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Formulation and Evaluation of Immediate Release Tablets of Nevirapine Solid Dispersions

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Abstract: *The objective of the present study was to develop immediate release tablets of Nevirapine in order to achieve rapid release in GIT which might result in enhanced absorption and thereby improved bioavailability. Six batches of solid dispersions of Nevirapine were prepared by using different ratios urea and PEG 6000 as Carriers. Drug–excipients interaction was carried out for pure drug and optimized formulations by using FTIR studies. Nevirapine tablets were formulated employing different synthetic polymers fusion dispersions by direct compression method. All the batches of immediate release tablets were evaluated with reference to different pre-compression and post-compression parameters. Based evaluation of different parameters it was concluded that formulation of immediate release tablets of Nevirapine was successfully done and F4 shows 100% at 60 min.*

Keywords: *Nevirapine, Urea, PEG 6000, Croscarmallose Sodium and Starch Glycolate*

1. INTRODUCTION

Oral drug delivery is the simplest and easiest way of administering drugs. But the major problem in oral drug formulations is low and erratic bioavailability, which mainly results from poor aqueous solubility. Hence the formulation of poorly soluble compounds for oral delivery is the most challenging aspects in the pharmaceutical industry. In case of poorly water soluble drugs, dissolution is the rate limiting step in the process of drug absorption. So, bioavailability problems are prevalent with extremely hydrophobic drugs (aqueous solubility < 0.1 mg / ml at 370 C) due to erratic or incomplete absorption from GIT.1 Thus improvement of aqueous solubility in such case is valuable goal to effectively formulate them into bioavailable drug products. Various techniques have been used to improve the solubility/dissolution rate of poorly water soluble drugs.2, 3among them, the solid dispersions are one of the most attractive techniques to improve the poor aqueous solubility of drugs.

Nevirapine is an antiretroviral drug that is currently used in the treatment of human immunodeficiency virus type 1 (HIV-1)infections.4,5 The model drug belongs to Biopharmaceutical Classification System (BCS) class II (low solubility/high permeability), poses a challenge in achievement of optimal dissolution kinetics from the dosage form.6 Drug release is a crucial and limiting step for oral drug bioavailability, particularly for drugs with low gastrointestinal solubility and high permeability. Hence this work is planned to improve dissolution characteristics of the model drug by increasing its release and solubility through solid dispersion technique

2. MATERIALS AND METHODS

Nevirapine was obtained as a gift sample from BMR Chemicals, Hyderabad. Urea and Poly ethylene Glycol were obtained from SVR Labs Hyderabad. All the excipients and solvents used are analytical grade.

3. METHOD OF PREPARATION

3.1. Preparation of Solid Dispersions by Kneading Method

Dispersions were prepared in the ratios of 1:1, 1:2 (Drug: carrier) with urea and PEG 400. Initially weighed amount of drug and carrier (urea and PEG 400) were placed in a mortar and were ground

with pestle for few minutes. Then few ml of alcohol: water (1:1) was added and then triturated until alcohol: water gets evaporated. Then the obtained dry dispersions were preserved in a desiccator for overnight. The dry dispersion was then passed through the 100# mesh sieve and is stored in moisture free area till further use.

Table1. *Nevirapine and Polymer Complexes.*

Method	Drug to Carrier	Drug to Carrier ratio	Formulation Code
Kneading Method	NEP:UR	1:0.5	UR1
	NEP:UR	1:1	UR2
	NEP:UR	1:2	UR3
	NEP:PEG	1:0.5	PEG1
	NEP:PEG	1:1	PEG2
	NEP:PEG	1:2	PEG3

3.2. Formulation of Immediate Release Tablets of Nevirapine

The solid dispersion equivalent to 145 mg of drug was taken then mixed with directly compressible diluent in a plastic bag. Magnesium stearate, Aerosil and lactose were passed through sieve no. 60, mixed and blended with initial mixture in the plastic container followed by compression of the blend using a punching machine to produce round tablets.

Table2. *Batches prepared for screening of Superdisintegrant*

S.No	Ingredients	F1	F2	F3	F4
1	Complexed drug	145	145	145	145
2	Lactose	99.5	97	99.5	97
3	SSG	2.5	5	-	-
4	CCS	-	-	2.5	5
5	Mag. Stearate	3	3	3	3
6	Aerosil	3	3	3	3
7	Total Wt	250	250	250	250

**All values are expressed in mg/tablet*

3.3. Evaluation of Solid Dispersions

All the prepared dispersions were evaluated for the following parameters as per IP.

3.3.1. Drug Content Uniformity

Drug equivalent to 20 mg of the dispersions was weighed transferred into a 100ml volumetric flask, the dispersion was solubilized in 20ml alcohol and finally the volume was adjusted to 100ml with 0.2% w/v SLS. From the obtained stock, dilutions were made such that we finally obtain 10µg/ml solution. The obtained solution was assayed for drug content using a U.V. spectrophotometer at 258nm. The drug content is calculated from the absorbance obtained with the help of the calibration curve. The results are given in Table 17 (n=3).

3.3.2. In – Vitro Dissolution Studies

Dissolution rate of Nevirapine from all the dispersions was performed using dissolution testing apparatus with paddle. The dissolution fluid was 900ml of 0.1N HCl with Containing 0.0072% w/v SLS, a speed of 50rpm and a temperature of 37±0.5°C was used in each test. Samples of dissolution medium (5ml) were withdrawn at different time intervals (5, 10, 15,20,30,45 and 60min), suitably diluted and assayed for Nevirapine by measuring the absorbance at 290nm. The dissolution experiments were conducted in triplicate and the results are tabulated in Tables 18, 19 and shown in Figs 5, 6.

3.4. Evaluation of Immediate Release Tablets

3.4.1. Pre-Compression Parameters

3.4.1.1. Angle of Repose

Angle is determined using funnel. The accurately weighed powder was taken in a funnel. The height of the funnel is adjusted in such a way the tip of the funnel just touches apex of the head of the blend.

The powder is allowed to flow through the funnel freely onto the surface. The diameter of the powder cone is measured, and angle of repose is calculated using the following equation.

TanØ = h\r

Where h and r the height of the cone and radius cone base respectively.

3.4.1.2. Bulk Density

Apparent bulk density is determined by pouring a weighed quantity of blend into graduated cylinder and measuring the volume and weight. Bulk density is calculated using the following formula:

Bulk density = Weight of powder/bulk volume of powder

3.4.1.3. Hausner's Ratio

The Hausner's ratio is a number that is correlated to the flow ability of a powder or granular material.

Hausner's ratio = tapped bulk density/LB

3.5. Compressibility Index

The compressibility index is measure of the propensity of the powder to be compressed. As such, they are measures of the relative importance of inter-particulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter-particulate interactions, and a greater difference between bulk and tapped densities will be observed. These differences are reflected in the compressibility index.

3.6. Post Compression Parameters

3.6.1. Weight Variation

Twenty tablets were randomly selected from each batch, individually weighed, the average weight and the standard deviation of 5 tablets was calculated.

3.6.2. Hardness

Hardness or tablet crushing strength (Fc); the force required to break a tablet in a diametric compression was measured using a MONSANTO tablet hardness tester.

3.6.3. Friability

Friability of tablets was determined using the Roche friabilator (USP). Preweighed sample of tablets was placed in the friabilator and was subjected to 100 revolutions at 25 rpm. Tablets were dedusted using a soft muslin cloth and reweighed.

Percent friability = [initial wt- final wt/ initial wt] × 100

3.6.4. Drug Content

Three tablets from each formulation were weighed accurately and powdered. Powder equivalent to 100mg of Nevirapine was dissolved in 20ml alcohol and the volume was adjusted to 100ml with 0.2% w/v SLS. The resultant solution was then subsequently diluted with distilled water assayed for the drug by using UV spectrophotometer at 258nm. The drug content is calculated from the absorbance obtained with the help of the calibration curve.

3.6.5. In – Vitro Dissolution Studies

Dissolution rate of Nevirapine from all formulations was performed using dissolution testing apparatus (paddle). The dissolution fluid was 900ml of 0.1N HCL Containing 0.0072% w/v SLS, a speed of 50 rpm and a temperature of 37±0.5°C was used in each test. Samples of dissolution medium (5ml) were withdrawn at different time intervals (5,10,20,30,45 and 60min), suitably diluted and assayed for Nevirapine by measuring the absorbance at 258nm by using U.V. spectrophotometer. The dissolution experiments were conducted in triplicate and the results are tabulated.

3.6.6. FTIR Studies

FTIR Spectra of the optimized batches of solid dispersions of Nevirapine were studied to confirm the compatibility of the API with the excipients. FTIR spectroscopy was obtained by the FTIR

spectrophotometer (Brucker) using the potassium bromide pellets and the scanning range used was 4400 to 400 cm-1 at a scan period of 1min.

4. RESULTS AND DISCUSSION

In the present study, Kneading method was employed to prepare solid dispersion. In this case, solid dispersion were prepared at 1:0.5, 1:1 & 1:2 ratios of drug and different synthetic polymers. The solid dispersion prepared were evaluated for drug content uniformity and dissolution rate. Drug contents in various solid dispersion were found to be within 100±5% of the theoretical amount.

Table3. *Drug Content of Complexes is mentioned in the Table*

S.No	Complexionmethod	Drug: CarrierRatio	Complex Code	%Drug content
1	**Kneading Method**	1:0.5	UR1	98.2±3.65
		1:1	UR2	100±2.09
		1:2	UR3	100.1±3.79
		1:0.5	PEG1	99.94±1.6
		1:1	PEG2	100.1±3.83
		1:2	PEG3	100.2±1.72

The dissolution rate of Nevirapine from different synthetic polymers solid dispersions were studied in 0.1N HCl buffer of PH 1.2 and compared with that of pure drug. The dissolution data of Nevirapine dispersions are given in table no.15 and the dissolution profiles are shown in figure no.1

Table4. *Dissolution Profiles of NEV Solid Dispersions in 0.1N HCl*

Time (min)	% CDR						
	PURE DRUG	UR1	UR2	UR3	PEG1	PEG2	PEG3
0	0	0	0	0	0	0	0
5	5.5	35.5	38.6	41.5	54.5	39.6	48.4
10	21.6	56.34	59.44	59.47	74.24	58.65	59.42
15	25.88	60.80	64.56	76.28	83.64	71.42	76.82
30	27.86	73.32	79.62	83.54	86.87	75.65	80.82
45	28.69	85.64	89.69	92.95	91.35	81.95	83.58
60	30.24	9265	96.65	99.68	92.65	94.25	98.58

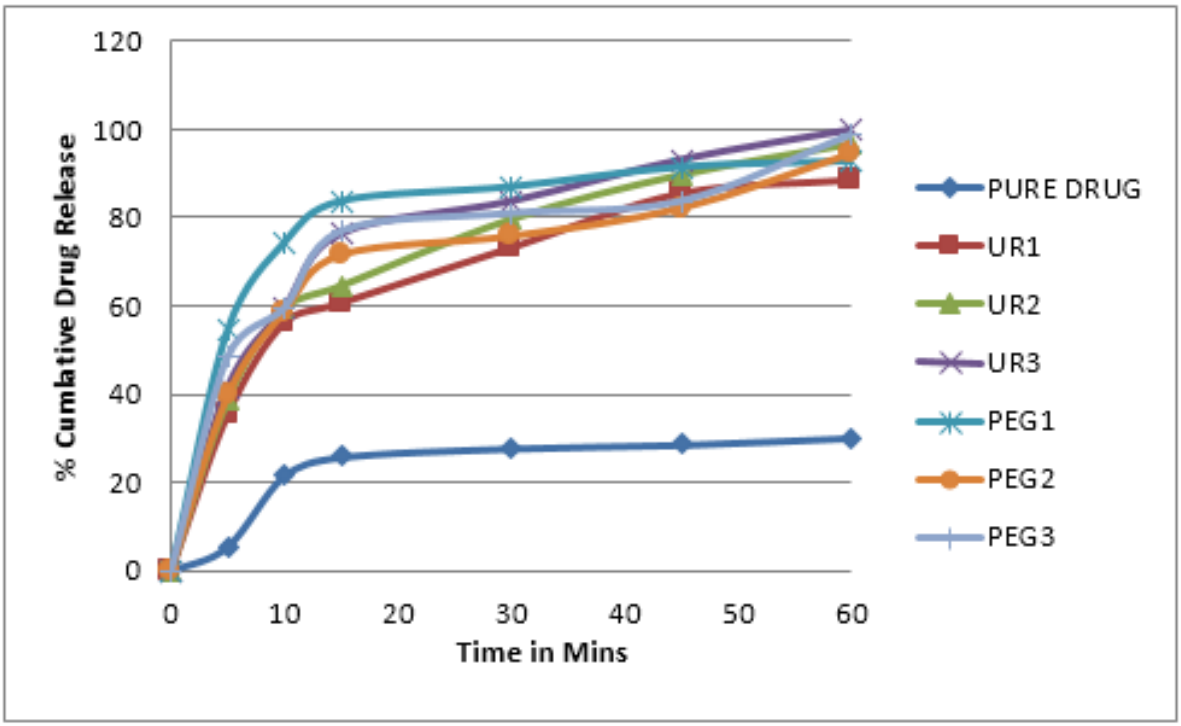

Figure2.*Cumulative % Drug Release of Nevirapine Solid Dispersions*

The dissolution data were analyzed as per zero-order and first-order kinetics. The model that best fits the dissolution data was evaluated by calculating the correlation coefficient (r) between the two

variables namely time and percent dissolved in the zero-order model and time and log percent remaining in the first order model. The 'r' values were found to be relatively higher in the case of first order model in all the cases. Thus the dissolution on Nevirapine as such and from various ratios of different synthetic polymers followed first-order kinetics.

Drug polymer interactions were studied by FT-IR analysis. Figure no.2 showed the FT-IR spectra of pure Nevirapine. The characteristic peaks confirmed the structure of Nevirapine. The same peaks were also reported in Fig 3&4 i.e. all drug loaded solid dispersions. There was no change or shifting of characteristic peaks in drug loaded solid dispersions suggested that there was no significant drug polymer interaction which indicates the stable nature of drug in all formulations.

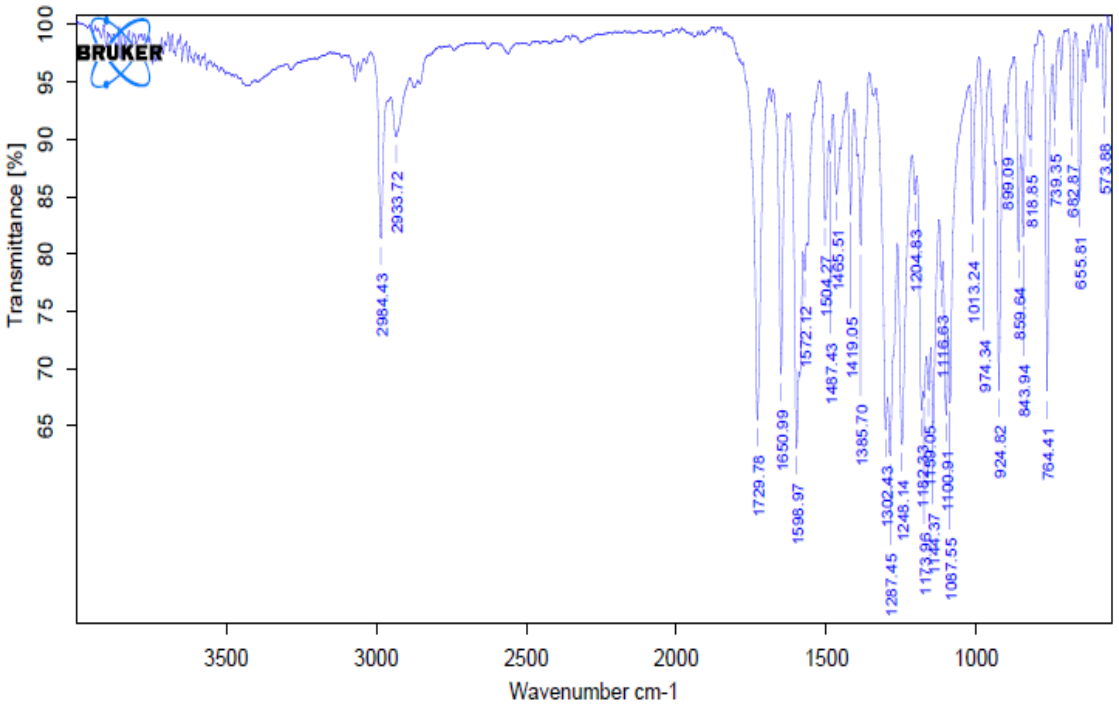

Fig2. *FTIR Spectrum of Nevirapine*

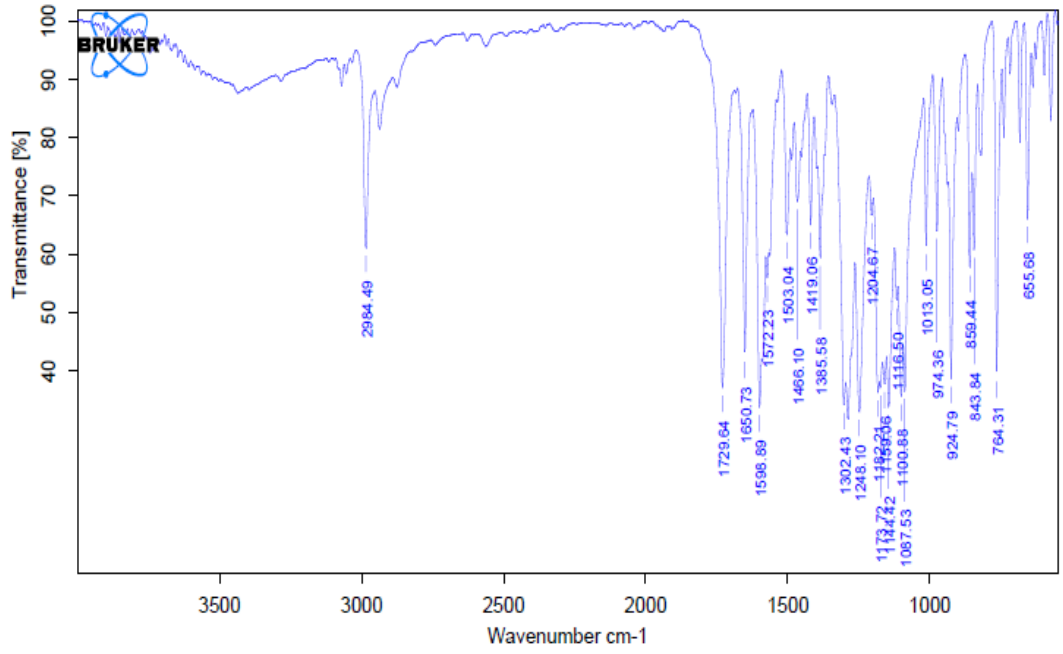

Fig3. *FTIR Spectrum of 1:2 Physical mixture of Drug: Urea*

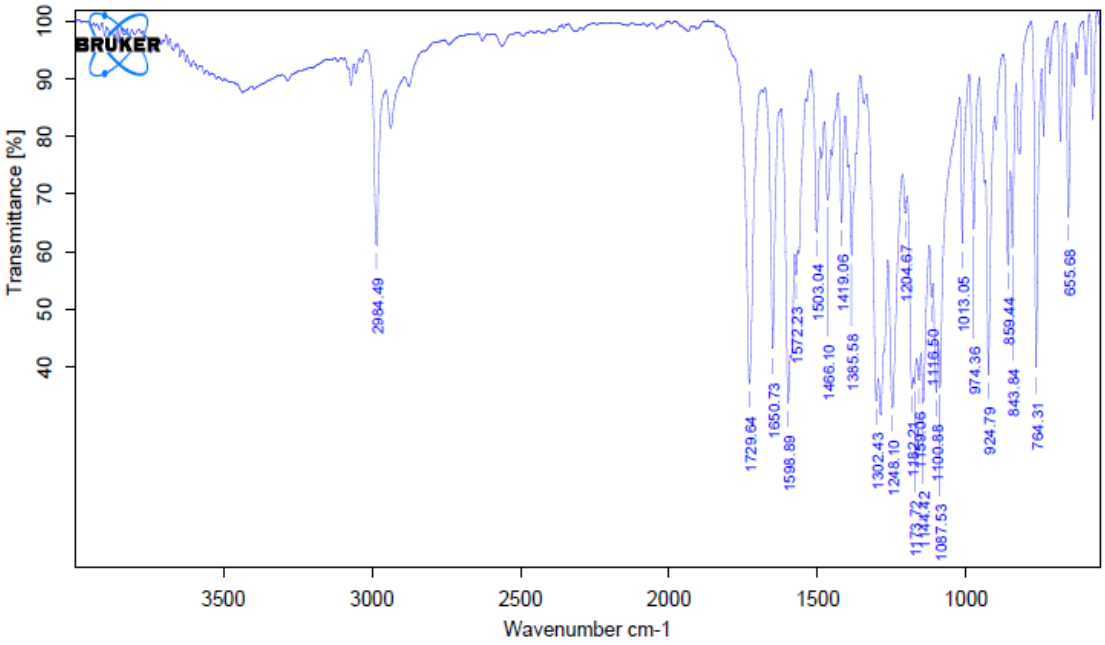

Fig4. *FTIR Spectrum of 1:2 Physical mixture of Drug: PEG*

Solid dispersion of polymers with Nevirapine exhibited higher dissolution rate. The feasibility of formulating into tablet dosage forms is evaluated. Nevirapine tablets were formulated employing different synthetic polymers fusion dispersions by direct compression method. The tablets were prepared as per the formulae given in Table no.2. Direct compression method was tried for the preparation of tablets. In the case of direct compression, sodium starch glycolate and Croscarmalose sodium as a super disintegrant was added to improve the disintegration property of solid dispersions. The feasibility of formulating solid dispersions in synthetic polymers into tablet was evaluated by preparing tablets in each case employing drug-polymers fusion dispersions.

Table5. *Results of Pre-Compression Parameters of Tablet Blend*

Formulation code	F1	F2	F3	F4
Angle of repose	33.55±0.596	34.21±0.602	34.45 ±0.4	32.08±0.78
Bulk Density	0.565 ±0.004	0.572±0.0034	0.574 ± 0.06	0.572 ±0.007
Tapped density	0.646 ±0.0046	0.651 ±0.0046	0.660 ± 0.05	0.663 ±0.007
Compressibility index	12.53	11.82	12.63	12.20
Hausner's ratio	1.143	1.134	1.14	1.15

** Values are mean ± SD, n=3*

Table6. *Results of Post-Compression Parameters*

Formulation code	F1	F2	F3	F4
Hardness	3.26±0.057	3.3±0.057	3.33±0.05	3.23±0.115
Thickness	42.513±0.0	2.513±0.05	2.513±0.5	2.513±0.05
Friability	0.264±0.05	0.069±0.05	0.231±0.1	0.296±0.25
Weight variation	99.95 ±1.8	99.8 ±1.7	98.4 ±1.7	100.3 ±1.6
Wetting Time (Sec)	28±0.67	29±0.12	18±0.4	10±0.22
Disintegration time	32±0.52	33±0.86	19±0.9	16±0.45
% Drug content	99.89±0.04	101.54±0.12	100.62±0.1	100.62±0.1

**Values are mean ± SD, n=3*

All the solid dispersion tablets were prepared were found to contain the drug within limitsof the labeled claim (Table No.6). Hardness of the tablets was in the range 3 -4 kg/sq.cm, and was satisfactory. The percentage weight loss in the friability test was less than 0.6% in all the tablets prepared. All the tablets prepared by direct compression method disintegrated rapidly within 4.0 minutes (Table no.6).

Dissolution rate of drug from the tablets formulated employing solid dispersions was studied using an USP tablet dissolution apparatus type II 8 station dissolution rate test apparatus (Disso Labindia) with a paddle stirrer at 75 rmp and at a temperature of 370 ± 0.50 in a 0.1N HCl as dissolution fluid.Samples of dissolution medium (5ml) were withdrawn through a filter (0.45 µ) at different time intervals, suitably diluted, and assayed for Nevirapine at 258nm. The dissolution experiments were conducted in triplicate. The results are given in table no.15 and dissolution profiles of various tables are shown in Figure no.5.

Table7. *In-Vitro Drug Release for All Tablets Formulation*

Time (Min)	F1	F2	F3	F4
0	0	0	0	0
5	55.56	56.42	56.84	58.98
10	68.42	70.86	71.96	72.63
15	76.98	80.83	82.69	86.96
30	82.22	85.07514	88.64	90.22
45	88.82	89.25	93.24	95.68
60	94.28	93.82	96.64	99.98

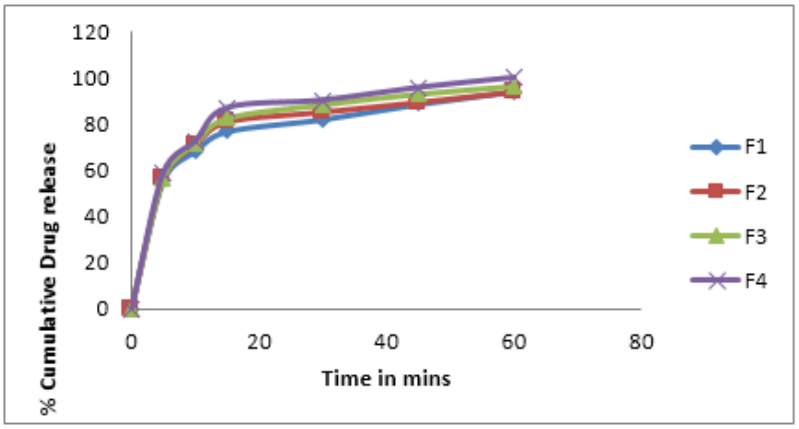

Fig5. *Percent Cumulative Drug Release of all Formulations*

All the tablets formulated employing solid dispersions in synthetic polymers gave rapid and higher dissolution rate of Nevirapine. Dissolution from all the tablets followed first order kinetic with correlation coefficient 'r' above 0.9470. The increasing order of dissolution rate of Nevirapine from tablets observed with various synthetic polymers was CCS >SSG. The mechanism of release for the best formulations was determined by finding the Correlation Coefficient (r) value for each kinetic model viz. zero order and first order. Thus from the results it can be said that the drug release follows first order kinetics.

5. Conclusion

The present work on enhancement of dissolution rate of Nevirapine tablets by solid dispersion technique utilize PEG 400 and urea to increase the solubility of the formulation in 3hrs time period. F4 formulation showed better drug release of 100% drug release at the end of 60th minute compared to other formulations So F4 is the optimized formulation. Among the polymers used the role of PEG 400 and urea is noteworthy in enhancing the dissolution rate. Drug–excipients interaction was carried out for pure drug and optimized formulations by using FTIR study. In this analysis drug-excipients compatibility interaction were not observed. From the results obtained it was concluded that the optimized formulation follows First-order release kinetics

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