STUDIES TO ENHANCE DISSOLUTION PROPERTIES, PREPARATION AND IN-VITRO EVALUATION OF NELFINAVIR EXTENDED-RELEASE MATRIX TABLETS

Amit Kumar*, Dr Anwar Iqbal Khan, Dr. Navjot Singh

NRI Institute of Pharmacy, Bhopal

***Corresponding Author**

Amit Kumar

E- mail: bpart0001@gmail.com

ABSTRACT

Nelfinavir is an antiviral (HIV protease inhibitor) used in the treatment of AIDS. Solid dispersions of Nelfinavir-pvp-k30 were prepared in different molar ratios (1:1, 1:3, 1:5, 1:7) by solvent evaporation method. Likewise physical mixtures were prepared in previous mentioned ratio. Nelfinavir-PVP dispersions were used for preparation of controlled release formulation. Matrix tablets were prepared by direct compression technology using various polymers such as Guargum, HPMC-K100M, and ethyl cellulose. Total of 9 formulations were prepared by varying concentrations of polymer blends. The formulations were evaluated for various quality control tests. All the formulations were found to be satisfactory and reproducible. Comparison study was done between formulation F2 and F3. Both contain same amount of guargum (22.2 %) and same amount of Ethyl cellulose (2.2%),but F2 contain 15% of PVP and F3 contain 15% of HPMC. Formulation F3 retarded the drug release for a prolonged period of time. Therefore, from the above study it is cleared that drug-retarding property of HPMC with ethyl cellulose plays a major role with retarding property from PVP. The *in-vitro* release pattern of the optimized formulation was analyzed by fitting the dissolution data into various kinetic models. It was seen that R^2 value was higher when fitted to Higuchi model followed by zero order equation.

KEYWORD: Nelfinavir, Solid dispersions, extended-release, matrix tablets, antiviral, HPMC

INTRODUCTION

The oral route of drug administration is the most common and preferred method of delivery due to convenience and ease of ingestion[1]. Although the oral route of administration is preferred, for many drugs it can be a problematic and inefficient mode of delivery for a number of reasons[2]. Limited drug absorption resulting in poor bioavailability is paramount amongst the potential problems that can be encountered when delivering an active agent via the oral route[3]. Drug absorption from the gastrointestinal (GI) tract can be limited by a variety of factors with the most significant contributors being poor aqueous solubility and/or poor membrane permeability of the drug molecule[4]. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include[5,6], Enhancing solubility and dissolution rate of poorly water-soluble drugs and Enhancing permeability of poorly permeable drugs[7]. Acquired immune deficiency syndrome or acquired immunodeficiency syndrome (AIDS or Aids) is a collection of symptoms and infections resulting from the specific damage to the immune system caused by the human immunodeficiency virus (HIV) in humans, and similar viruses in other species (SIV, FIV, etc.) [8]. Nelfinavir is an antiviral (HIV protease inhibitor) used in the treatment of AIDS. Due to poor aqueous solubility, it is give rise to difficulties in the design of pharmaceutical dosage forms and leads to its poor and variable oral bioavailability[9,10]. Thus, an attempt was made to increase the solubility of drug by preparing it in solid dispersions forms. The main objective involved in the proposed project is to enhance the solubility of poor water soluble antiviral drugs by employing suitable solubility enhancement techniques like solid dispersion and then develop oral controlled release drug delivery systems in order to obtain better therapeutic efficacy.

MATERIALS AND EXPERIMENTAL WORK

Materials

Nelfinavir (API), polyvinylpyrrolidone, Poloxamer, Magnesium Stearate, Microcrystalline Cellulose, Ethylcellulose and Hypromellose were used. All used all solvents and reagents were analytical grade.

Analytical method and its Validation

A spectrophotometric method based on the measurement of absorbance at 232 nm phosphate

buffer pH-6.8 was used in present Study for estimation of Nelfinavir. The method was validated for linearity, precision and accuracy. Beer lamberts law was obeyed in the range 2-50µg/ml.When a standard drug solution was assayed repeatedly (n=6) the mean error (accuracy) and relative standard deviation (precision) was found to be 0.6 and 0.8 % respectively. No interference from the excipients used was observed. Thus, the method was found suitable for estimation of Nelfinavir contents in dissolution fluid.

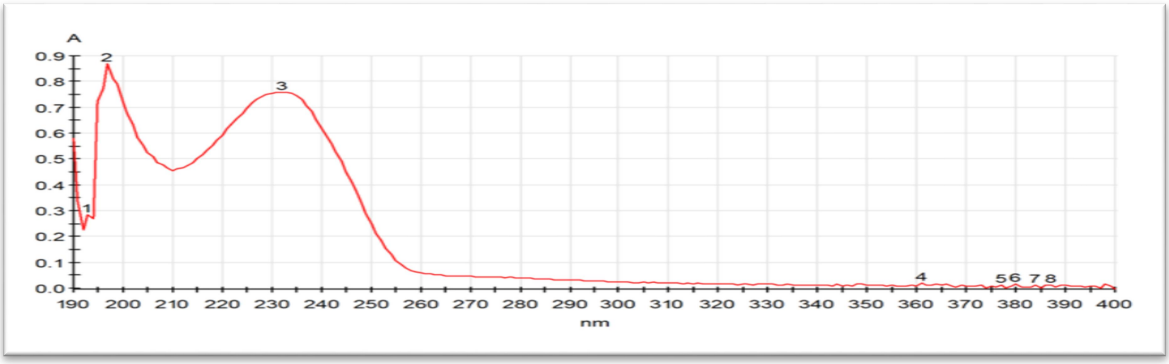

Figure 1: Spectra of Nelfinavir in Phosphate buffer (pH 6.8)

Preparation of Standard Curve

Weighed accurately 25 mg of Nelfinavir was placed in a 25 ml volumetric flask and then volume was made upto 25 ml with ethanol. (Stock solA). From stock A 0.1, 0.2, 0.3, 0.4, 0.5 ml of solution was pippeted out and placed in different 10 ml volumetric flasks and then volume was made upto mark with phosphate buffer(pH-6.8) From the above-prepared concentration, 10 ppm was subjected to UV spectrophotometer for lambda max scanning. λ-max was noted as 232 nm.

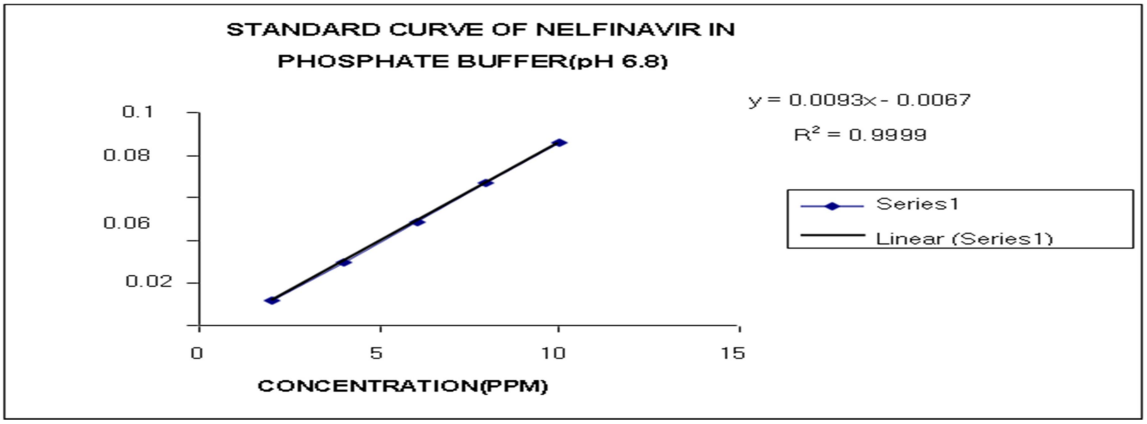

Figure 2: Standard curve of Nelfinavir in phosphate buffer (pH-6.8)

Physico-Chemical Characterization of the Drug

Flow properties of drug were measured by using Angle of Repose, Density Measurement, Bulk Density, Tapped density, Percentage Compressibility and Hausner's Ratio parameters.

Table 1: Illustration of all the Physico-chemical characteristics of Nelfinavir

Experiment	Result
Bulk density	0.76 g/ml
Tapped density	0.8 g/ml
Carr's index	5 %
Hausner's ratio	1.05
Angle of repose	26.08^0

Solubility Determination

A cleaned and dried graduated test tube of 10 ml was taken and 10 ml of phosphate buffer (pH 6.8) was poured into it. Then with a spatula small, unknown quantity of Nicardipine was added to it and dissolved properly by shaking with hand. The above procedure of addition of drug and then shaking was continued until the drug went into solution that means until a clear solution was obtained. At the moment when the drug was undissolved in the solution even after shaking with hand that means a supersaturated solution, the test tube containing the drug with solvent was subjected for shaking in a mechanical shaker for 12 hr. The above solution was then filtered, dilutions were made and absorbance was noted in UV Spectrophotometer at 232 nm. Solubility was found to be 2.532 mg/ml. Likewise, solubility was determined in phosphate buffer of pH 7.2 And the solubility was found to be as follows:

Table No. 2: Solubility values of Nelfinavir in different pH ranges

pH	Solubility(mg/ml)
6.8	2.532
7.2	1.903

Phase Solubility Studies

Phase solubility studies were performed according to the method reported by Higuchi and

Connors. An excess amount (5 mg) of Nelfinavir was added to the phosphate buffer (pH 6.8) solution of pvp-k30 (molecular weight = 50000) at various concentrations (5 to 25 mM /L). The contents were sealed with Aluminium foils and stirred for 72 hours at 30°C ± 1°C in a mechanical shaker. After equilibrium, the samples were filtered and absorbance was noted at 232nm (Thermoscientific UV/ Vis spectrophotometer).

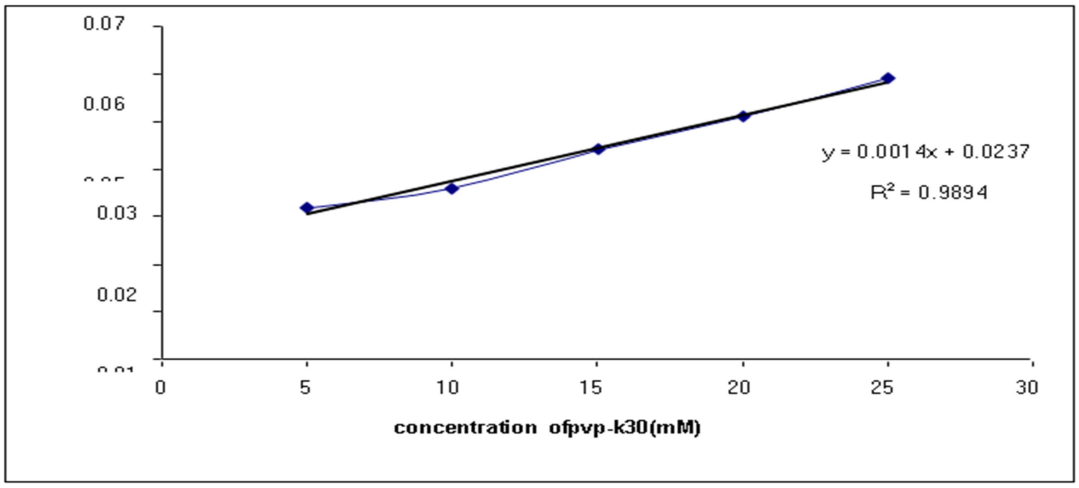

Figure 3: Phase solubility curve of Nelfinavir and PVP-K30

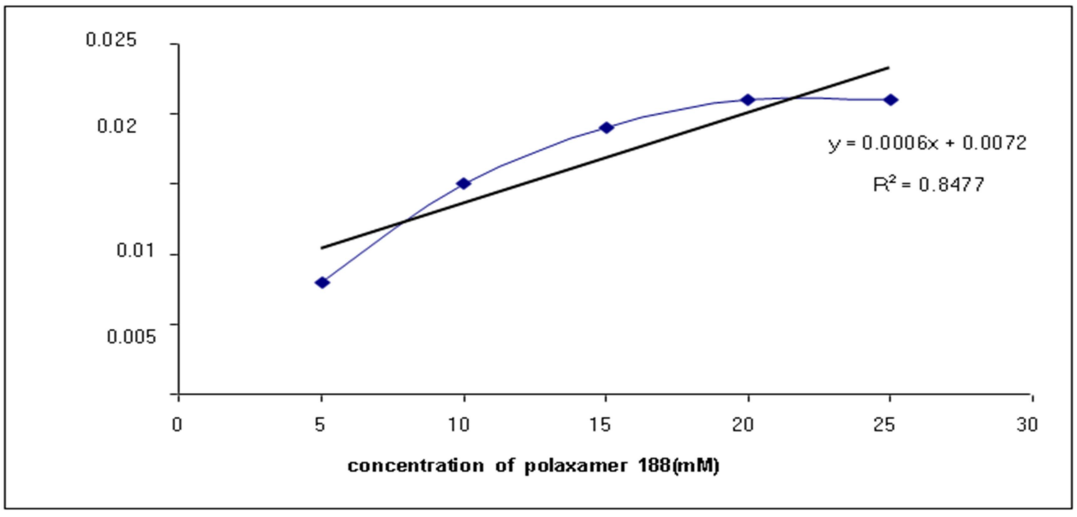

Figure 4: Phase solubility curve of Nelfinavir and Poloxamer-188

Preparation of drug-PVP-K30 solid dispersions: Drug- PVP-K30 solid dispersions were prepared using solvent evaporation method. Four different drugs: carrier ratios (1:1, 1:3, 1:5, and 1:7) were used.The respective amount of carrier (PVP-K30) was dissolved in ethanol (30 ml)

and Nelfinavir was added in parts with continuous stirring. The solvent was then removed by evaporation at 40 degree Celsius. The solid dispersions prepared were pulverized and sifted (80#) and stored in adesiccators.

Preparation of Drug-PVP physical mixtures: Accurately weighed quantity of drug and carrier as per respective molar ratios (1:1, 1:3, 1:5, 1:7) was taken in a mortar and pestle. Geometric dilution technique was used for preparation of it.

Drug content estimation: An accurately weighed quantity of kneaded complex and physical mixtures equivalent to 25 mg of drug was taken into a 50 ml volumetric flask and dissolved in minimum amount of ethanol and the volume was made up to the mark with phosphate buffer (pH 6.8) and assayed for drug content using UV double beam spectrophotometer at 232 nm.

Table No. 3: Drug content percentage of physical mixtures (PM) and solid dispersions(SD)

Drug: PVP ratio	Nelfinavir CONTENT %	
	PVP-K30 -PREPARATION	
	PM	SD
1:1	69.23	76.65
1:3	62.29	72.36
1:5	58.26	68.46
1:7	51.89	66.46

***In-vitro* Evaluation of Nelfinavir- PVP Preparations**

Dissolution studies were conducted for Nelfinavir Solid dispersion and physical mixture using USP paddle type apparatus at 37 ± 0.5^0C at 70 rpm. 900 ml of phosphate buffer (pH 6.8) was used with Tween-80(1.6% v/v) as dissolution medium. The drug, inclusion complex and physical mixture was filled in hard gelatin capsule shell so as to contain an equivalent of 50 mg of pure Nelfinavir at various time intervals, 5 ml of sample was withdrawn from a fixed position of the vessel and replaced with fresh dissolution medium. The absorbance of filtered sample was noted at 232 nm. The drug released at varioustime intervals was calculated.

Table No. 4: % Cumulative Drug Release Values of Nelfinavir

Time Interval (in min)	Pure Drug % CDR	CUMULATIVE PERCENTAGE DRUG RELEASE							
		SOLID DISPERSION				PHYSICAL MIXTURE			
		1:1	1:3	1:5	1:7	1:1	1:3	1:5	1:7
0	0	0	0	0	0	28.02	32.57	41.79	52.41
10	26.8	32.4	43.4	51.4	62.4	31.58	35.91	44.56	55.64
20	30.048	35.08	47.741	54.985	65.246	34.89	39.01	46.16	58.07
30	32.566	39.493	50.063	56.603	69.56	38.75	41.3	50.07	62.44
40	33.78	43.018	53.676	60.512	72.784	41.3	44.75	52.64	65.67
50	34.386	45.537	55.996	64.034	75.202	43.95	48.36	53.27	66.89
60	34.99	47.352	59.209	67.253	76.515	46.66	49.88	55.01	68.45
70	35.393	49.562	60.627	69.071	78.715	47.66	51.25	56.83	70.05
80	35.895	50.773	61.835	70.281	79.835	48.55	53.05	58.07	72.35
90	34.798	51.58	63.041	70.688	81.341	48.85	54.45	59.01	73.55
100	36.792	50.385	64.148	70.89	81.949	28.02	32.57	41.79	52.41

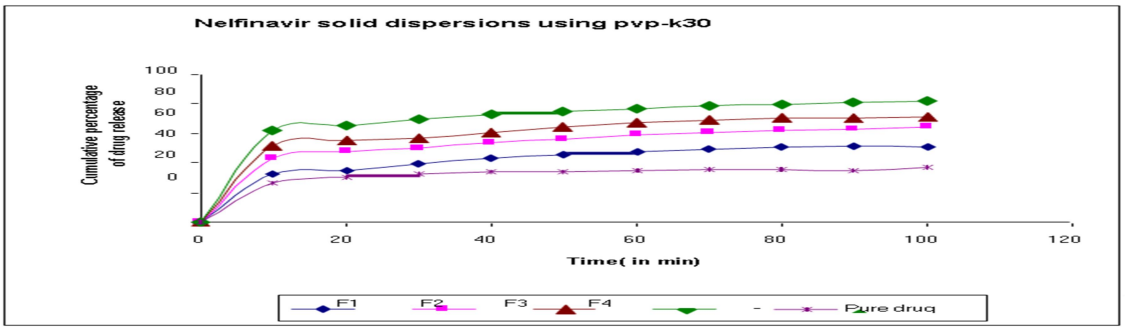

Figure 5: Comparative dissolution profiles between solid dispersions andpure drug

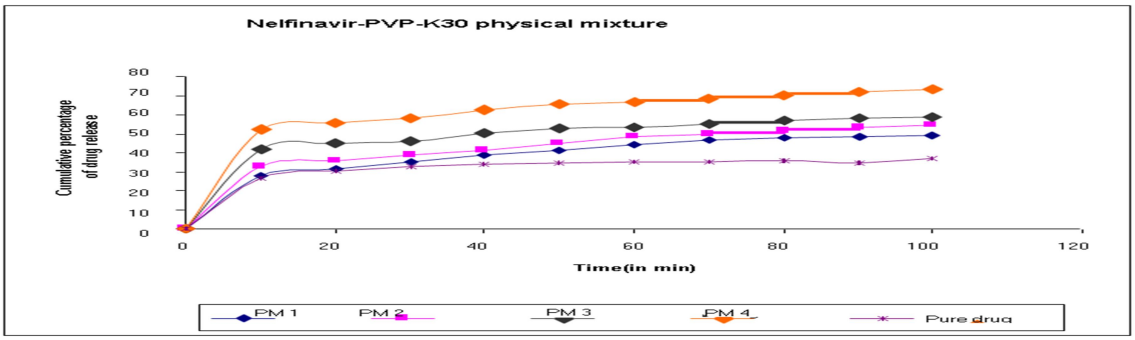

Figure 6: Comparative dissolution profiles between physicalmixtures and pure drug

Preparation of Solid Dispersion with Poloxamer by Solvent EvaporationMethod

Four different drugs: carrier ratios (1:1, 1:3, 1:5, and 1:7) were used. The respective amount of carrier (Poloxamer-188) was dissolved in ethanol (30 ml) and Nelfinavir was added in parts with continuous stirring. The solvent was then removed by evaporation at 40 ^{O}C. The solid dispersions prepared were pulverized and sifted (80#) and stored in adesiccators.

Preparation of drug -polaxamer physical mixtures: The physical mixtures of Nelfinavir with Polaxamer-188 were prepared by mixing accurately weighed quantities of drug and carrier in above stated proportions in a glass mortar and sifted through mess no (80#).

Drug content estimation: An accurately weighed quantity of solid dispersions and physical mixtures equivalent to 25 mg of drug was taken into a 50 ml volumetric flask and dissolved in minimum amount of ethanol and volume was made up to the mark with phosphate buffer(pH 6.8) and assayed for drug content using UV double beam spectrophotometer at 232 nm.

Table No. 5: Drug content percentage of physical mixtures (PM) and soliddispersions (SD)

Drug: Poloxamer Ratio	Nelfinavir Content %	
	Poloxamer -Preparation	
	PM	SD
1:1	74.56	74.26
1:3	70.83	71.22
1:5	59.57	63.59
1:7	60.12	61.13

***In-vitro* evaluation of Nelfinavir-Poloxamer solid Dispersions**

Dissolution studies were conducted for pure Nelfinavir, solid dispersions and physical mixture using USP paddle type apparatus at 37 ± 0.5^{0}C at 70 rpm. 900 ml of phosphate buffer (pH 6.8) was used with Tween-80(1.6% v/v) as dissolution medium. The drug, inclusion complex and physical mixture was filled in hard gelatin capsule shell so as to contain an equivalent of 50 mg of pure Nelfinavir .At various time intervals, 5 ml of sample was withdrawn from a fixed position of the vessel and replaced with fresh dissolution medium. The absorbance of filtered sample was notedat 232 nm. The drug released at various time intervals was calculated.

Table No 6: percentage cumulative drug release values of Nelfinavir from physical mixtures and solid dispersions

Time Interval (in min)	Pure Drug % CDR	CUMULATIVE PERCENTAGE DRUG RELEASE							
		SOLID DISPERSION				PHYSICAL MIXTURE			
		1:1	1:3	1:5	1:7	1:1	1:3	1:5	1:7
0	0	0	0	0	0	0	0	0	0
10	26.8	28.3	32.2	38.6	34.3	22.31	28.04	35.55	30.55
20	30.049	29.957	36.579	46.414	39.791	24.58	31.47	38.6	33.74
30	32.566	32.566	39.502	53.157	43.62	26.69	33.61	41.17	35.89
40	33.78	35.98	43.018	57.594	46.141	3186	37.18	45.71	39.03
50	34.387	39.899	45.838	59.718	49.555	33.93	40.66	49.08	41.54
60	34.99	42.821	50.153	61.63	53.074	35.68	44.94	54.68	43.25
70	35.393	45.037	50.477	63.741	53.893	37.45	47.63	58.15	45.79
80	35.896	45.449	51.079	65.252	55.998	38.21	48.33	59.42	47.88
90	34.798	45.951	51.582	64.961	57.209	39.68	49.81	61.8	51.5
100	36.792	46.454	52.585	65.159	57.516	41.13	50.11	62.04	52.35

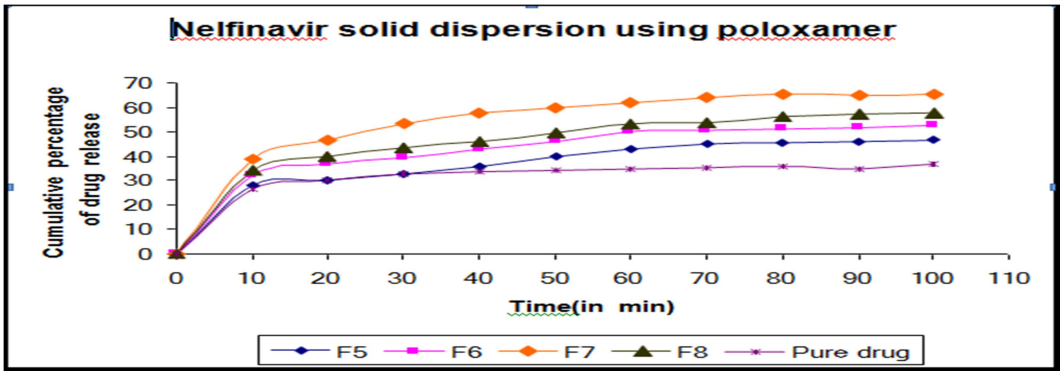

Figure 7: Comparative dissolution profiles between solid dispersionsand pure drug

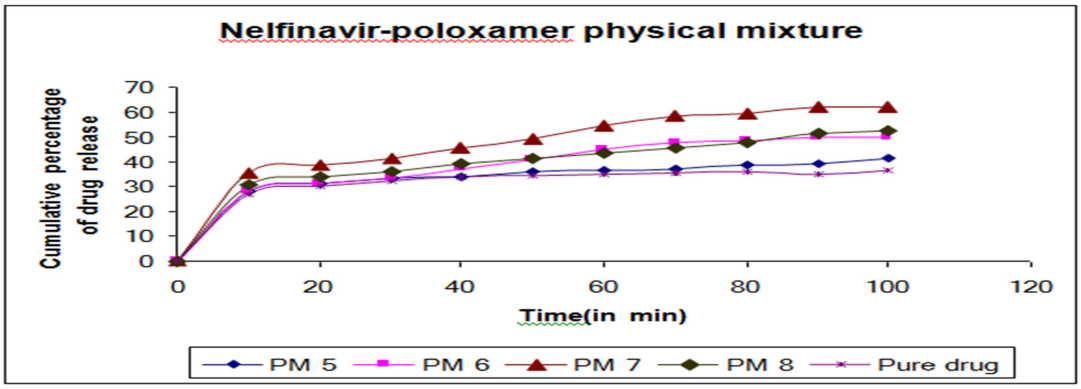

Figure 8: Comparative dissolution profile between physical mixturesand pure drug

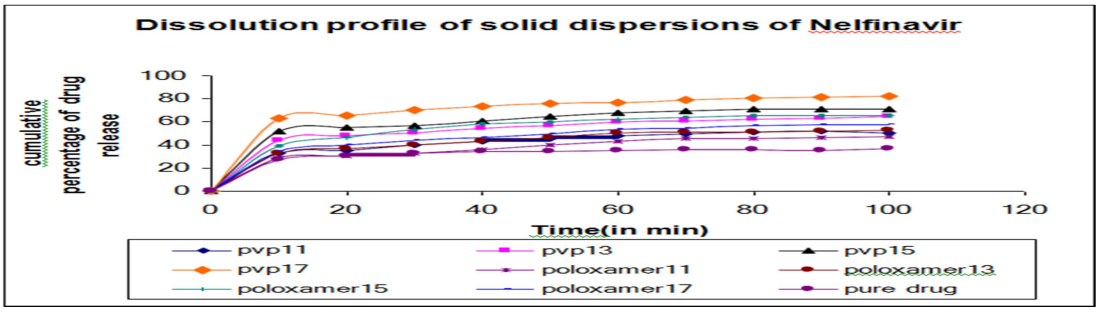

Figure 9: comparative dissolution profile between all formulationsand pure drug

Drug-Polymer Compatibility Study by FT-IR

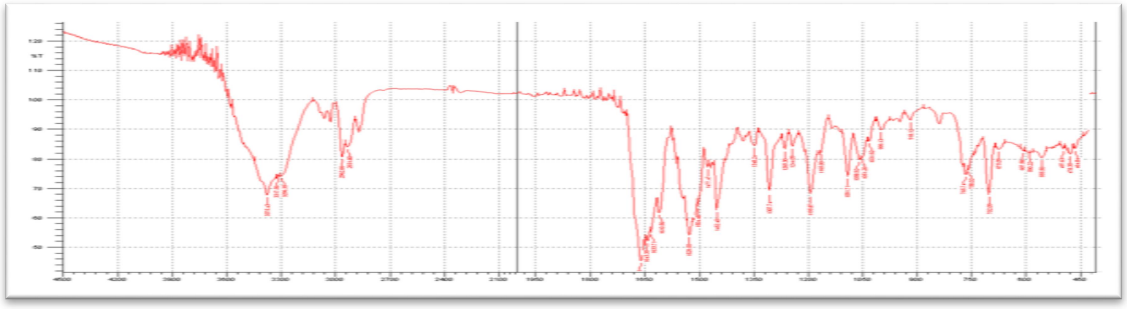

Figure 10: FTIR spectrum of pure drug (Nelfinavir)

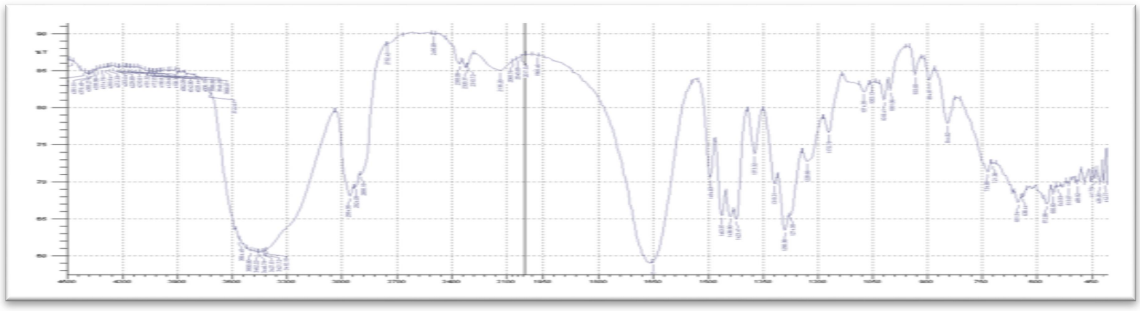

Figure 11: FTIR spectrum of PVP-K30

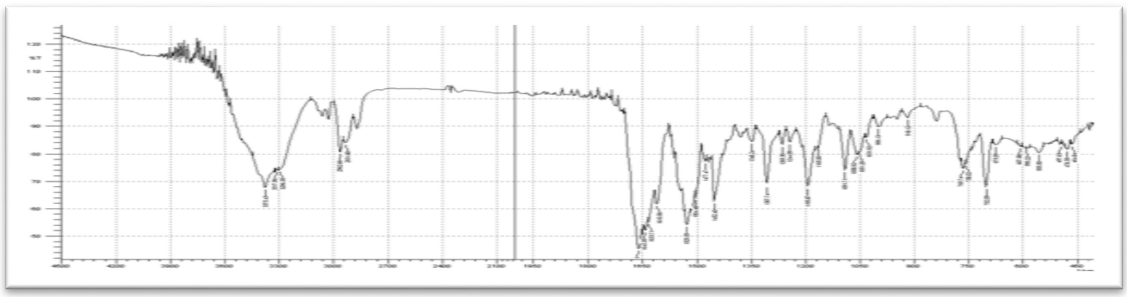

Figure 12: FTIR spectrum of poloxamer-188

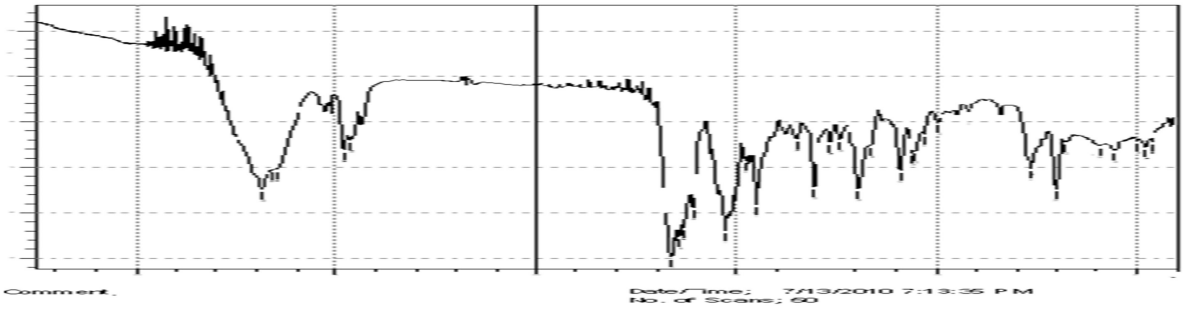

Figure 13: FTIR spectrum of Poloxamer-188 with Nelfinavir

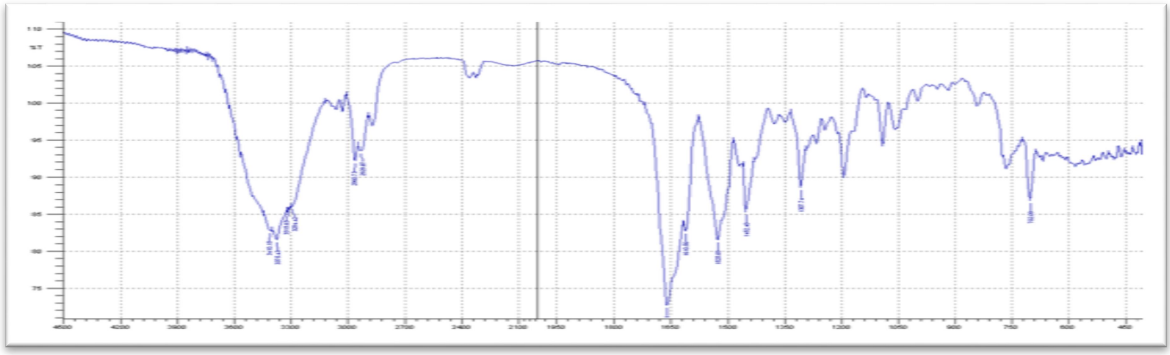

Figure 14: FTIR spectrum of PVP-K30 with Nelfinavir

Formulation of Matrix Tablets of Nelfinavir

Here the drug is homogenously dispersed throughout a rate-controlling medium. Hydrophobic and hydrophilic matrices are used to control the release of the drug having different solubility properties. The drug Nelfinavir was selected for the formulation of matrix tablets. Different polymers like Hydroxy propyl methylcellulose, (HPMC K100M), Guar gum, PVP-K30 and Ethyl cellulose were used in the present study. Diluents like Microcrystalline- cellulose (MCC) & lubricants like Magnesium stearate and aerosil were used in all the formulations. All the formulations were formulated by direct compression method.

Formulation of CR tablets of Nelfinavir using HPMC K100M and Ethyl cellulose, Guar gum and PVP-K30

Matrix tablets were prepared by compressing hydrophilic polymer (HPMC K100M),guar gum,pvp-k30 and hydrophobic polymer (Ethyl cellulose) with dispersed drug. First, all the ingredients along with drug were weighed according to the formula given in the following Table

and mixed in a polythene bag for 15mins.Then the mixture was passed through 20 mesh screen & further mixed with magnesium stearate for 4mins for the purpose of lubrication. The resulting mixture was fed in to the die of 10-station tablet punch machine (Rimek Minipress-I, India) to produce tablets of 450 mg using biconcave punches of 8 mm diameter.

Table No. 7: Formulation of Nelfinavir CR Tablets

Ingredients	Quantities of ingredients / Tablets (mg)								
	Batch Number								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Nelfinavir dispersion	250	250	250	250	250	250	250	250	250
Guar gum	-	100	100	-	180	100	-	100	-
HPMC K100M	-	-	70	100	-	80	100	-	180
PVP-K30	180	70	-	80	-	-	70	80	-
Ethylcellulose	-	10	10	-	-	-	10	-	-
MCC	18	18	18	18	18	18	18	18	18
Aerosil	1	1	1	1	1	1	1	1	1
Magnesium Stearate	1	1	1	1	1	1	1	1	1
TOTAL	450	450	450	450	450	450	450	450	450

Physico-chemical evaluation of powdered-mixtures

The prepared powdered mixtures were subjected to the following characterization prior to compression as their properties were going to play the critical role in formulation of the tablets with a flawless approach.

Table No. 8: Physico-chemical Properties of Powdered Mixtures

Formulation No.	Bulk density(X ± SD)	Tappeddensity (X ± SD)	Carr'sIndex %	Hausner 's ratio	Angle ofrepose (X ± SD)
F1	0.436 ± 0.01	0.501± 0.002	12.97	1.14	3022 ± 0.21
F2	0.489 ± 0.06	0.493 ± 0.02	10.36	1.008	29.36 ± 0.22
F3	0.428 ± 0.002	0.510 ± 0.017	16.07	1.19	30.05 ± 0.16
F4	0.465 ± 0.011	0.521 ± 0.021	10.74	1.12	28.42 ± 0.18
F5	0.492 ± 0.015	0.529 ± 0.003	6.99	1.07	30.08 ± 0.48
F6	0.433 ± 0.012	0.538 ± 0.016	19.51	1.24	32.56 ± 0.12
F7	0.482 ± 0.003	0.522 ± 0.003	7.66	1.08	30.62 ± 0.04
F8	0.421 ± 0.011	0.514 ± 0.022	18.09	1.22	30.22 ± 0.28
F9	0.473 ± 0.002	0.497 ± 0.007	6.82	1.05	28.16 ± 0.04

Data are represented as mean ± standard deviation, n=3

Evaluation of Matrix Tablets:

The compressed tablets were evaluated for their important parameters that affect the release of drug. The parameters include weight variation, thickness, hardness, friability, tablet disintegration, drug content and in-vitro drug release pattern.

Weight variation: Twenty tablets of each batch were weighed; their average weight was calculated and compared with the weight of each tablet. The tolerance in weight variation was allowed according to USP XXVI.

Diameter: Control of physical dimensions of tablet such as diameter and tablet to tablet uniformity are essential for consumer acceptance. The diameter of the tablet can be used as initial controlled parameter. Ten tablets of each batch was measured using vernier caliper and was tried to control within 5% variation of the standard value. The average diameter of tablets of each formulation is given in the Table.

Hardness Test: Ten tablets of each batch were selected and their hardness was measured using Pfizer hardness tester. It measures the pressure required to break a diametrically placed matrix tablet. The results on the hardness of all formulations are provided in the Table.

Friability Test: Ten tablets were weighed and placed in the Roche fribilator test apparatus. The tablets were exposed to rolling and repeated shocks, resulting from free falls within the apparatus. After 100 revolutions, the tablets were reduced and weighed again. The friability was determined using following formula as the percentage loss in weight of the tablets. It should be less than 1%.

$$\%\ \boldsymbol{Friability} = \left[1 - \frac{weight\ of\ tablets\ after\ test}{weight\ of\ tablets\ before\ test}\right] X\ 100$$

Drug content estimation: Drug content of each tablet was estimated employing the standard spectrophotometric method. Drug content estimation for Nelfinavir was carried out by measuring the samples at 232nm using Thermo-scientific 164 double beam UV/Vis. spectrophotometer and comparing the content from a calibration curve prepared with pure Nelfinavir with phosphate buffer. The percentage drug contents of all formulations are given in the Table.

Table No. 9: Physico-Chemical Properties of Prepared Tablets

Formulation No.	Avg. Wt. (mg) (X ± Sd)	Hardness kg/cm^2)(X±Sd)	Diameter (cm)(X ± Sd)	Drug Content (X ± Sd)	Friability
F1	447.22 ± 0.479	5.08 ± 0.322	10.98 ± 0.039	99.234 ± 0.604	0.013
F2	448.08 ± 0.644	4.6. ± 0.289	10.67 ± 0.062	98.64 ± 0.712	0.025
F3	448.12 ± 0.712	5.06 ± 0.365	10.68 ± 0.048	99.37± 0.235	0.011
F4	447.86 ± 0.666	4.68 ± 0.441	10.32 ± 0.038	97.579 ± 0.413	0.026
F5	447.76 ± 0.764	6.08 ± 0.284	10.57 ± 0.048	99.885 ± 0.524	0.018
F6	447.98 ± 0.212	4.98 ± 0.462	10.38 ± 0.041	99.372 ± 0.228	0.021
F7	449.12 ± 0.462	5.66 ± 0.287	10.98 ± 0.037	99.895± 0.463	0.013
F8	448.18 ± 0.518	4.69 ± 0.423	10.76 ± 0.44	98.79 ± 0.182	0.029
F9	449.02 ± 0.341	6.02 ± 0.501	10.83 ± 0.039	98.23 ± 0.231	0.016

Data are represented as mean ± standard deviation, n=3

***In-vitro* Dissolution Study:** *In-vitro* dissolution studies were designed to carry out in such a way that they simulate in vivo conditions. The purpose of *in-vitro* release study was to provide a fast, easily performed and in-expensive method that correlates with the performance of dosage form in human subjects. The conditions of *in-vitro* dissolution test were well defined, standardized and enable comparison among various results. The *in-vitro* dissolution study, the dissolution was done in pH 6.8 phosphate buffer.

Mechanism of Drug Release

To find out the mechanism of drug release from hydrophilic matrices, the dissolution data of tablets of each batch was treated with different kinetic equations, namely zero order, 1st order, Higuchi, Hixon-crowell, Korsemeyer and Peppas etc.

Table No. 10: Cumulative percentage of drug released from the formulations

Time (Hrs)	CUMULATIVE PERCENTAGE OF DRUG RELEASE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	15.09	6.818	6.818	7.071	7.092	8.001	8.102	5.541	13.339
1	25.806	19.212	12.318	19.102	21.337	22.163	19.168	9.409	25.25
2	38.831	33.338	23.083	29.623	32.339	30.943	33.134	20.822	38.118
3	56.059	56.613	41.303	43.822	47.183	50.411	44.259	28.061	51.234
4	60.721	68.062	48.548	47.675	55.901	63.153	54.521	34.326	57.031

5	69.563	75.071	63.823	56.209	64.761	71.007	62.662	46.228	63.637
6	73.002	80.05	79.641	67.73	75.029	80.958	68.026	52.018	74.731
7	81.952	85.262	88.401	75.183	87.038	88.521	76.046	63.892	85.957
8	90.232	91.516	90.315	89.227	91.738	92.342	79.235	81.193	94.012
9	97.562	95.045	94.781	95.283	98.483	98.152	85.156	95.295	97.628
10		99.246	95.402	95.283			90.067	98.484	
11			99.124				98.562		

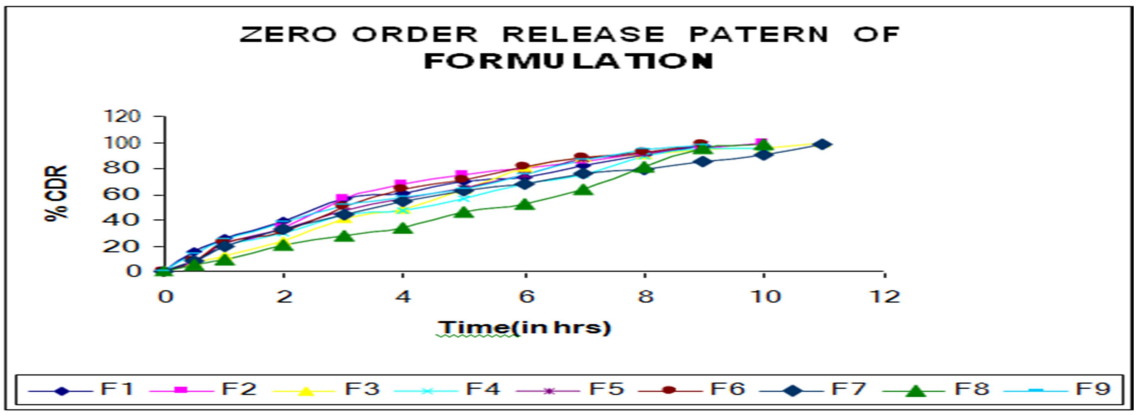

Figure 15: **Zero order release profiles of formulations**

Table No. 11: Regression analysis of different release kinetics

Formulations	Zero order	First-order	Higuchi	Korsemey-Peppas	Release exponent (n) values
F1	0.9484	0.9385	0.9913	0.9916	0.625
F2	0.9247	0.9826	0.9725	0.9525	0.851
F3	0.9776	0.9562	0.9558	0.9836	0.9122
F4	0.9543	0.8712	0.972	0.9792	0.8089
F5	0.9777	0.9417	0.9775	0.9721	0.847
F6	0.9587	0.9806	0.9763	0.9723	0.8287
F7	0.9865	0.9969	0.9886	0.9789	0.7548
F8	0.9854	0.8516	0.911	0.9938	0.9658
F9	0.9687	0.9112	0.9835	0.9794	0.655

Table No. 12: Release of Nelfinavir from optimized matrix tablet F-7

Drug Release order/model	R^2 (coefficient of correlation)
Zero order release model	0.9543
First order release model	0.9969
Higuchi model	0.9886
Korsemeyer-peppas	0.9789

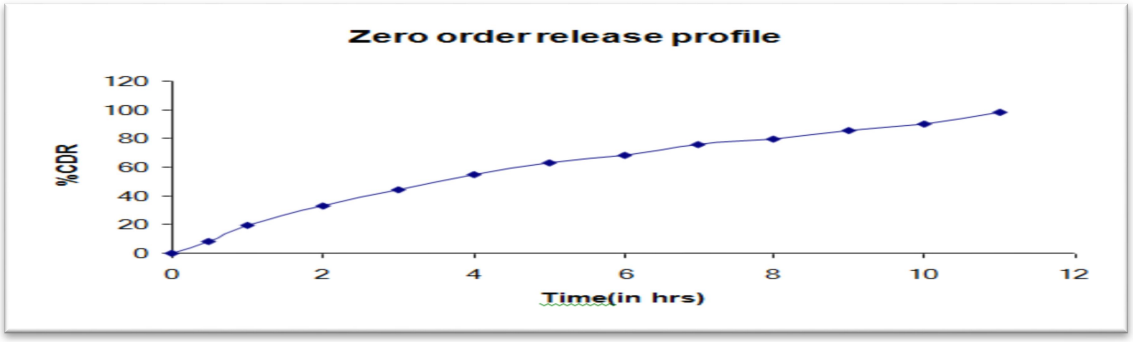

Figure 16: **Zero order release profile of formulation F7**

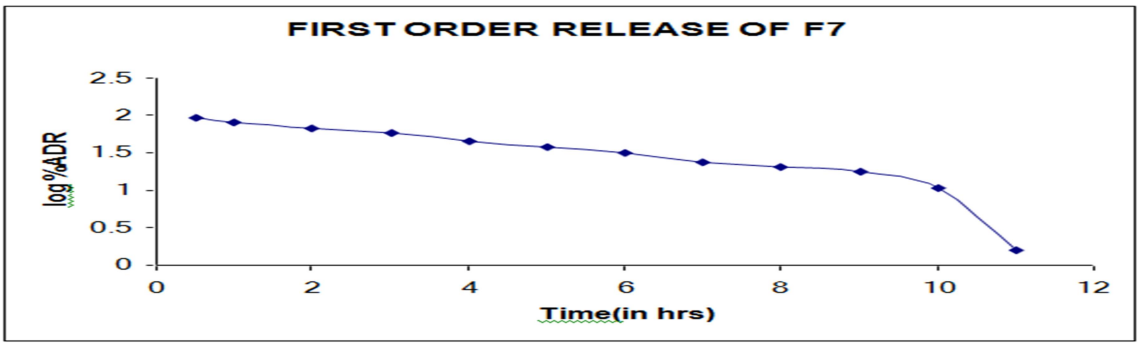

Figure 17: First order release profile of formulation F7

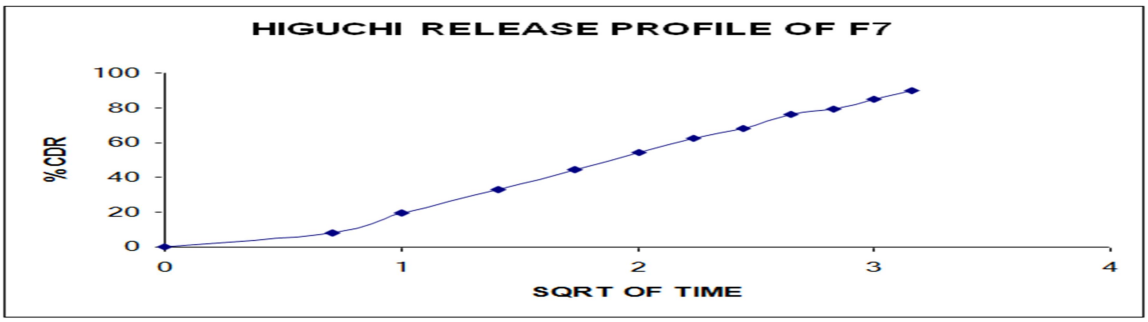

Figure 18: Higuchi release profile of formulation F7

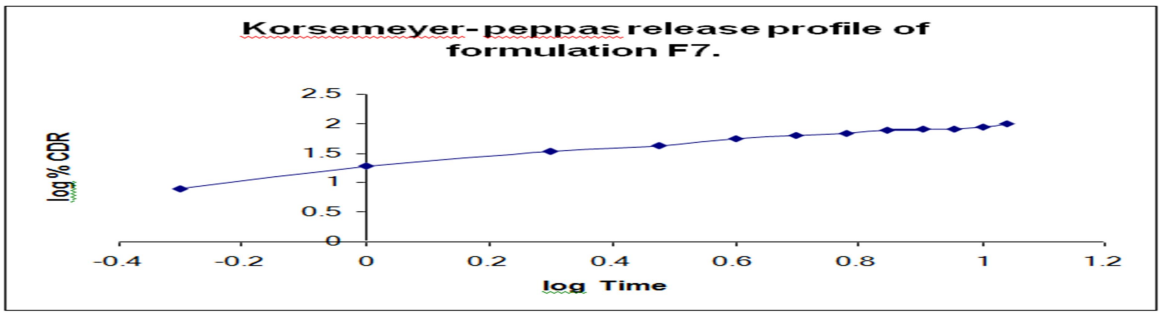

Figure 19: **Korsemeyer- peppas release profile of formulation F7**

RESULTS AND DISCUSSION

Nelfinavir is an antiviral (HIV protease inhibitor) used in the treatment of AIDS. Due to poor aqueous solubility, it is give rise to difficulties in the design of pharmaceutical dosage forms and leads to its poor and variable oral bioavailability. Thus, an attempt was made to increase the solubility of drug by preparing it in solid dispersions forms.

In present work, solid dispersions of Nelfinavir with PVP-K30 and Nelfinavir with Polaxamer-188 was tried to improve the solubility and dissolution rate. To explore the effect of Pvp-K30 and Poloxamer-188 concentration on the solubility of Nelfinavir, phase solubility studies were performed. The phase solubility diagram for the complex formation between Nelfinavir and PVP-K30 is shown in Fig no-3 and Nelfinavir-Poloxamer-188 is shown in Figure 4. In case of PVP the aqueous solubility of Nelfinavir was increased linearly as a function of the concentration of PVP. The phase solubility diagram of Nelfinavir-PVP dispersions can be classified as AL type according to Higuchi and Connors. Because the straight line had a slope less than unity, the increase in solubility was due to the formation of a 1:5M complex in solution. The apparent solubility constant (Kc) obtained from the slope of phase solubility diagram was found to be 0.0731. The value of the Kc indicated that Nelfinavir-PVP complex is quite stable.

Solid dispersions of Nelfinavir-PVP-K30 were prepared in different molar ratios (1:1, 1:3, 1:5, 1:7) by solvent evaporation method. Likewise physical mixtures were prepared in previous mentioned ratio. The percentage of drug content of all prepared complexes along with the physical mixtures was estimated. Result displayed that 1:1M complex has higher dug content of about 76.65%. Dissolution profiles of pure Nelfinavir, Nelfinavir-PVP-K30 dispersions and physical mixtures were determined. A comparative dissolution profile of all prepared dispersions with pure drug displayed in fig no-5 and physical mixtures were established, displayed in fig no- 6. It can be seen that after 20 minutes only 30 % pure drug is dissolved and even after 100 minutes only 36 % drug goes into solution where as in case of Nelfinavir and PVP-K30 complex prepared by solvent evaporation method in a 1:7 molar ratio 38.6% drug was released within 10 minutes and 65.15% was seen after 100 minutes. Hence, it can be said that inclusion complexes shows higher dissolution than pure drug and physical mixtures. Solid dispersions were also prepared in same ratios by using Polaxamer-188 as carrier. The percentage of drug content of all

prepared solid dispersions along with thephysical mixtures was estimated.

Dissolution profiles of pure Nelfinavir, Nelfinavir-Poloxamer-188 surface solid dispersions and physical mixtures were determined. A comparative dissolution profile of all prepared solid dispersions and physical mixtures were established. It can be seen that after 20 minutes only 30 % pure drug is dissolved and even after 60 minutes only 34.99 % drug goes into solution where as in case of Nelfinavir-Poloxamer prepared by solvent evaporation method in 1:5 molar ratio 52.41 % drug was released within 10 minutes and almost 66.89 % was released seen after 60 minutes. The dissolution rate of Nelfinavir was strongly dependent on the relative concentration of the drug to Poloxamer ratio. The dissolution rate of Nelfinavir from Poloxamer solid dispersions was increased with increment in Poloxamer concentration upto drug: carrier ratio of 1:5. The further increase in amount of Poloxamer in solid dispersions decreased the dissolution rate. The decreased in dissolution rate of the solid dispersions containing higher polymer proportions might be caused by leaching out of the carrier during dissolution which could form a concentrated layer of solution around the drug particles there by reducing the migration of the release drug particles to the bulk of the solution.

Solid dispersion of Nelfinavir with-PVP showed higher solubility than the solid dispersions with Poloxamer. So Nelfinavir-PVP dispersions were used for preparation of controlled release formulation. Matrix tablets were prepared by direct compression technology using various polymers such as Guar gum, HPMC-K100M, Ethyl Cellulose. Total of 9 formulations were prepared by varying concentrations of polymer blends. The formulations were evaluated for various quality control tests. All the formulations were found to be satisfactory and reproducible. Tablet hardness was found to be good (between 4.5-6 kg/cm^2) depending compression force applied and friability was less than 0.5 %. Formulation F1 contain 40 % PVP-K30 showed 15 % release within 0.5 hrs of dissolution study and showed 97 % of drug release up to 9 hr of dissolution study. Formulation F2 contain 22.22 % guar gum showed 6.8 % release within 0.5 hrs of dissolution study and showed 99 % of drug release up to 10 hr of dissolution study. Formulation F3 and F4 respectively contain 22.22 % guar gum and 22.22% of HPMC showed 99 % of drug release up to 11 hr of dissolution study and showed 95 % of drug release up to 10 hr of dissolution study. Similarly F5 and F6 contain 40% and 22.2% of guar gum, both of them showed 98 % of drug release up to 10 hr and 9 hr of dissolution study. Formulation F8

containing 22.2% of guar gum showed. 98 % of drug release up to 11 hr of dissolution study. Formulation F9 containing 40% of HPMC showed. 97 % of drug release up to 9 hr of dissolution study. Formulation F1 and F 9 showed more amount of drug release within first half hour. Sudden release of medicaments from F1 and F9 could be due to sudden bursting of tablet. A comparison study was done between formulation F4 and F7. Formulations F4 (without EC) and F7 (containing EC) both containing same amount of HPMC but F7 showing the drug release for a prolonged period of time. This could be due to presence of ethyl cellulose that acts as hydrophobic diffusion barrier. Therefore it is cleared that presence of Ethyl cellulose extended release of drug. Formulation F7 have shown better drug retarding ability upto 11 hr.

Another comparison study was done between formulation F2 and F3. Both contain same amount of guar gum (22.2 %) and same amount of Ethyl cellulose (2.2%), but F2 contain 15% of PVP and F3 contain 15% of HPMC. Formulation F3 retarded the drug release for a prolonged period of time. Therefore, from the above study it is cleared that drug-retarding property of HPMC with ethyl cellulose plays a major role with retarding property from PVP. The *in-vitro* release pattern of the optimized formulation was analyzed by fitting the dissolution data into various kinetic models. It was seen that R^2 value was higher when fitted to Higuchi model followed by zero order equation. This indicated a higuchi release from the optimized Nelfinavir matrix tablets. As the 'n'- value for formulation in between 0.5 to 1 which indicates the predominant matrix swelling and erosion.

CONCLUSION

The experimental work concluded that the Solid dispersions with PVP shown as a successful approach to improve the dissolution rate of Nelfinavir in comparison to solid dispersion prepared with Poloxamer . The phase solubility study indicated the formation of Nelfinavir-PVP dispersions at 1:5M ratio in solution with a stability constant of 0.0734. The Solid dispersion of Nelfinavir at 1:5M prepared by solvent evaporation method showed significantly higher dissolution in comparison with powder drug, solid dispersions and physical mixtures. An IR study shows no evidence of interaction between the drug and carrier. Different formulations were designed by the optimized solid dispersion into matrix tablet dosage forms. An *in-vitro* dissolution study was carried out in simulated gastric fluid and in intestinal fluid. As the

concentration of sodium alginate increased, they automatically delayed drug release. The release results were fitted to different kinetic model. Formulation F7 showed release of 99% for a period of 11 hrs, moreover, obeyed higuchi kinetic model.

CONFLICTS OF INTERESTS

There are no conflicts of interests.

REFERENCES

1. Allen LVJ, Yanchick VA and Maness DD. Dissolution rates of corticosteriods utilizing sugar glass dispersions. J. Pharm. Sci., 1977;66(4): 494-496.
2. Amidon GL, Lennernas H, Shah VP and Crison JR. Theoretical basis for a biopharmaceutical drug classification: the correlation of in vitro drug product dissolution and *in vivo* bioavailability. Pharm Res., 1995;12(3): 413-420.
3. Bayomi MA, Abanumay KA and Al-Angary AA. Effect of inclusion complexation with cyclodextrins on photostability of nifedipine in solid state. Int. J. Pharm., 2002;243(1-2):107-117.
4. Savic R, Eisenberg A, Maysinger D. Block copolymer micelles as delivery vehicles of hydrophobic drugs: Micelle-cell interactions. J Drug Target 2006;14:343-355.
5. Ahuja N, Katare OP, Singh B. Studies on dissolution enhancement and mathematical modeling of drug release of a poorly water-soluble drug using water-soluble carriers. Eur J PharmBiopharm 2007;65:26-38.
6. R. D. Reddy, Solid Dispersion Technology, University College Cork British Pharmaceutical Conference, Manchester 2008
7. Dberg A, Gibaldi M, Kanig L, “Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures II experimental evaluation of a eutectic mixture: urea-acetaminophen system”, J. Pharm. Sci. 1966; 55; 482-487.
8. Dr. Smarajit Jana and Mike Bailey; *AIDS* Action Newsletter; 26; Nov. 1994
9. Ashish Chandwani , Jonathan Shuter , Lopinavir / ritonavir in the treatment Of HIV-1 infection: a review Therapeutics and Clinical Risk Management 2008:4(5); 1023.
10. K. Chowdary, G. Kamalakara, Indian J. Pharm. Sci. 2002;64:142.