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Development and *in vivo* Evaluation of Nelfinavir Extended Release Trilayer Matrix Tablets in the Management of AIDS

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ABSTRACT

The purpose of this investigation was to design and develop trilayer matrix tablets of Nelfinavir prepared by direct compression method and consisted of middle active layer with different grades of hydroxypropyl methylcellulose (HPMC), PVK K 30 and MCC. Barrier layers are prepared with Polyox WSR 303, Xanthan gum, microcrystalline cellulose and magnesium stearate. Based on the evaluation parameters, drug dissolution profile and release drug kinetics DF8 was found to be optimized formulation. The developed drug delivery system provided prolonged drug release rates over a period of 24 h. The release profile of the optimized formulation (DF8) was described by the Zero-order and best fitted to Higuchi model. From in vivo bioavailability studies the extended release of Nelfinavir from trilayer matrix tablets also provides for higher plasma drug content and improved bioavailability. The results indicate that the approach used could lead to a successful development of low biological half life Nelfinavir with controlled drug release in the effective management of AIDS.

Keywords: Nelfinavir, AIDS, HPMC, Polyox WSR 303, Geomatrix, Bioavailability studies.

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INTRODUCTION

There are many ways to design modified release dosage forms for oral administration and one of them is multi layered matrix tablet. One to three layer matrix tablets is a drug delivery device, which comprises a matrix core containing the active solute and one or more barriers incorporated during tablet preparing process. [1] The barrier layers delay the interaction of active solute with dissolution medium, by limiting the surface available for the solute release and at the same time controlling solvent penetration rate. [2-3]

Hydrophilic polymers have been given considerable attention in the formulation of controlled release drug delivery systems for various drugs. HPMC K4M, HPMC K15M are a few representative examples of the hydrophilic polymers that have been extensively used in the formulation of controlled release systems. [4] Guar gum is soluble in water, it swells in gastric fluid to

produce a highly viscous layer around the tablet through which the drug can slowly diffuse [5] and is used for the fabrication of matrices with uniform drug release characteristics. [6-7]

There have been different approaches to achieve zero-order drug release from dosage forms for sustained plasma concentration. Among different approaches to achieve zero-order release from hydrophilic matrix technologies, multilayer matrices have been widely evaluated and developed for commercial products under the trade name of Geomatrix. The technology makes use of bilayer or trilayer tablets to modulate the release and to achieve constant release. [8]

Nelfinavir mesylate (NFV) is an anti-viral drug, used in the treatment of Acquired Immunodeficiency Syndrome (AIDS). Poor oral bioavailability and shorter half-life (3.5–5 h) remain a major clinical limitation of NFV leading to unpredictable drug bioavailability and frequent dosing. In this context, the objective of the present study was to formulate NFV control release trilayer tablets by Geomatrix technology which can increase the oral bioavailability of sustained release of the drug.

MATERIALS AND METHODS

Materials

Nelfinavir pure drug was generous gift from Optimus Generics Ltd., Hyderabad, India. PVP K 30, Microcrystalline cellulose, HPMC K 4 M, HPMC K 15 M was obtained from Rubicon labs, Mumbai. Polyox WSR 303 was obtained from Aurobindo Pharma Ltd., Hyderabad and Xanthan Gum was gifted from MSN Labs Ltd. Hyderabad. All other chemicals used were of analytical grade.

Methods

Formulation of controlled release Nelfinavir trilayer matrix tablets

The trilayered matrix tablets of Nelfinavir were prepared by direct compression method. The first step in the formulation was to develop the middle active layer so as to give at least 90% drug release during 12 hours. The release profile of this layer might not be of constant rate type but would be preferably of constantly falling rate type. This layer would then be sandwiched between barrier layers (Upper & Lower layers) so as to continue the drug release for 24 h. [9-10]

Preparation of middle active layer of Nelfinavir trilayered tablets

Twenty-seven formulations (F1-F27) for active layer were prepared by direct compression method using 3^3 Response surface method (3 variables and 3 levels of polymers) by using Design of experiment software with polymers like different HPMC grades and Guar gum. All the formulations were varied in concentration of polymers, magnesium stearate constituted in all the formulations. These materials were screened through #60 and mixed together in motor by using pestle. Final mixtures were compressed by using 12 mm diameter flat punches on a sixteen-station rotary tablet press. Formulation trials of active layer were depicted in Table 1. The prepared tablets were subjected to dissolution studies. [11]

Preparation of upper and lower layers of Nelfinavir trilayered tablets

The barrier layers were formulated employing hydrophobic swellable polymer polyox WSR 303 the swelling erosion modeling fillers which include water soluble MCC, EC and Xanthan gum. The procedure adopted to make the compacts was via direct compressions. For the first procedure the Polyox, xanthan gum and the filler were mixed in mortar and lubricated with magnesium stearate. Formulation of upper and lower layers was depicted in Table 2. [12]

Formulation of extended release trilayered tablets of Nelfinavir

The powder mixtures required for active and barrier layers were weighed accurately and thoroughly mixed using mortar and pestle for about 20 minutes. Initially, the volume of die cavity (12 mm, round) was adjusted equivalence to the weight of trilayered matrix tablets (950 mg). Then the pre-weighed amount of powder equivalent to bottom layer (100 mg) was taken and placed in the die cavity and slightly compressed for uniform spreading. The upper punch was lifted up and the granules equivalent to 750 mg of the drug was placed over the bottom layer in the die cavity and again slightly compressed. The remaining volume of the die cavity was filled with pre-weighed (100 mg) amount of powder equivalent to top layer and compressed with the full force of compression on rotary tablets press to obtain trilayered tablets (Table 2). Tri-layered matrix tablets of each composition were compressed and tested for their friability, Hardness, drug content and drug release characteristics with a suitable number of tablets for each test. [13]

Evaluation of trilayer matrix tablets of Nelfinavir

Hardness, Thickness, Friability, Weight variation, Content Uniformity and *In vitro* Swelling Studies were conducted.

In-vitro drug release profile

In vitro drug release studies for developed trilayer matrix tablets were carried out by using dissolution apparatus II paddle type (Electrolab TDL-08L). The drug release profile was studied in 900 ml Phosphate buffer pH 6.8 at 37 ± 0.5°C temperature. The amount of drug release was determined at different intervals upto 24 h by UV visible spectrophotometer (Shimadzu UV 1800) at 254 nm.

Drug release kinetics

To describe the kinetics of the drug release from matrix tablet, mathematical models such as Zero-order, First order and Higuchi, models were used. The criterion for selecting the most appropriate model was chosen on the basis of the goodness-or fit test.

Drug excipients compatibility studies

Fourier Transform Infrared Spectroscopy (FTIR) studies were performed.

SEM studies

The surface and shape characteristics of Tablets were determined by scanning electron microscopy (SEM) (HITACHI, S-3700N). Photographs were taken and recorded at suitable magnification.

Stability studies

The stability study of the formulated Nelfinavir trilayer tablets were carried out under different conditions according to ICH guidelines using stability chamber (REMI make). Accelerated Stability studies were carried out at 40°C / 75% RH for the best formulations for 6 months. The tablets were characterized for the hardness, friability, drug content and cumulative % drug released during the stability study period.

Table 1: Formulation trials of middle active layer of Nelfinavir

F. Code	Nelfinavir	HPMC K4M	HPMC K15M	Guar Gum	PVP K-30	MCC	Mg Stearate	Total
F1	625	24	20	16	8	53	4	750
F2	625	32	20	16	8	45	4	750
F3	625	24	28	16	8	45	4	750
F4	625	32	28	16	8	37	4	750
F5	625	24	20	24	8	45	4	750
F6	625	32	20	24	8	37	4	750
F7	625	24	28	24	8	37	4	750
F8	625	32	28	24	8	29	4	750
F9	625	24	28	24	8	37	4	750
F10	625	32	24	20	8	37	4	750
F11	625	28	20	20	8	45	4	750
F12	625	28	28	20	8	37	4	750
F13	625	28	24	16	8	45	4	750
F14	625	28	24	24	8	37	4	750
F15	625	28	24	20	8	41	4	750
F16	625	28	20	24	8	41	4	750
F17	625	28	20	16	8	49	4	750
F18	625	28	28	20	8	37	4	750
F19	625	32	20	20	8	41	4	750
F20	625	28	28	16	8	41	4	750
F21	625	32	24	16	8	41	4	750
F22	625	32	24	20	8	37	4	750
F23	625	32	28	20	8	33	4	750
F24	625	24	24	20	8	45	4	750
F25	625	32	24	24	8	33	4	750
F26	625	24	24	16	8	49	4	750
F27	625	28	24	16	8	45	4	750

Table 2: Composition of Nelfinavir trilayered matrix tablet

INGREDIENTS	AF8	BF8	CF8	DF8	EF8	FF8	GF8	HF8
MIDDILE ACTIVE LAYAER (F8) (750 mg)								
Nelfinavir	625	625	625	625	625	625	625	625
HPMC K 4 M	32	32	32	32	32	32	32	32
HPMC K 15 M	28	28	28	28	28	28	28	28
Guar Gum	24	24	24	24	24	24	24	24
PVP K30	08	08	08	08	08	08	08	08
MCC Cellulose	29	29	29	29	29	29	29	29
Magnesium stearate	04	04	04	04	04	04	04	04
UPPER AND LOWER LAYER (100 mg)								
Polyox WSR 303	20	25	30	35	40	42.5	45	50
Xanthan gum	40	40	38	35	35	32.5	30	30
Ethyl cellulose	12	10	14	12	15	12	12	12
MCC	25	22	15	15	07	10	10	05
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5

Table 3: Physico-chemical evaluation properties of Nelfinavir trilayered tablets

F. Code	*Weight variation (mg)	#Thickness (mm)	#Hardness (Kg/Cm²)	#Friability (%)	# Content uniformity (%)	Swelling index (%)
AF8	951.65 ± 1.2	7.0 ± 0.12	7 ± 0.12	0.52 ± 0.01	95.23 ± 0.63	83 ± 0.76
BF8	948.69 ± 0.8	7.1 ± 0.06	8.1 ± 0.06	0.55 ± 0.02	97.04 ± 0.06	83 ± 0.72
CF8	948.04 ± 0.5	7.1 ± 0.06	7.1 ± 0.06	0.63 ± 0.03	95.56 ± 0.14	82 ± 0.64
DF8	950.05 ± 0.0	7.1 ± 0.12	7.2 ± 0.11	0.50 ± 0.01	99.11 ± 1.01	96 ± 0.81
EF8	950.54 ± 0.4	7.1 ± 0.03	7 ± 0.00	0.62 ± 0.02	94.23 ± 0.8	73 ± 1.03
FF8	950.78 ± 0.4	7.3 ± 0.10	7.1 ± 0.06	0.66 ± 0.01	95.45 ± 0.31	82 ± 0.84
GF8	950.65 ± 0.3	7.1 ± 0.10	7.1 ± 0.10	0.58 ± 0.02	94.11 ± 0.49	80 ± 0.72
HF8	949.57 ± 0.2	7.3 ± 0.25	7.3 ± 0.40	0.69 ± 0.01	98.23 ± 0.51	95 ± 0.79

*Values are expressed in mean ± SD :(n=20)
#Values are expressed in mean ± SD :(n=3)

Table 4: *In vitro* Drug Release Profile for Prepared Extended release trilayered Tablet of Nelfinavir (AF8-HF8)

Time (h)	AF8	BF8	CF8	DF8	EF8	FF8	GF8	HF8	Marketed Product
0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
1	17.77 ± 0.04	09.14 ± 1.85	18.35 ± 1.11	16.95 ± 0.25	14.05 ± 1.32	10.68 ± 1.78	19.46 ± 0.18	16.12 ± 0.22	24.35 ± 1.78
2	27.04 ± 0.15	18.26 ± 1.66	22.87 ± 1.18	27.93 ± 1.28	25.60 ± 0.48	21.54 ± 1.68	28.87 ± 0.59	29.23 ± 0.96	36.87 ± 1.68
4	36.24 ± 0.18	29.45 ± 0.52	31.64 ± 2.22	37.09 ± 2.21	36.30 ± 1.88	31.76 ± 0.18	39.97 ± 0.46	40.34 ± 0.28	45.64 ± 0.18
6	49.78 ± 1.85	37.86 ± 0.63	42.56 ± 1.85	40.72 ± 0.51	45.40 ± 1.56	42.89 ± 1.15	50.67 ± 0.61	56.12 ± 0.17	56.56 ± 1.15
8	59.98 ± 2.24	48.04 ± 0.98	53.78 ± 1.56	60.77 ± 0.18	55.50 ± 1.86	52.98 ± 1.98	61.89 ± 0.86	68.72 ± 1.85	65.78 ± 1.98
12	71.44 ± 1.18	62.18 ± 1.78	63.69 ± 1.18	76.36 ± 0.16	68.76 ± 1.28	62.43 ± 1.77	72.67 ± 0.19	72.45 ± 1.72	73.69 ± 1.77
16	75.88 ± 1.29	77.14 ± 2.18	79.89 ± 1.75	84.23 ± 0.25	80.27 ± 1.28	82.90 ± 1.65	84.78 ± 0.32	85.56 ± 1.11	81.89 ± 1.65
20	78.07 ± 1.75	80.27 ± 1.85	82.43 ± 1.62	95.02 ± 0.48	84.58 ± 1.32	86.32 ± 0.52	88.45 ± 0.11	90.58 ± 0.45	88.43 ± 0.52
24	80.98 ± 1.24	81.04 ± 1.98	84.78 ± 1.26	98.72 ± 1.15	86.50 ± 1.81	89.98 ± 1.58	94.89 ± 1.86	92.72 ± 1.35	93.78 ± 1.52

Table 5: Release order kinetics of optimized and marketed product

S. No	Formulation	Zero order R^2	First order R^2	Higuchi Model R^2	Korsmeyer-Peppas model R^2	n
1	DF8	0.993	0.913	0.934	0.954	0.865
2	Marketed Product	0.933	0.951	0.923	0.947	0.848

Table 6: Comparison of pharmacokinetic parameters of Nelfinavir Optimized formulation and Marketed product

Parameters	Nelfinavir optimized formulation (DF8)	Marketed product
C_{max} (µg/ml)	92.21 ± 0.03	66.00 ± 0.01
AUC_{0-t} (µg h/ml)	586.12 ± 0.01	434.19 ± 0.01
$AUC_{0-\infty}$ (µg h/ml)	835.12 ± 0.02	545.18 ± 0.02
T_{max} (h)	6.01 ± 0.04	4.00 ± 0.01
$t_{1/2}$ (h)	9.25 ± 0.004	7.12 ± 0.05

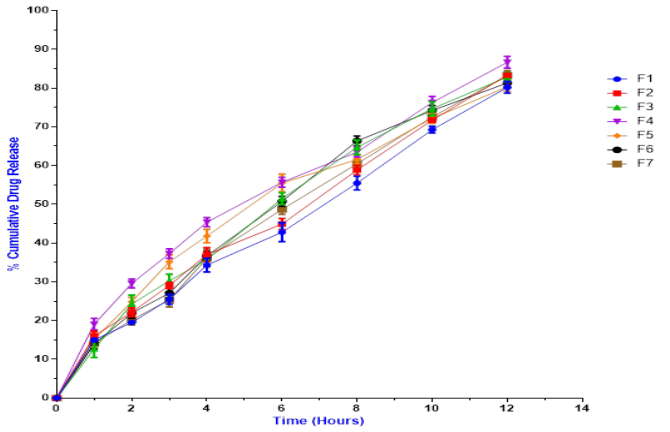

Fig. 1: *In vitro* dissolution studies of Nelfinavir middle active layer tablets F1-F7

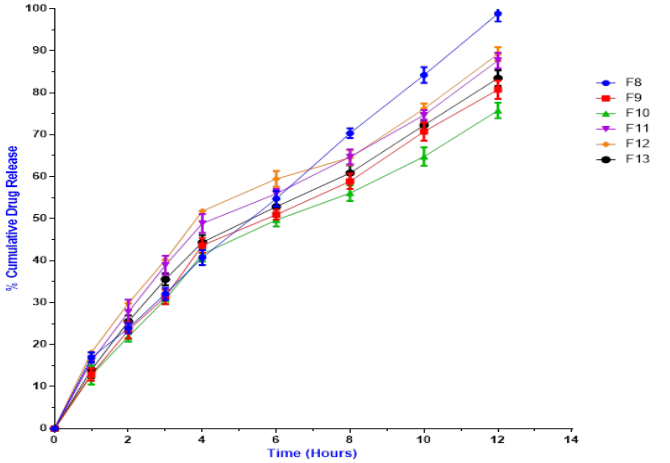

Fig. 2: *In vitro* dissolution studies of Nelfinavir middle active layer tablets F8-F13

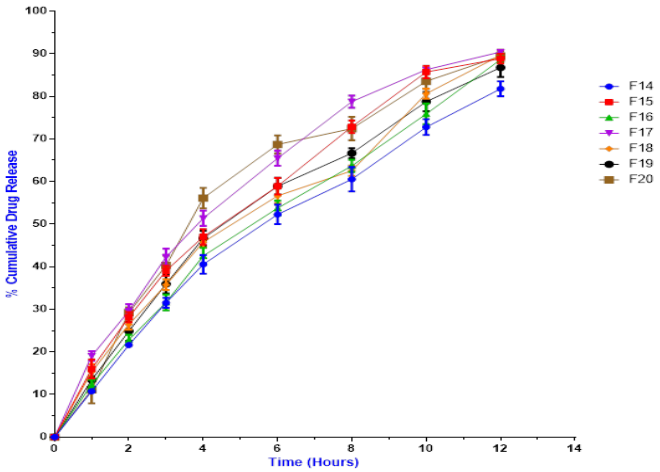

Fig. 3: *In vitro* dissolution studies of Nelfinavir middle active layer tablets F14-F20

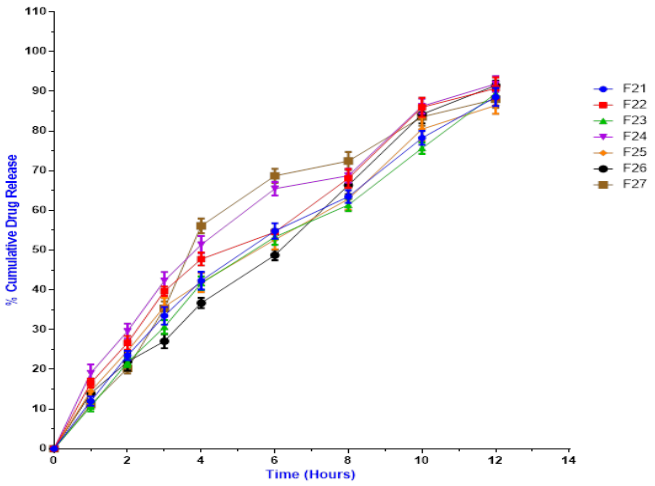

Fig. 4: *In vitro* dissolution studies of Nelfinavir middle active layer tablets F21-F27

Fig. 5: Preparation of trilayer matrix tablets of Nelfinavir

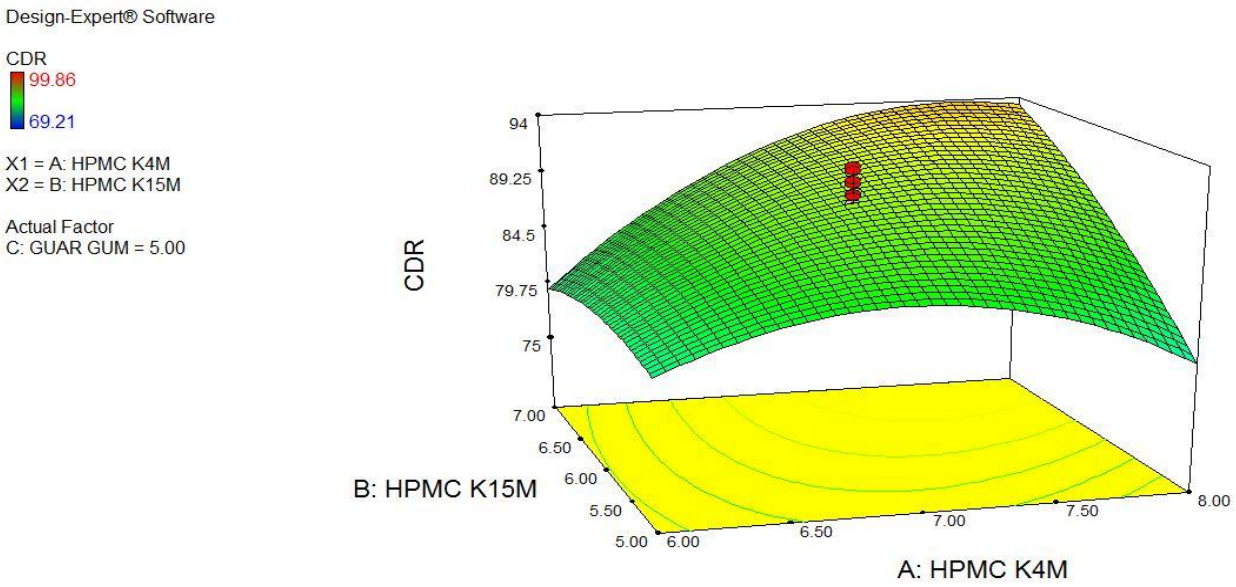

Fig. 6: Response surface plot showing the influence of amount of polymer on the release profile of Nelfinavir for % Cumulative Drug Release.

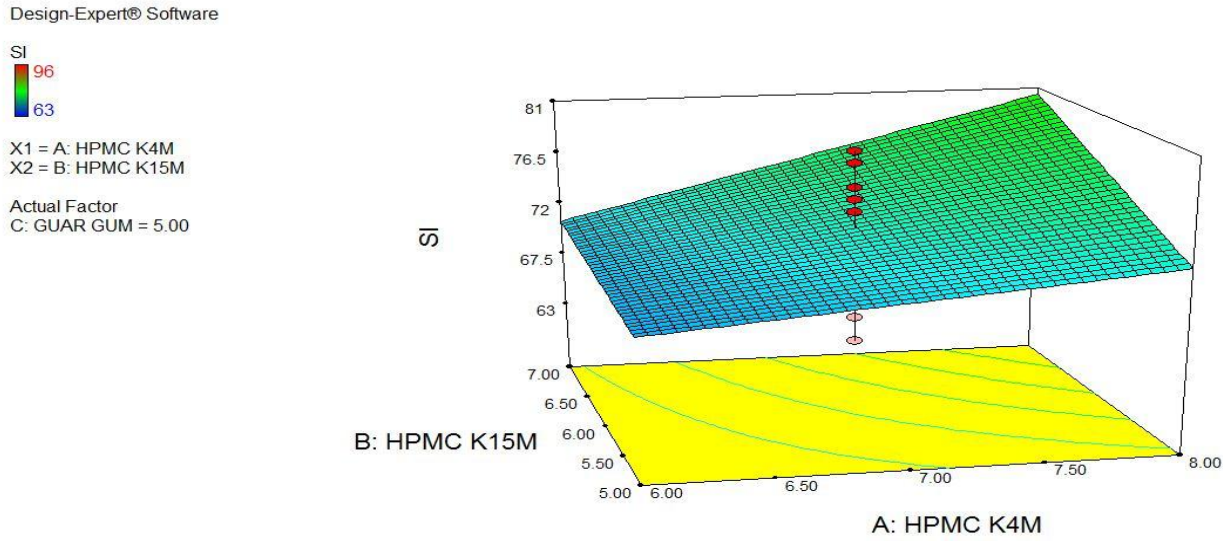

Fig. 7: Response surface plot showing the influence of amount of polymer on Swelling Index of Nelfinavir

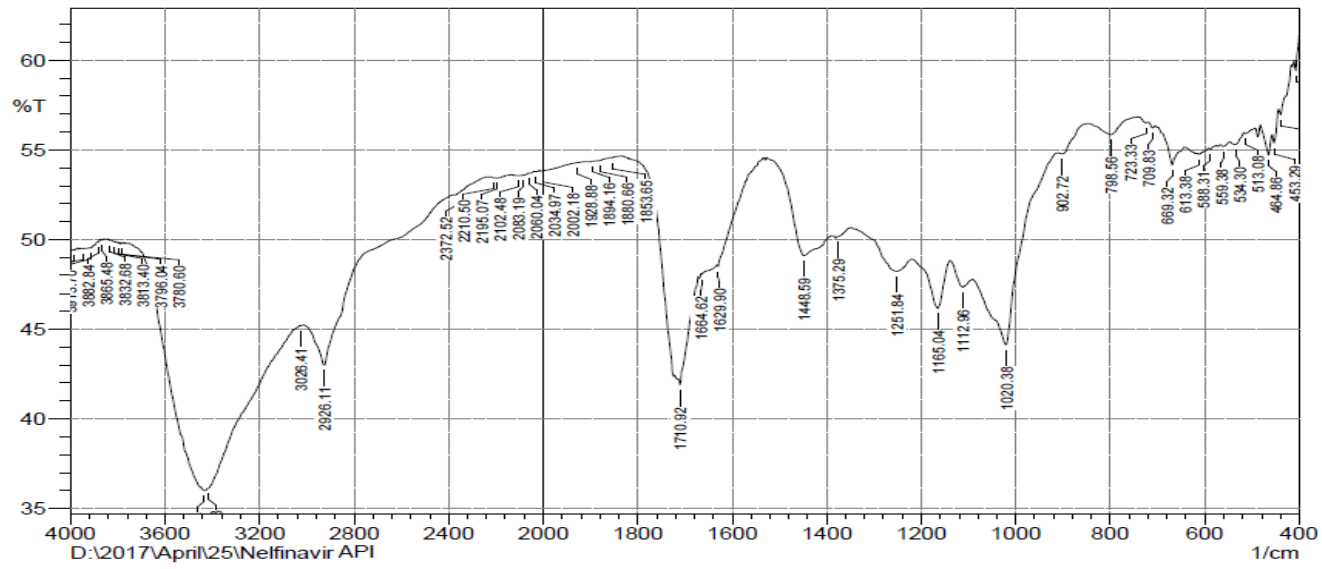

Fig. 8: FT-IR spectrum of pure drug Nelfinavir

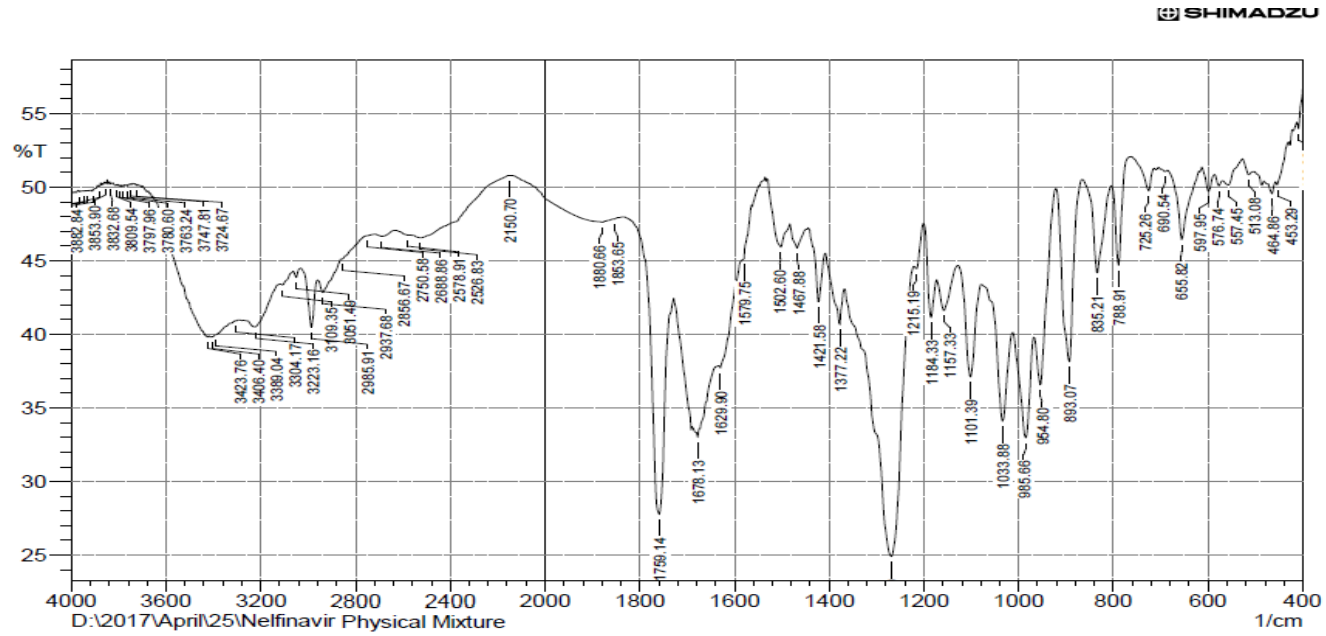

Fig. 9: FT-IR spectrum of Nelfinavir Physical mixture

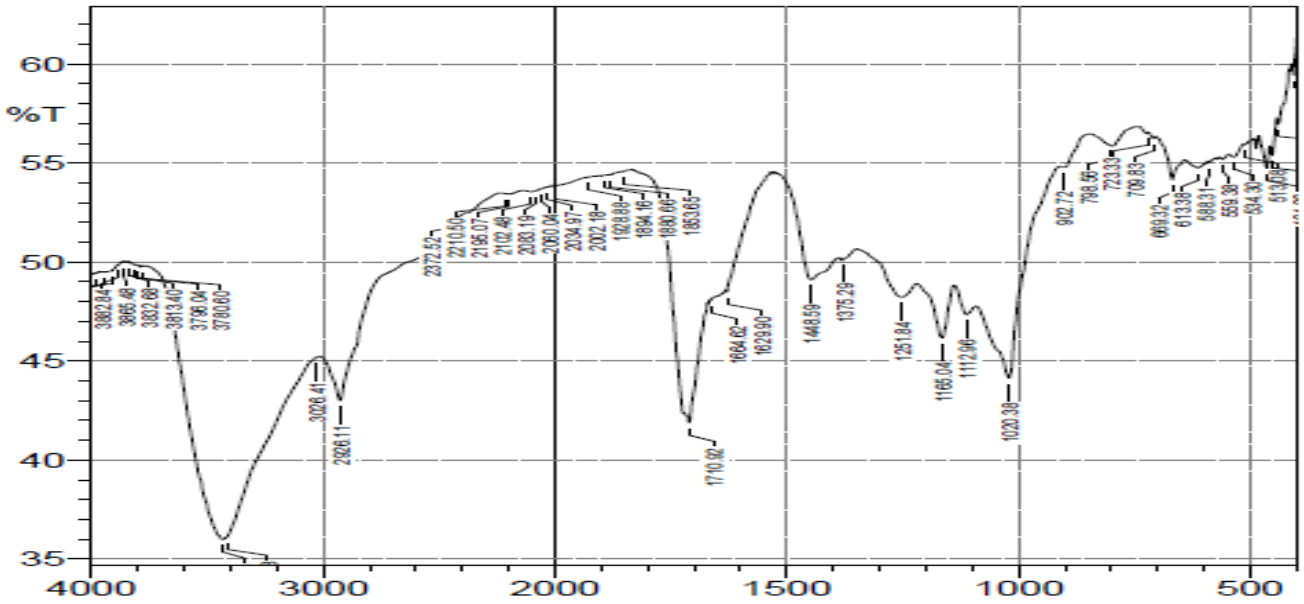

Fig. 10: FT-IR spectrum of optimized formulation DF8

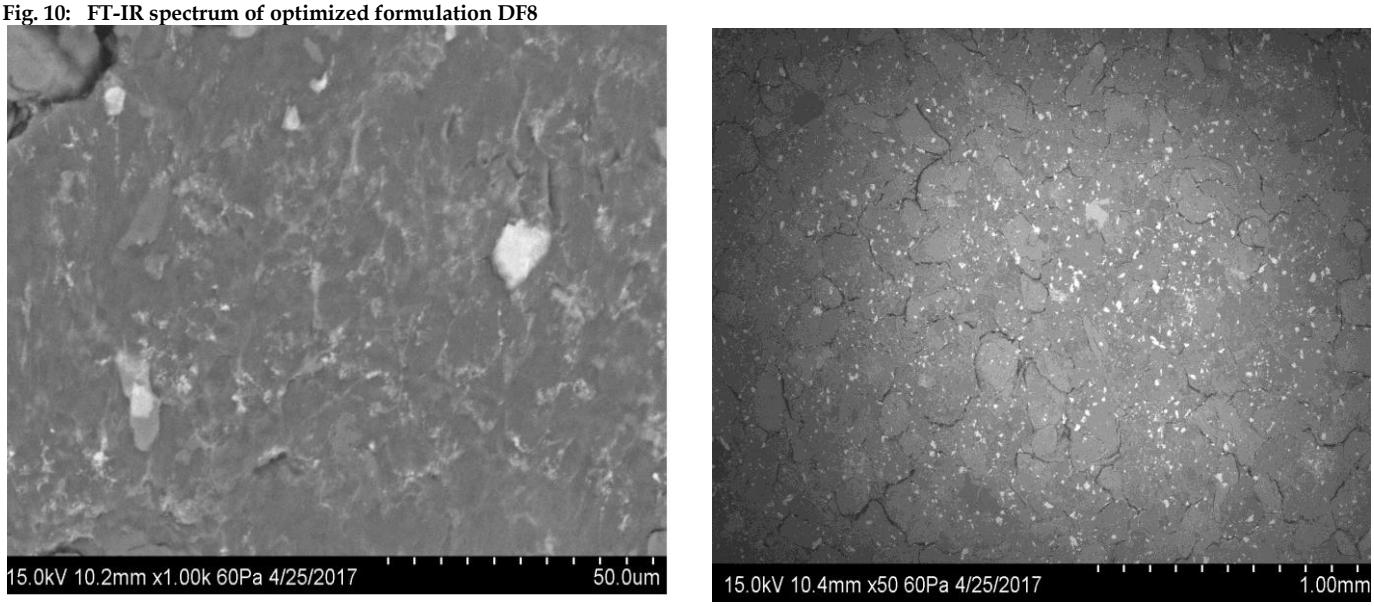

Fig. 11: SEM studies for optimised DF8

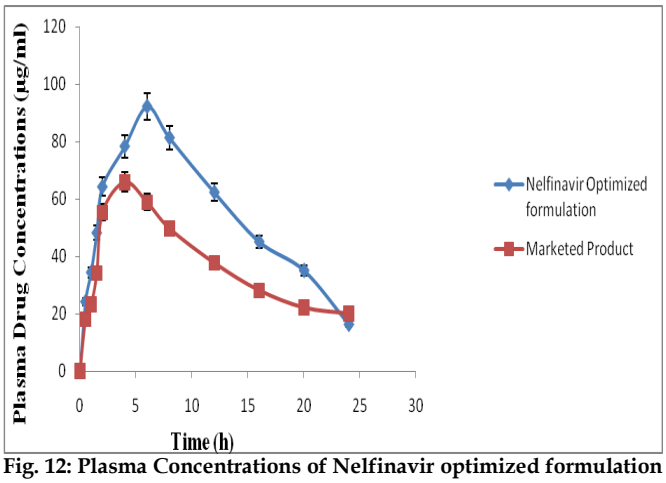

Fig. 12: Plasma Concentrations of Nelfinavir optimized formulation and Marketed Product at different time intervals

In vivo bioavailability studies of Nelfinavir

Animal Preparation

Male rabbits were (weighing 2-3 kg) selected for this study, all the animals were healthy during the period of the experiment. Animals were maintained at room temperature 25°C, Relative Humidity 45% and 12 h alternate light and dark cycle with 100% fresh air exchange in animal rooms, uninterrupted power and water supply and rabbits were fed with standard diet and water ad libitum. The protocol of animal study was approved by the institutional animal ethics committee (IAEC NO:IAEC/1657/CMRCP/T2/Ph.D-16/61).

In vivo study design [14]

The rabbits were randomly divided into two groups each group contains six animals. The group A was received prepared Nelfinavir matrix tablets (625 mg), marketed product (625 mg) was administered group B with equivalent dose of animal body weight. Blood samples (approximately 0.5ml) were obtained with syringes by marginal ear vein at 0, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 20 and 24 hours post dose. During collection, blood sample has been mixed thoroughly with heparin in order to prevent blood clotting. Plasma was separated by centrifugation of the blood at 5000 rpm in cooling centrifuge for 5 min to 10 minutes and stored frozen at −20°C until analysis.

HPLC study

For HPLC C18 column with 5µm particle size and the mobile phase of acetonitrile-50 mmol/L ammonium formate buffer, pH 4.1 (52:48, by volume) at a flow rate of 0.5 mL/min. nelfinavir the internal standard ritonavir were detected at 218 nm, Internal standard ritonavir was used. The retention time was 4.72 min and 11.12 min for nelfinavir and ritonavir respectively. [15]

Preparation of Plasma Samples for HPLC Analysis

Rabbit plasma (0.5 ml) samples were prepared for chromatography by precipitating proteins with 2.5 ml of ice-cold absolute ethanol for each 0.5 ml of plasma. After centrifugation the ethanol was transferred into a clean tube. The precipitate was re suspended with 1 ml of Acetonitrile by vortexing for 1 min. After centrifugation (5000 – 6000 rpm for 10 min), the Acetonitrile was added to the ethanol and the organic mixture was taken to near dryness by a steam of nitrogen at room temperature.

Pharmacokinetic analysis

The pharmacokinetic parameters employed to evaluate were maximum plasma concentration (C_{max}), time to attain C_{max} i.e., T_{max} and $t_{½}$ values, area under plasma concentration–time curve from zero to the last sampling time (AUC_{0-t}), area under plasma concentration–time curve from zero to infinity ($AUC_{0-\infty}$). AUC_{0-t} was calculated by the linear trapezoidal rule and $AUC_{0-\infty}$ from the following formula.

$$AUC_{0-\infty} = AUC_{0-t} + C_t / K_E$$

RESULTS AND DISCUSSION

Preparation of middle active layer

The matrix tablets of Nelfinavir were prepared without the barrier layers. All the formulation trails were subjected to *in vitro* dissolution to determine the release profiles. From the above results, among all the formulations the formulation F8 was decided as optimized formulation for active layer based on the highest drug release i.e. 98.86 ± 1.86 within 12 hours when compared with other preparations (Figure 1 - 4). Formulation F8 was chosen as active layer for further studies.

Evaluation of trilayer matrix tablets of Nelfinavir

The prepared trilayer tablets were shown in Figure 5 and the evaluation parameters were found to be within the IP limits (Table 3).

The Swelling study of trilayered matrix tablet of Nelfinavir was given in Table 3 showed that the swelling index of the tablet increases with increase in time up to 12 hours, this may be attributed to the fact that the erosion of biodegradable polymer Xanthan gum. This indicates that the drug will remain in intestinal region till drug is released completely from the delivery system and promotes evacuation after its release (Table 3).

In vitro dissolution studies of trilayer matrix tablets of Nelfinavir

The release of Nelfinavir from different formulations was carried out and the results are depicted in Table 4. The trilayer tablets extended the drug release upto 24 hrs. The highest drug release was found in the formulation DF8 i.e 98.72% within 24 h. DF8 was found to be optimized formulation based on the dissolution and other evaluation parameters. The marketed product drug release was found to be 93.78% up to 24 h.

Release order kinetics

From the above results it is apparent that the regression coefficient value closer to unity in case of zero order plot i.e. 0.996 indicates that the drug release follows a zero order mechanism (Table 5). This data indicates a lesser amount of linearity when plotted by the first order equation. Hence it can be concluded that the major mechanism of drug release follows zero order kinetics.

From the above results it is apparent that the regression coefficient value closer to unity in case of First order plot i.e. 0.951 indicates that the drug release follows a first order mechanism. This data indicates a lesser amount of linearity when plotted by the zero-order equation. Hence it can be concluded that the major mechanism of drug release follows first order kinetics.

Further, the translation of the data from the dissolution studies suggested possibility of understanding the mechanism of drug release by configuring the data in to various mathematical modelling such as Higuchi and Korsmeyer-Peppas plots. Further the n value obtained from the Korsemeyer-Peppas plots i.e. 0.947 indicating non Fickian (anomalous) transport thus it projected that delivered its active ingredient by coupled diffusion and erosion.

Design of Experiment

This method is mainly used to explain the effect of one factor on other factor, whether this effect is significant or not, If significant how it influence the response. In this present work the effect of one factor (Guar Gum) on other two factors (HPMC K 4M, HPMC K 15M) is explained (Figure 6).

In the above graph the effect of Guar Gum on % cumulative drug release is examined and it clearly indicates that there is a very significant effect of Guar Gum on % cumulative drug release. The formulations with all 3 factors shown % cumulative drug release in between 69.21-99.86 but when Guar Gum is removed from the formulations the maximum % CDR is near 69.21. This is the effect of factor (Guar Gum**)** on response (Figure 7).

There is a negligible effect on Swelling Index of formulations because all formulations have excellent Swelling property and there is slightly influence on Swelling Index by Guar Gum.

Characterization

FT-IR

Overall there was no alteration in peaks of Nelfinavir pure drug (Figure 8) and optimized formulation (Figure 10), suggesting that there was no interaction between drug & excipients. FTIR spectrum of pure drug and other polymers are shown in (Figure 9). There is additional peaks appeared or disappeared hence no significant changes in peaks of optimized formulation was observed when compared to pure drug indicating absence of any interaction.

SEM studies

SEM further confirmed both diffusion and erosion mechanisms to be operative during drug release from the optimized formulation (DF8). Initially, tablet matrix showed swelling with pore formation that is clearly visible from SEM image. At the end of 24 h, the matrix was intact and pores had formed through it. SEM images also show the formation of gel structure indicating swelling and pore formation on the tablet surface (Figure 11).

Stability studies

Optimized formulation DF8 was selected for stability studies on the basis of high cumulative % drug release. Stability studies were conducted for 6 months according to ICH guidelines. From these results it was concluded that, optimized formulation is stable and retained their original properties with minor differences.

***In vivo* bioavailability studies of Nelfinavir**

Mean plasma concentration profiles of prepared Nelfinavir optimized formulation and marketed product are presented in Figure. Nelfinavir optimized formulation and marketed product exhibited as sustained release *in vivo* study. All the pharmacokinetics parameters displayed in Table. T_{max} value for the marketed drug (4.00 ± 0.01 h), T_{max} of the test drug (6.01 ± 0.04 h) suggests slower absorption. This delayed absorption of test preparation is most likely due to the sustained release of the drug. The C_{max} of marketed drug was lower 66.00 ± 0.01µg/ml, when compared with optimized formulation 92.21 ± 0.03µg/ml. The half-life of the marketed drug (7.12 ± 0.05 h) was low which indicates rapid removal of the drug from plasma. This was also supported by the high elimination rate constant value. On the other hand, the test formulation exhibited higher half-life (9.25 ± 0.004 h) and low elimination rate constant values indicating slower drug disposition and prolonged effect. However, the $AUC_{0-\infty}$ values for the two formulations (test 835.12 ± 0.02µg h/ml and marketed 545.18 ± 0.02µg h/ml) were significantly different. Statistically, AUC_{0-t} of the optimized trilayer tablet was significantly higher (p<0.05) as compared to marketed formulation and the results are summarized in Table 6 and figure 12.

It was concluded that trilayer matrix tablets of Nelfinavir could be successfully prepared by direct compression technique using different polymers combination. Nelfinavir tablets were prepared by direct compression and consist of middle active layer with different grades of HPMC, MCC and PVP K30, upper and lower layers were prepared with Polyox WSR 303, Xanthan gum, microcrystalline cellulose, ethyl cellulose and Magnesium stearate. Based on the evaluation parameters, drug dissolution profile and release drug kinetics DF8 was found to be optimized formulation. The developed drug delivery systems showed prolonged and complete drug release rates over a period of 24 h. From in vivo bioavailability studies the extended release of drug from trilayer matrix tablets also provides for higher plasma drug content and improved bioavailability These results also demonstrated the suitability of three-layered tablet formulation of Nelfinavir to provide controlled release for prolonged period of time and improved linearity for Nelfinavir in comparison to marketed product in the effective management of AIDS with patient compliance.

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