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Research

Formulation And In Vitro Characterization Of Nelfinavir Extended-Release Tablets

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Abstract

The current work was focused to formulate and evaluate extended release tablets of Nelfinavir. Eudragit RL, Ethyl Cellulose and Carbopol p934 are matrix polymer can be used in formulation of extended release dosage form. Nelfinavir was considered as ideal drug for extended release formulation. The extended release matrix of Nelfinavir were prepared by direct compression method in differ matrix polymers ratio. Pre formulation studies have been performed for the Active Pharmaceutical Ingredient. Drug Excipient compatibility studies have been performed and the tablets have been prepared in eight different formulations with the change in the ratios of polymers. These tablets are evaluated for various parameters including the release of drug by using dissolution studies. Hence the study resulted in the development of Nelfinavir extended release tablets N4 formulation was considered as optimized formulation. The Kinetic treatment of selected formulation N4 showed that the release of drug follows Zero order models.

Keywords: Nelfinavir, Eudragit RL, Ethyl Cellulose, Carbopol p934 and extended release tablets.

INTRODUCTION

Historically, oral drug administration has been the predominant route for drug delivery. It is known to be the most popular route of drug administration due to the fact the gastrointestinal physiology offers more flexibility in dosage form design than most other routes. A major challenge for the pharmaceutical industry in drug development is to produce safe and efficient drugs, therefore properties of drugs and the way in which they are delivered must be optimized.

A controlled release drug delivery system delivers the drug locally or systemically at a predetermined rate for a specified period of time. The goal of such systems is to provide desirable delivery profiles that can achieve therapeutic plasma levels. Drug release is dependent on polymer properties, thus the application of these properties can produce well characterised and reproducible dosage forms.

Oral route still remains the most popular for drug administration by virtue of its convenience to the patient. A sizable portion of orally administered dosage forms, so called conventional, are designed to achieve maximal drug bioavailability by maximizing the rate and extent of absorption. While such dosage forms have been useful, frequent daily administration is necessary, particularly when the drug has a short biological half life. This may result in wide fluctuation in peak and trough steady-state drug levels, which is undesirable for drugs with marginal therapeutic indices. Moreover, patient compliance is likely to be poor when patients need to take their medication three to four times daily on chronic basis. Fortunately, these short comings have been circumvented with the introduction of controlled release dosage forms. These dosage forms are capable of controlling the rate of drug delivery, leading to more sustained drug levels and hence therapeutic action.

Hydrophillic matrix systems are among the most commonly used means for oral controlled drug delivery as they can reproduce a desirable drug profile and are cost effective. The primary mechanism of drug release from hydrophilic matrices occurs when the polymer swells on contact with the aqueous medium to form a gel layer on the surface of the system. The drug then releases by dissolution, diffusion and/or erosion.

TERMINOLOGY

A list of important terms that describe different modified release dosage forms are defined below.

Modified release dosage forms (MRDF): Defined as those dosage forms whose drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms.

Controlled release (CR): The drug is released at a constant (zero order) rate and the drug concentration obtained after administration is invariant with time.

Delayed release: The drug is released at a time other than immediately after administration.

Extended release (ER): Slow release of the drug so that plasma concentrations are maintained at a therapeutic level for a prolonged period of time (usually between 8 and 12 hours).

Prolonged release: The drug is provided for absorption over a longer period of time than from a conventional dosage form. However, there is an implication that onset is delayed because of an overall slower release rate from the dosage form.

Repeat action: Indicates that an individual dose is released fairly soon after administration, and second or third doses are subsequently released at intermittent intervals.

Sustained release (SR): The drug is released slowly at a rate governed by the delivery system.[1]

ZERO ORDER DELIVERY

Zero order, or constant rate release of drug is desirable in order to minimize swings in drug concentration in the blood. In conventional dosage forms rapid increase in concentration is followed by a rapid decrease, and little time is spent inside the so-called therapeutic range, which is bounded below by a minimum effective concentration (MEC) and above by a minimum toxic concentration (MTC). Frequent repetitive dosing is required to maintain concentration within these limits, and compliance and control are difficult [2].

Dosage forms that prolong release can maintain drug concentration within the therapeutic range for extended periods and minimize episodes of underexposure or toxicity. A well designed system displays a narrow, predictable residence time distribution in the gastrointestinal (GI) tract, and releases drug by a controlled mechanism. Zero order release leads, in principle, to the best control of plasma concentration. Such control leads to constant drug effect, provided the drug's pharmacokinetic and pharmacodynamic properties, including absorption, distribution, metabolism, and excretion (ADME), and its pharmacodynamic properties relating plasma concentration to drug effect, are stationary.

MATERIALS AND METHODS

Nelfinavir Procured From Mylan, Hyderabad. Provided by SURA LABS, Dilsukhnagar, Hyderabad. Eudragit RL from Elder Pharmaceuticals Pvt Ltd, Dehradun (India), Ethyl Cellulose
From Elder Pharmaceuticals Pvt Ltd, Dehradun (India), Carbopol p934 from Elder Pharmaceuticals Pvt Ltd, Dehradun (India), Povidone from Merck Specialities Pvt Ltd, Mumbai, India, Aerosil from Merck Specialities Pvt Ltd, Mumbai, India, Magnesium Stearate from S.D. Fine Chem. Ltd. Mumbai MCC PH 102 S.D. Fine Chem. Ltd. Mumbai.

Analytical method development

Determination of Wavelength

10mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From secondary stock solution again 1ml was taken it in to another volumetric flask and made it up to 10 ml with media (working solution - 10µg/ml). The working solution was taken for determining the wavelength.

Determination of Calibration Curve

10mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From secondary stock solution required concentrations were prepared (shown in Table 8.1 and 8.2) and those concentrations absorbance were found out at required wavelength.

Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Formulation development of Tablets

All the formulations were prepared by direct compression. The compositions of different formulations are given in Table. The tablets were prepared as per the procedure given below and aim is to prolong the release of Nelfinavir. Total weight of the tablet was considered as 500mg.

Table 1: Ingredients categories

S.No	INGREDIENTS	USES
1.	Nelfinavir	API
2.	Eudragit RL	Polymer
3.	Ethyl Cellulose	Polymer
4.	Carbopol p934	Polymer
5.	Povidone	Tablet disintegrant
6.	Aerosil	Anticaking agent
7.	Magnesium Stearate	Lubricant
8.	MCC PH 102	Adsorbent; Suspending agent

Procedure

1) Nelfinavir and all other ingredients were individually passed through sieve no ≠ 60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method.

Table 2: Formulation composition for tablets

INGREDIENTS (MG)	FORMULATION							
	N1	N2	N3	N4	N5	N6	N7	N8
Nelfinavir	250	250	250	250	250	250	250	250
Eudragit RL	10	10	10	10	10	10	10	10
Ethyl Cellulose	25	50	75	100	-	-	-	-
Carbopol p934	-	-	-	-	25	50	75	100
Povidone	10	10	10	10	10	10	10	10
Aerosil	4	4	4	4	4	4	4	4
Magnesium Stearate	4	4	4	4	4	4	4	4
MCC PH 102	QS	QS	QS	QS	QS	QS	QS	QS
Total weight(100)	500	500	500	500	500	500	500	500

All the quantities were in mg

RESULT AND DISCUSSION

The present study was aimed to developing extended release tablets of Nelfinavir using various polymers. All the formulations were evaluated for physicochemical properties and *in vitro* drug release studies.

Analytical Method

Graphs of Nelfinavir were taken in 0.1N HCl and in pH 6.8 phosphate buffer at 250 nm and 253 nm respectively.

Table 3: Observations for graph of Nelfinavir HCl in 0.1N HCl (250 nm)

Conc. [µg/ml]	Absorbance
0	0
5	0.125
10	0.231
15	0.334
20	0.458
25	0.561

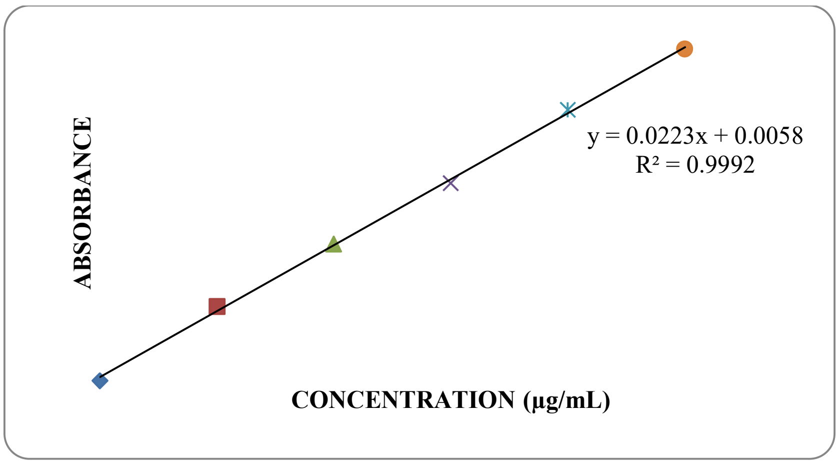


Fig 1: Standard graph of Nelfinavir in 0.1N HCl

Table 4: Observations for graph of Nelfinavir in pH 6.8 phosphate buffer (253nm)

Concentration [µg/ml]	Absorbance
0	0
5	0.134
10	0.252
15	0.357
20	0.492
25	0.599

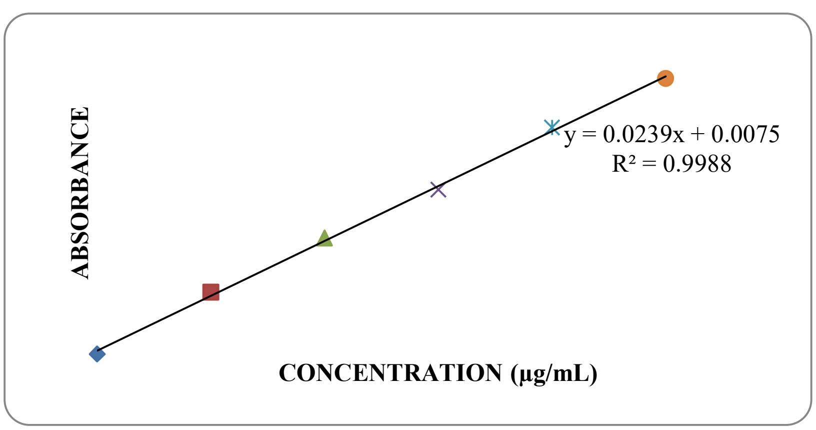


Fig 2 : Standard graph of Nelfinavir pH 6.8 phosphate buffer (253 nm)

Preformulation parameters of powder blend

Table 5: Pre-formulation parameters of Core blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
N1	26.05±0.65	0.307	0.444	13.46	1.16
N2	25.94±0.56	0.384	0.434	17.85	1.22
N3	26.02±0.61	0.267	0.307	13.33	1.15
N4	26.21±0.93	0.346	0.404	14.35	1.16
N5	26.28±0.33	0.323	0.376	14.09	1.16
N6	25.81±0.61	0.393	0.453	13.24	1.15
N7	26.10±0.53	0.318	0.368	13.58	1.16
N8	26.21±0.32	0.312	0.358	12.84	1.15

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.267 to 0.393 (gm/cm^3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.307 to 0.453 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 17.85 which show that the powder has good flow properties. All the formulations has shown the hausner ratio below 1.22 indicating the powder has good flow properties.

Quality Control parameters for tablets

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the compression coated tablet.

Table 6: *In-vitro* quality control parameters for tablets

Formulation codes	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)
N1	499.36	4.1	0.86	5.15	97.10
N2	497.25	4.5	0.64	5.69	99.91
N3	497.62	4.7	0.53	5.14	98.68
N4	500.04	4.9	0.42	5.55	99.42
N5	498.12	4.0	0.54	5.20	100.13
N6	496.74	4.2	0.45	5.48	99.71
N7	498.37	4.9	0.36	5.92	97.82
N8	499.86	4.0	0.24	5.48	96.86

Weight variation test

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet and was shown in the Table 8.4. The average weight of the tablet is approximately in range of 496.74 to 500.04 mg, so the permissible limit is ±7.5% (>500 mg). The results of the test showed that, the tablet weights were within the pharmacopoeia limit.

Hardness test

Hardness of the three tablets of each batch was checked by using Pfizer hardness tester and the data's were shown in Table 8.4. The results showed that the hardness of the tablets is in range of 4.0 to 4.9 kg/cm^2, which was within IP limits.

Thickness

Thickness of three tablets of each batch was checked by using Micrometer and data shown in Table-8.4. The result showed that thickness of the tablet is raging from 5.14 to 5.92 mm.

Friability

Tablets of each batch were evaluated for percentage friability and the data were shown in the Table 8.4. The average friability of all the formulations was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

Drug content

Drug content studies were performed for the prepared formulations. From the drug content studies it was concluded that all the formulations were showing the % drug content values within 96.86-100.13 %.

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

***In-Vitro* Drug release studies**

Table 7: Dissolution data of Nelfinavir tablets

TIME (H)	CUMULATIVE % OF DRUG RELEASE							
	N1	N2	N3	N4	N5	N6	N7	N8
0	0	0	0	0	0	0	0	0
1	20.25	15.42	14.62	12.62	27.04	24.65	15.42	14.62
2	37.26	24.73	19.86	15.86	35.69	32.59	24.73	19.86
3	42.16	39.63	25.35	23.35	41.46	38.34	39.63	25.35
4	58.01	48.04	30.45	28.45	56.97	43.40	48.04	30.45
5	68.26	57.25	39.8	36.08	62.54	58.29	53.25	39.85
6	77.19	66.33	47.25	42.25	79.06	64.85	57.33	47.25
7	82.64	70.41	58.24	50.24	85.39	70.22	63.41	58.24
8	98.19	85.84	65.73	68.73	97.93	78.78	71.84	65.73
9		90.8	71.34	77.34		85.46	76.08	71.34
10		97.35	87.52	81.52		93.34	81.26	77.52
11			98.17	96.17		98.27	90.14	80.17
12				99.18			96.72	89.81

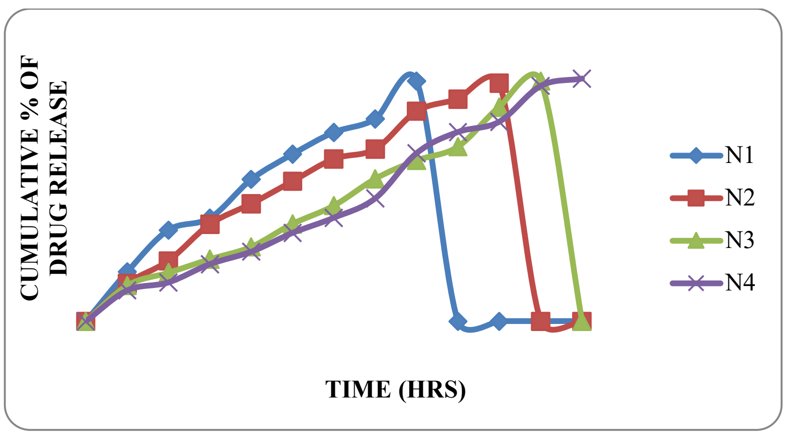


Fig 3: Dissolution profile of Nelfinavir (N1 to N4 formulations)

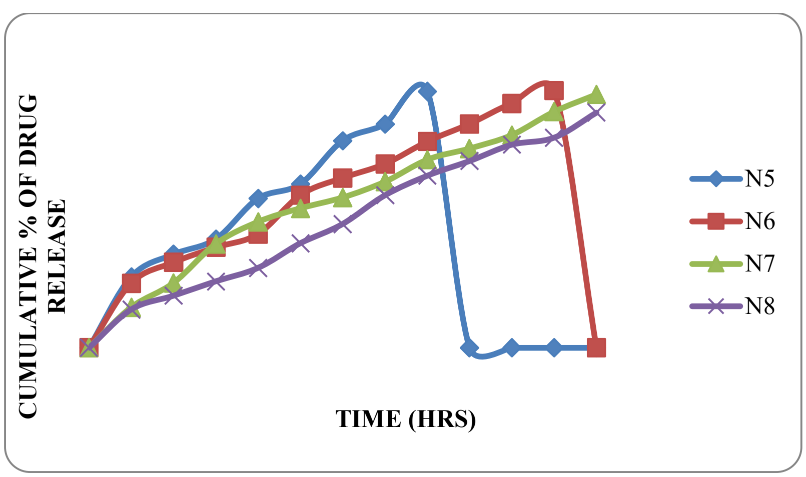


Fig 4: Dissolution profile of Nelfinavir (N5 to N8 formulations)

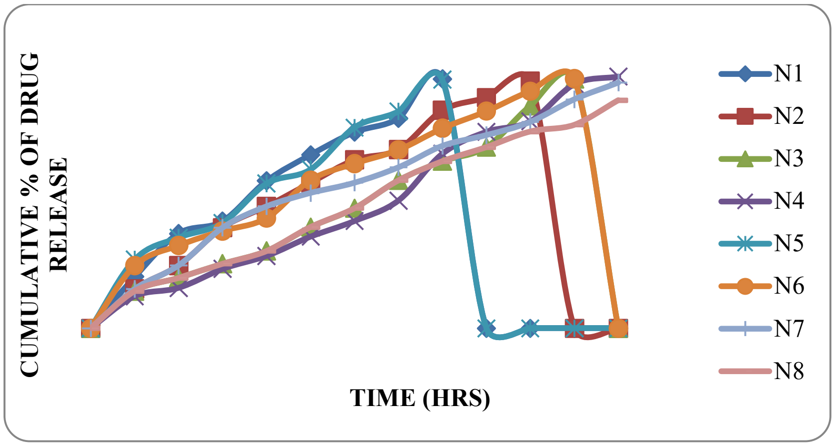


Fig 5: Dissolution profile of Nelfinavir (N1-N8 formulations)

From the dissolution data it was evident that the formulations prepared with Eudragit RL and Ethyl Cellulose as combination polymer were retard the drug release up to desired time period i.e., 12 hours in higher concentration of polymer.

Formulations prepared with Eudragit RL and Carbopol p934 retarded the drug release in the concentration of 10 mg (Eudragit RL) and 50mg (Carbopol p934) (N6 Formulation) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 98.27% in 12 hours with good retardation.

From the above results it was evident that the formulation N4 is best formulation with desired drug release pattern extended up to 12 hours.

Application of Release Rate Kinetics to Dissolution Data

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Table 8: Release kinetics data for optimised formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
12.62	1	1.000	1.101	0.000	1.941	12.620	0.0792	-0.899	87.38	4.642	4.437	0.204
15.86	2	1.414	1.200	0.301	1.925	7.930	0.0631	-0.800	84.14	4.642	4.382	0.260
23.35	3	1.732	1.368	0.477	1.885	7.783	0.0428	-0.632	76.65	4.642	4.248	0.394
28.45	4	2.000	1.454	0.602	1.855	7.113	0.0351	-0.546	71.55	4.642	4.151	0.490
36.08	5	2.236	1.557	0.699	1.806	7.216	0.0277	-0.443	63.92	4.642	3.998	0.643
42.25	6	2.449	1.626	0.778	1.762	7.042	0.0237	-0.374	57.75	4.642	3.865	0.776
50.24	7	2.646	1.701	0.845	1.697	7.177	0.0199	-0.299	49.76	4.642	3.678	0.963
68.73	8	2.828	1.837	0.903	1.495	8.591	0.0145	-0.163	31.27	4.642	3.150	1.491
77.34	9	3.000	1.888	0.954	1.355	8.593	0.0129	-0.112	22.66	4.642	2.830	1.812
81.52	10	3.162	1.911	1.000	1.267	8.152	0.0123	-0.089	18.48	4.642	2.644	1.998
96.17	11	3.317	1.983	1.041	0.583	8.743	0.0104	-0.017	3.83	4.642	1.565	3.077
99.18	12	3.464	1.996	1.079	-0.086	8.265	0.0101	-0.004	0.82	4.642	0.936	3.706

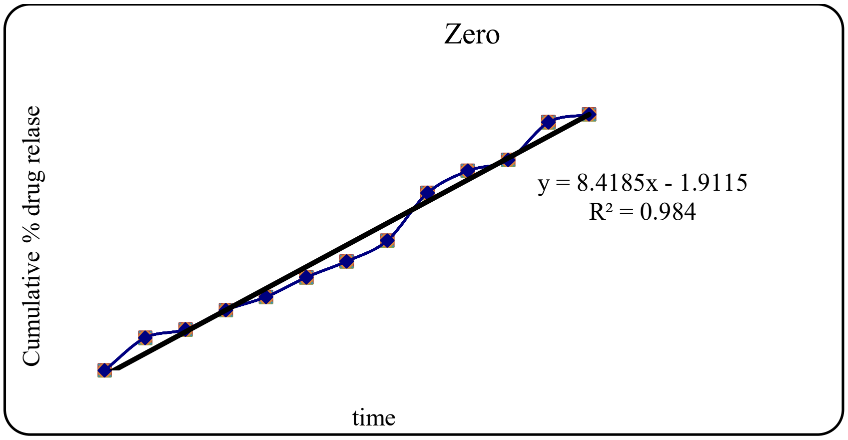


Fig 6: Zero order release kinetics graph

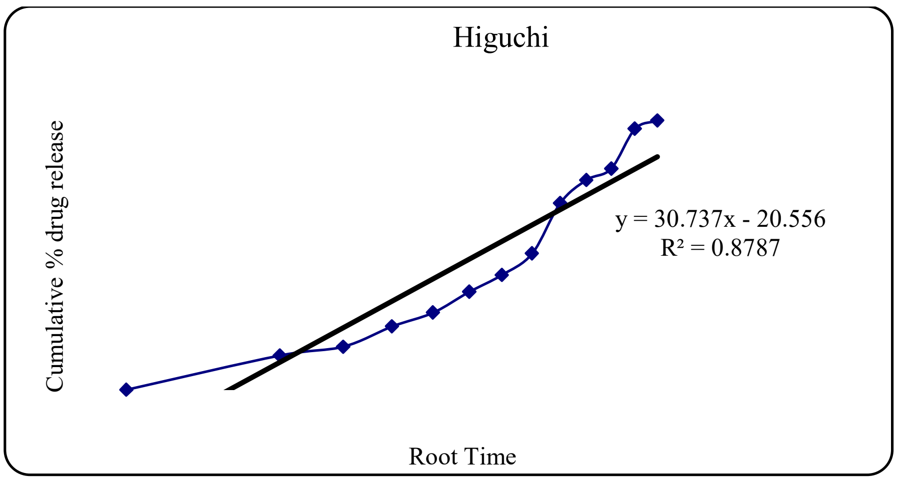


Fig 7: Higuchi release kinetics graph

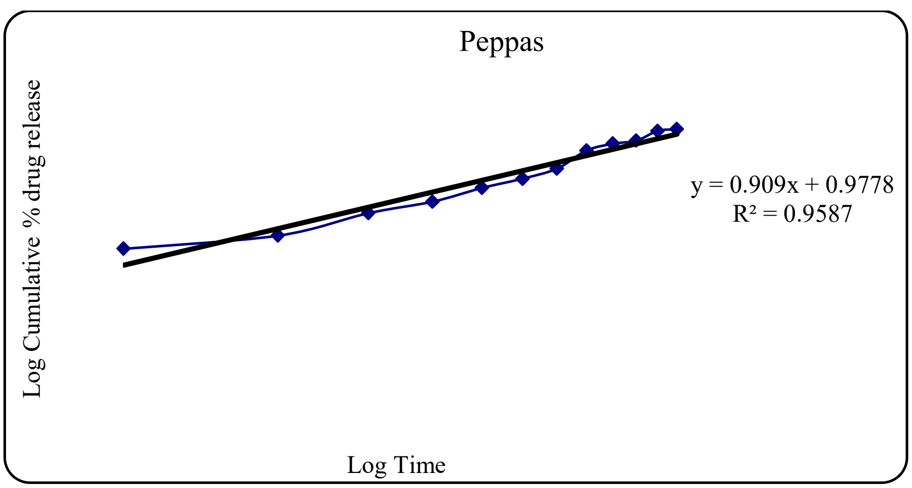


Fig 8: Kars mayer peppas graph

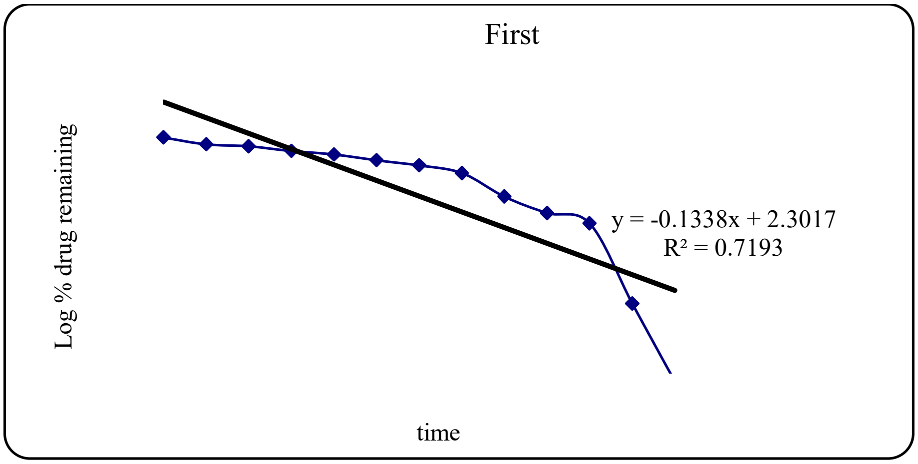


Fig 9: First order release kinetics graph

From the above graphs it was evident that the formulation N4 was followed Zero order release kinetics.

Drug – Excipient compatibility studies
Fourier Transform-Infrared Spectroscopy

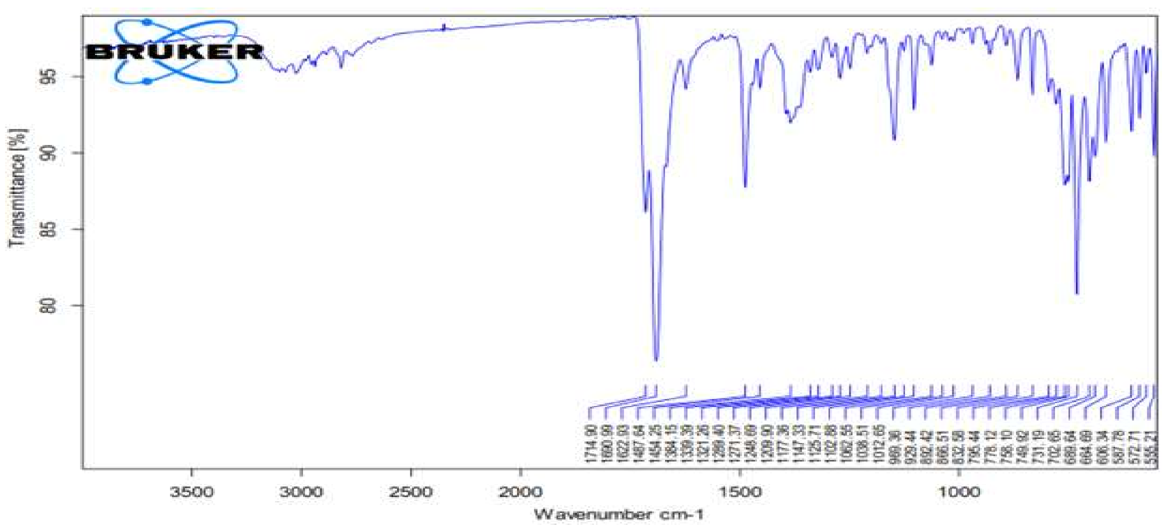


Fig 10: FT-TR Spectrum of Nelfinavir pure drug.

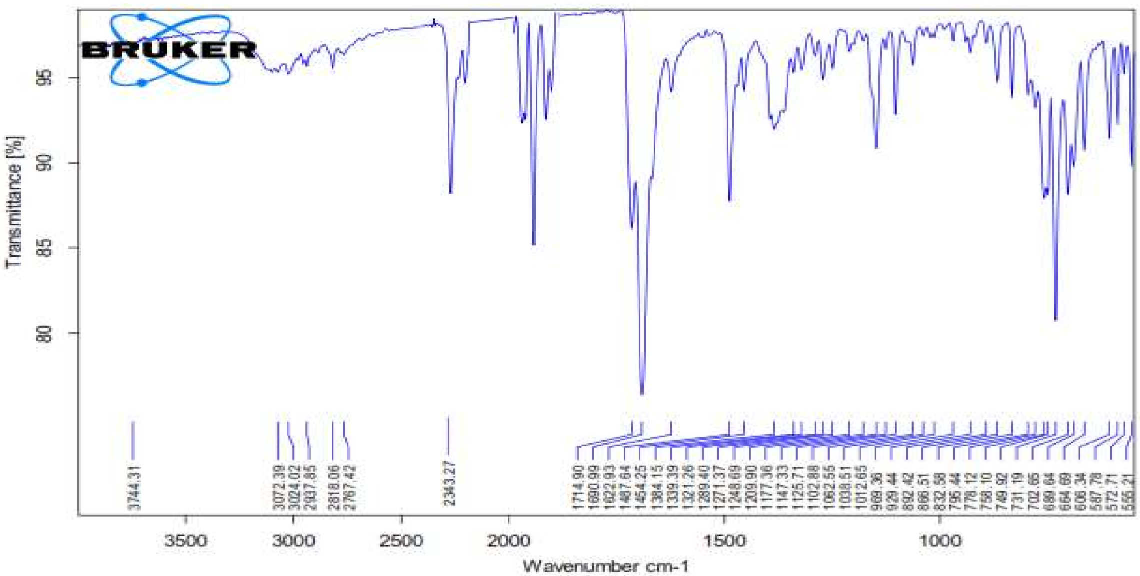
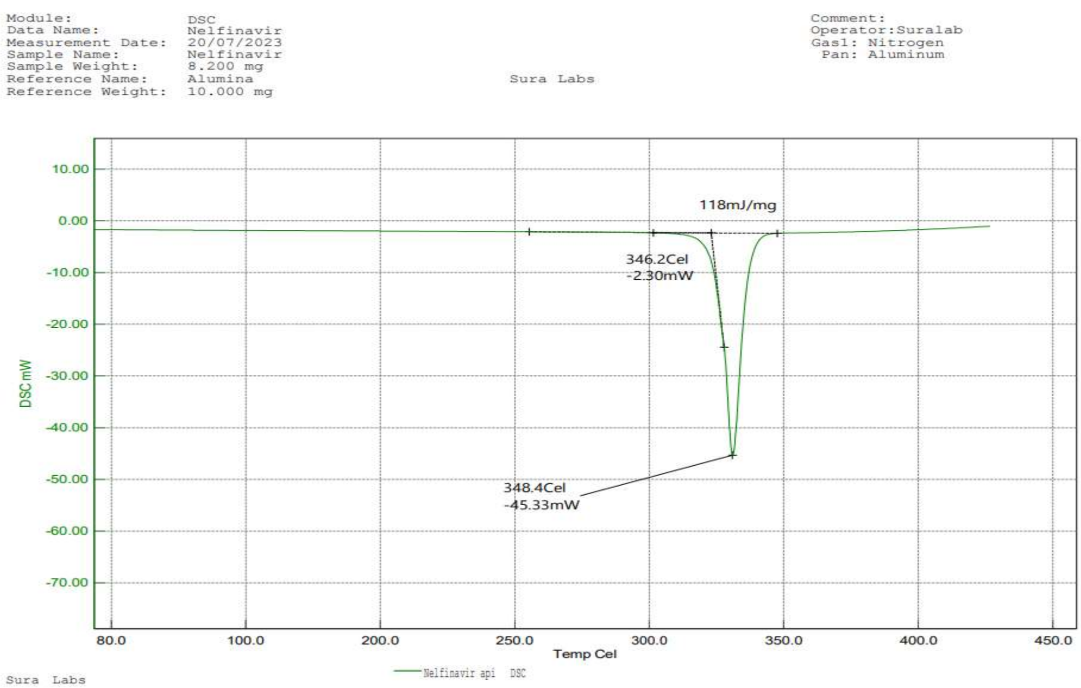


Fig 11: FT-IR Spectrum of Optimised Formulation



Graph 1: DSC graph of pure drug

Differential Scanning Calorimetry enables the quantitative detection of all processes in which energy is required or produced (endothermic or exothermic phase transformation). DSC curves obtained for pure drug is shown in figure. Pure powered Nelfinavir showed a melting endothermic at 348.4.0 C.

CONCLUSION

Nelfinavir is a medication used to treat HIV/AIDS. The objective of the study is to formulate and evaluate Nelfinavir extended release tablets to achieve Prolong Therapeutic effect.Extended release tablets of Nelfinavir is to be prepared by direct compression technique using various polymers, namely Eudragit RL, Ethyl

Cellulose and Carbopol p934. The FTIR spectra of Nelfinavir and physical mixture used for optimized formulation were obtained and these are depicted in above figures. From the FTIR data it was evident that the drug and excipients does not have any interactions. Hence they were compatible. In the preformulation studies the Micromeritic flow properties of the Blend were assessed by determining angle of repose, compressibility index, Hausner ratio. The results indicated good free flow of Nelfinavir. Tablet quality control tests such as weight variation, hardness, friability, thickness, and drug release studies in different media were performed on the compression tablet and found to be within limits. Dissolution of Nelfinavir from all the formulations developed was slow and spread over 12hrs. The results indicated that the formulations N1 to N8 fulfilled all the specifications of the physical properties prescribed for finished product. In the present study Eudragit RL+ Carbopol p934 combined polymers was found to play a great role in controlling the release of drug from the matrix system. Formulation N4 fulfilled all the specifications including dissolution rate test in alkaline fluids. Hence formulation N4 is considered as effective Product of Nelfinavir. While Compared with all other formulations prepared N4 gives satisfactory results. Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model and it was evident that the formulation N4 was followed Zero order release.

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