr. No.	Batch no.	Ratio	% solubility
1	B7	1:1	78.337%
2	B8	1:2	83.277%
3	B9	1:3	94.117%
4	B10	1:4	98.098%
5	B11	1:5	115.228%
6	B12	1:6	110.753%

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Solubility data for Nevirapine, physical mixture of NVP: HPMC E5LV, solvent evaporated mixtures of NVP: HPMC, in 0.1 N HCl are given in **table 2 and 3.** Solubility data of physical mixture of NVP: HPMC E5 LV showed that ratio 1:3 showed highest solubility that is 97.146%, in solvent evaporated mixtures of NVP:HPMC E5 LV ratio 1:4 shows highest solubility that is 98.098 %. Comparatively solvent evaporated mixture showed good solubility enhancement than the physical mixture of Nevirapine and HPMC E5LV.

Drug- Excipients interactions Study:

Drug-excipients interactions checked using FTIR spectrophotometer. The IR spectra of Nevirapine, HPMC E5 LV, NVP: HPMC by solvent evaporation method are as follows:

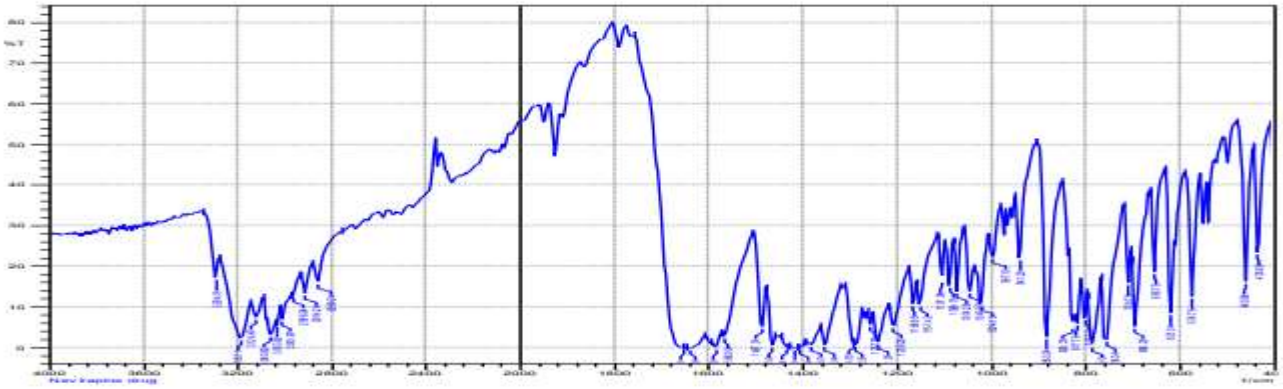

Figure 2: IR spectra of Nevirapine

Table 4: IR interpretation of Nevirapine (pure drug)

Sr. No.	Functional Group	Peaks observed in IR spectra of Nevirapine
1	Primary amine-NH	3294
2	Aromatic C-H	3060
3	Alkenes =C-H	3033
4	C=O	1585
5	Alkenes C=C	1647
6	Aliphatic aminesC-N	1155

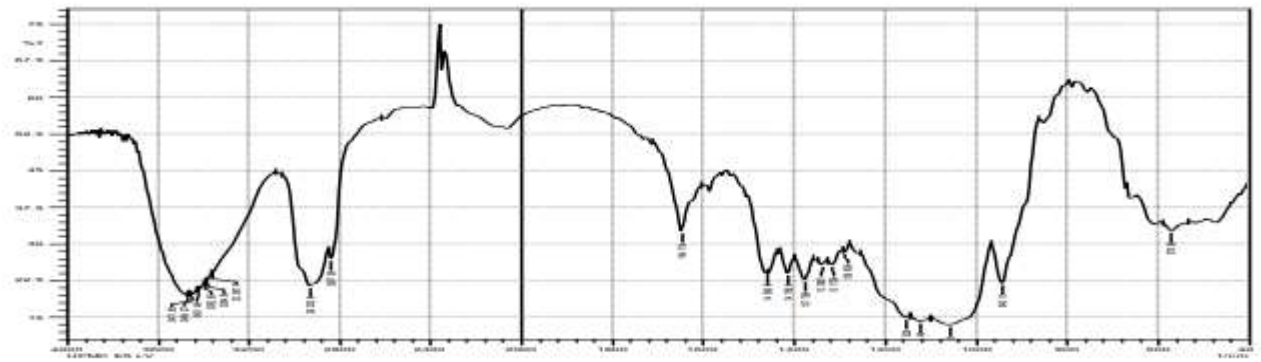

Figure 3: IR spectra of HPMC E5 LV

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Table 5: IR interpretation of HPMC E5 LV (polymer)

Sr. No.	Functional group	Peaks observed in IR spectra of HPMC
1	OH Sretch	3471
2	C=O Stretch	1647
3	Aromatic -CH	2933
4	C-C	1458
5	Aliphatic -C-H	2933

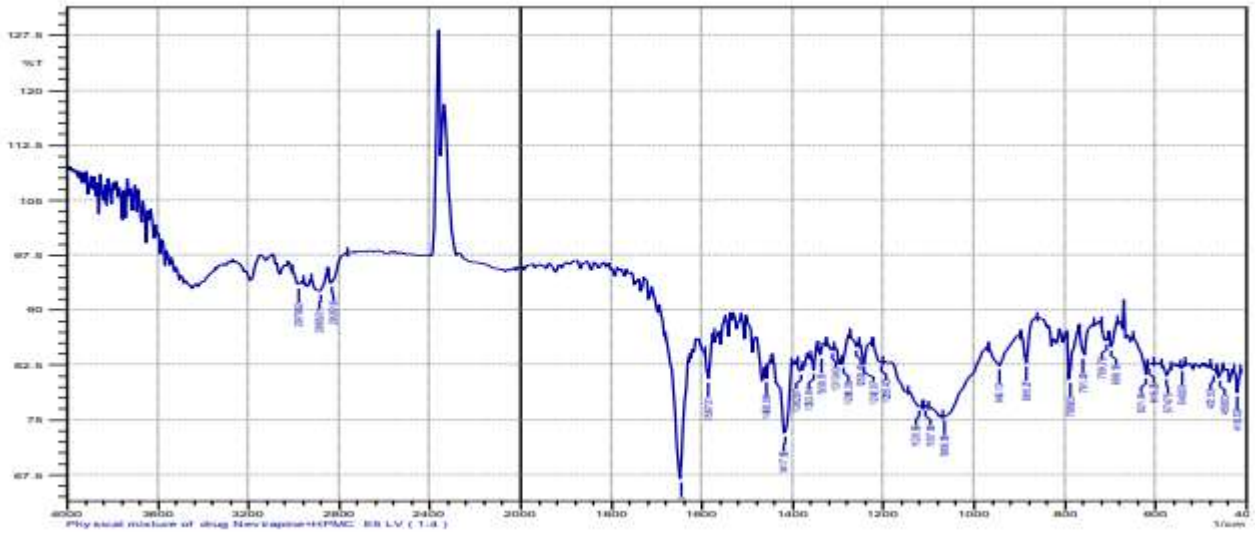

Figure 4: IR spectra of physical mixtures of NVP: HPMC E5LV

Table 6: IR interpretation of NVP: HPMC E5 LV Complex

Sr. No.	Functional group	Peaks observed in IR spectra of complex of NVP: HPMC
1	Aromatic C-H	3060
2	Alkenes =C-H	3033
3	C=O	1600
4	Alkenes C=C	1647
5	Aliphatic amine C=N	1155
6	C=O Stretch	1647
7	Aliphatic C-H	2933
8	C-C	1458

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On observing IR spectrums of Nevirapine, HPMC E5LV, and complex of NVP: HPMC E5LV it had been observed that peaks of –NH of Nevirapine at 3294 $cm^{-1}$and peaks of –OH of HPMC E5LV at 3471 cm^{-1} between them disappeared in the spectrum. Concluding that there was an interaction between –NH functional group of Nevirapine and –OH functional group of HPMC E5 LV. There may be dehydration reaction took place during interactionprocess.

Evaluation of powder blends of solid dispersion containing Nevirapine:

Table 7: Precompression parameters for F1 and F2

Formulation	Angle of repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Car's index %	Hausner's ratio
F1	40.99	0.44	0.50	11.11	1.12
F2	35.52	0.61	0.64	13.41	1.05

From the above result angle of repose of all batches was in between the 35- 41^0 , which indicates good flowability, bulk density and tapped density of all batches was found within range, compressibility of all batches was in between 12- 16%,which indicates good compression properties, Hausner's ratio > 1.25 indicates good flow properties.

Evaluation of formulated tablet and capsule of solid dispersion containing Nevirapine

Table 8: Evaluation parameters of tablet and capsule of solid dispersion containing Nevirapine

Formulation	Weight variation (mg)	Hardness Kg/cm^2	Thickness (mm)	Diameter (mm)	Friability %	Disintegration time(min)
F1(Tablet)	Passes	3.4	6.45	9.06	0.38	12.53
F2(Capsule)	Passes	-	-	-	-	-

All prepared formulations have passed the weight variation test, hardness of all formulations was found in 3- 3.5 Kg/cm^2, thickness of formulations was found 6.45, 5.03, 5.02 mm respectively, the diameter of all tablets were found 9.06mm, friability of all formulations was found to be less than 1%.

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In vitro dissolution study:

Table 9: Cumulative % drug release for F1, F2

Sr. no.	Time (min)	Cumulative % drug release	
		F1(Tablet)	F2 (Capsule)
1	15 min	81.87%	71.96%
2	30 min	91.93%	86.18%
3	45 min	100.38%	98.48%

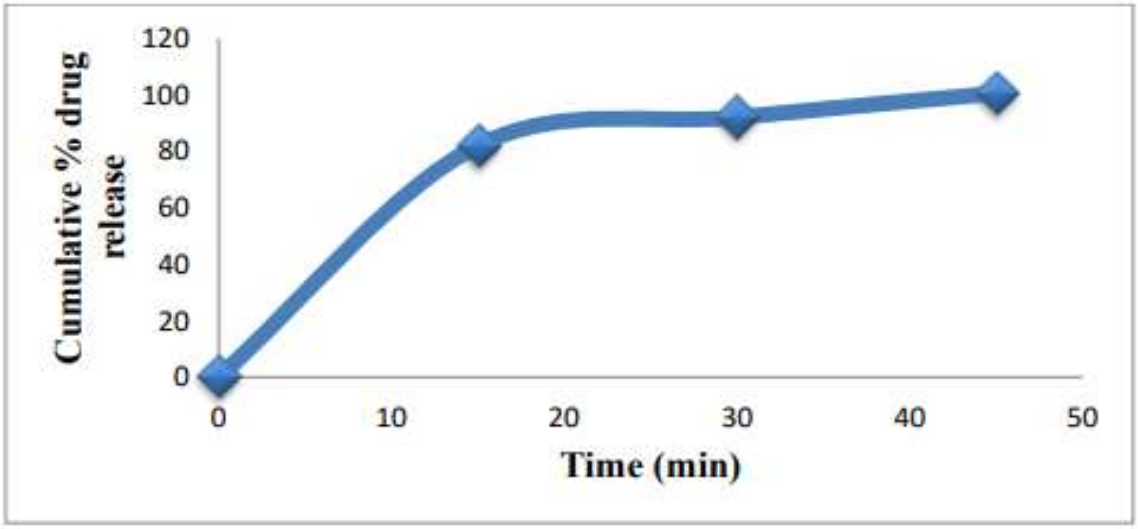

Figure 5: Dissolution data for F1 in 0.1 N HCl

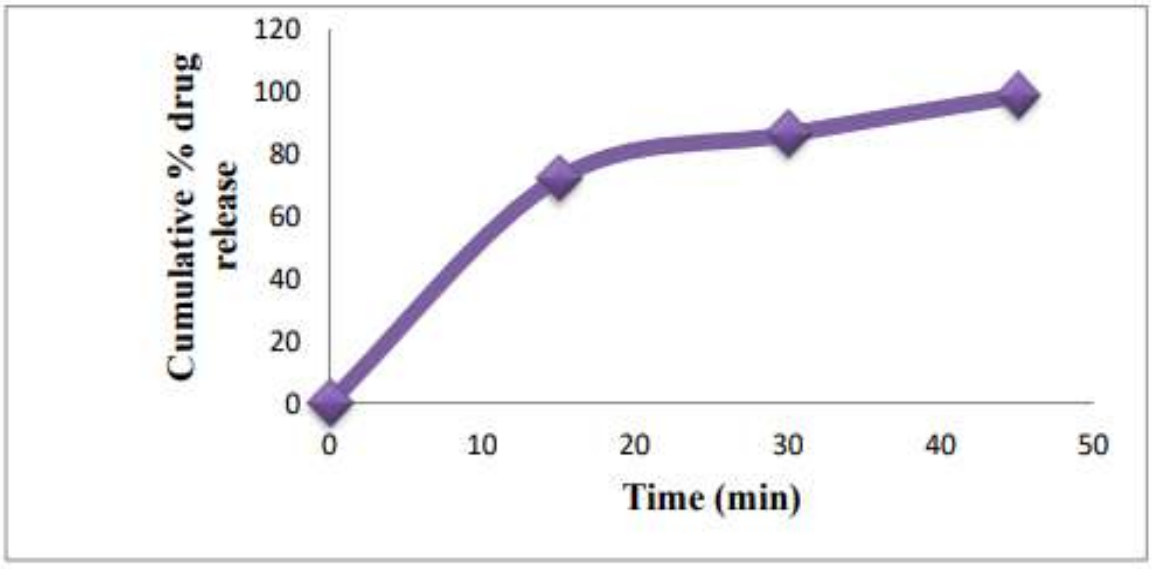

Figure 6: Dissolution data for F2 in 0.1 N HCl

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Stability study:

Table 10: Evaluation parameters of tablet and capsule of solid dispersion containing Nevirapine before and after stability study

Formulation	Before stability study			After stability study		
	Weight variation (mg)	Hardness Kg/cm^2	Thickness (mm)	Weight variation (mg)	Hardness Kg/cm^2	Thickness (mm)
F1 (Tablet)	passes	3.4	6.45	passes	3.2	6.47
F2(Capsule)	Passes	-	-	Passes	-	-

Table 11: Evaluation parameters of tablet and capsule of solid dispersion containing Nevirapine before and after stability study

Formulation	Before stability study			After stability study		
	Diameter (mm)	Friability %	Disintegration time(min)	Diameter (mm)	Friability %	Disintegration time(min)
F1(Tablet)	9.06	0.38	12.53	9.05	0.44	13.02
F2(Capsule)	-	-	-	-	-	-

Table 12: Cumulative percent drug release of formulations before and after stability study

Formulation	Before stability study			After stability study		
	Cumulative % drug release			Cumulative % drug release		
	15 min	30 min	45 min	15 min	30 min	45 min
F1(Tablet)	81.87%	91.93%	100.38 %	80.37%	91.07%	99.87%
F2(Capsule)	71.96%	86.18%	98.48%	69.83%	85.93%	98.18%

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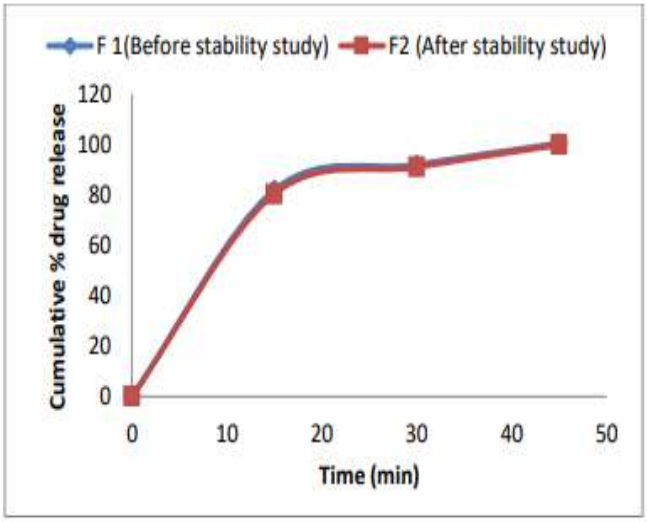

Figure 7: Cumulative % drug release of F1, before and after stability study

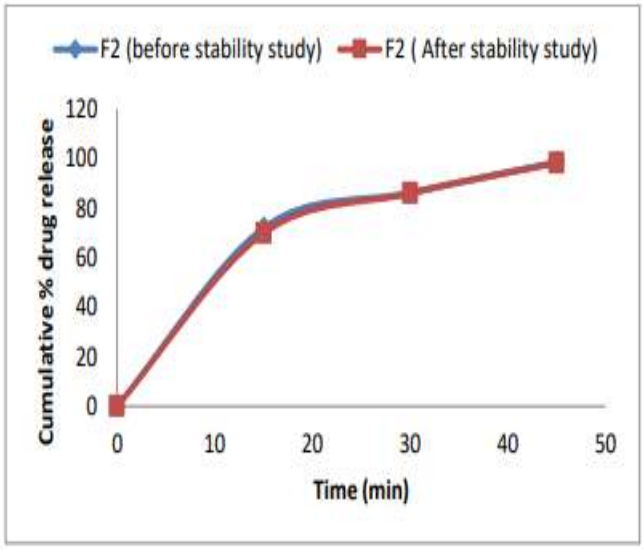

Figure 8: Cumulative % drug release of F2, before and after stability study

SUMMARY AND CONCLUSION

The present investigation deals with the enhancement of solubility of poorly water soluble drug that is Nevirapine by solid dispersion method by using two polymers HPMC E5 LV. Solid dispersion was prepared by two methods such as physical mixture and solvent evaporation method. Solid dispersion containing HPMC E5 LV with drug: polymer in 1:3 ratio prepared by physical mixture method and solid dispersion containing HPMC E5 LV with drug: polymer in 1:4 ratio prepared by solvent evaporation method is the best formulation among all solid dispersion.

The initial solubility of Nevirapine was found to be 16.13%, it increased 6 times by using HPMC E5 LV as polymer by physical mixture and solvent evaporation method by taking drug: polymer 1:3 and 1:4 ratio respectively, the solubility was found to be 97.14% and 98.09%. From the present study it can be concluded that the solubility of Nevirapine was enhanced by using HPMC E5 LV. F1, F2 was found to be optimised batches which can increased the solubility and dissolution rate of Nevirapine. And dissolution of Nevirapine was found to be 100.38%, 98.48% in 45 minutes respectively. Based on the study it may be concluded that Nevirapine tablets and Capsules can be prepared by solid dispersion was found to be ideal for improving the dissolution rate.

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