EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 5
Issue: 4
432-439
Year: 2018

STUDIES ON DEVELOPMENT OF GASTRORETENTIVE DOSAGE FORMS OF NELFINAVIR MESYLATE– AN ANTIRETROVIRAL DRUG, THROUGH THE STRATEGY OF MUCOADHESION

Jyothirmayee Devineni*, Nagamalleswara Rao[1] S. R. Buchi Naidu Nalluri[1] and Vijaya Ratna Jayanti[2]

[1]Department of Pharmaceutics, KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada-520010, AP, India.
[2]Department of Pharmaceutics, College of Pharmaceutical Sciences, Andhra University, Visakhapatnam-530003, AP, India.

***Corresponding Author: Jyothirmayee Devineni**
Department of Pharmaceutics, KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada-520010, AP, India.

Article Received on 06/02/2018 **Article Revised on 26/02/2018** **Article Accepted on 17/03/2018**

ABSTRACT

Objectives: The aim and objective of present investigation was development and *in vitro, in vivo* evaluation of oral controlled release (CR) mucoadhesive tablets of Nelfinavir Mesylate (NLF), an anti-retroviral drug. **Experimental: NLF** Mucoadhesive tablets were prepared by direct compression method using chitosan, carbopol and hydroxyl propylmethyl cellulose (HPMC K4M) as mucoadhesive and release retardant polymers. The effect of different concentrations (10%, 15%, 20%w/w) of polymers and solubilizing agents like cyclodextrins were studied on the NLF release from mucoadhesive tablets. Also the NLF compatibility with the excipients was evaluated by Fourier Transmittance Infrared Spectrometry (FTIR) and Differential Scanning Calorimetry (DSC). Optimized formulation was further subjected to bioavailability studies using prototype formulation to the rabbit body weight. **Results and Discussion:** The FTIR and DSC results indicated that there was no *in situ* interaction between NLF and the selected excipients of the formulations. Formulation containing 10% w/w chitosan as mucoadhesive/release retardant polymer and 10% w/w hydroxypropyl-β-cyclodextrin(F10) gave a complete and controlled release of NLF (99.99 ± 0.14%) at the end of 10 h and the NLF release followed diffusion mechanism. Comparative bioavailability studies were carried out on optimized formulation and NLF suspension. Formulation F10 showed better relative bioavailability than that of NLF suspension. **Conclusion:** The results of this study provide guidance for developing mucoadhesive tablet of NLF that give greater bioavailability, than existing dosage forms, and provide protection against Permeability-glycoprotein (p-gp) efflux. The time plasma concentration profiles clearly indicated a controlled release of NLF over a period of 10 hrs.

KEYWORDS: Nelfinavir mesylate, mucoadhesive polymers, cyclodextrins, Dissolution studies.

INTRODUCTION

Nelfinavir meyslate (NLF) is a poorly water soluble anti-retroviral drug (BCS- II and IV) used for the management of HIV infection and its absorption is dissolution rate limited.[1,4] NLF shows low and variable oral bioavailability because of p-gp efflux system, which can be avoided by modifying its release to occur more in the stomach where p-gp content is lowest.[5]

NLF shows more solubility in gastric pH than intestinal pH This is confirmed by the fact that the presence of food in the GI tract substantially increases the absorption of orally administered Nelfinavir.[6] The elimination half life of NLF is 3.5 to 5 hours.[7,8] Since, the elimination half life is short and its absorption window is only through stomach region, NLF requires enhanced dissolution and gastro retention for better therapeutic efficacy.

Mucoadhesive tablets are gstroretentive modified release formulations where the retention of the drug is extended for a considerable time so that absorption will be greater in the stomach when compared to conventional marketed immediate release formulations of NLF[Nelfin-625mg FC tab (Hetero HC), Retronel-250 mg (Alchemy), Nelvir-250 mg (Cipla), Viracept-250 mg (Agouron)]. Most of the research works were focused on the polymeric nanocarriers and microcapsules of NLF, solubility enhancement techniques such as beta-cyclodextrin inclusion complexes, solid dispersion techniques using modified starch.[9,13]

In the present study, we aim at developing mucoadhesive tablets of NLF using chitosan, carbopol and hydroxyl propylmethyl cellulose (HPMC K4M) as mucoadhesive polymers at different concentrations 10%w/w, 15%w/w, 20%w/w. Since NLF is poorly water soluble drug, its

release from the mucoadhesive tablets may not be sufficient for therapeutic efficacy. Literature survey revealed that the solubility of NLF was successfully enhanced by inclusion complexation with cyclodextrins.[9,11] Hence, in this investigation solubilizing excipients like hydroxyl propyl-β-cyclodextrins were included in the mucoadhesive tablets to enhance the solubility of NLF inorder to achieve therapeutically effective levels of NLF through gastric retention from mucoadhesive tablets.

MATERIALS AND METHODS

Reagents and chemicals

Nelfinavir mesylate was obtained from Lantec pharmaceuticals, Hyderabad. Chitosan was purchased from Sigma Aldrich, Mumbai. HPMC and MCC (Avicel PH-200) were obtained from Signet chemicals, Mumbai. Hydroxyl propyl-β- Cyclodextrins and Carbopol were obtained from FMC Biopolymer, Mumbai. Talc and magnesium stearate were purchased from SD fine chemicals Ltd., Mumbai. All other reagents were of analytical grade, and double distilled water was made in house. All solvents used in HPLC analysis were of HPLC grade and filtered using a 0.45µm nylon filter.

Analytical method

A UV-VIS spectrophotometric method based on the measurement of absorbance at 252 nm in methanol stock solution was used in the present research work for the estimation of NLF *in vitro* studies.

HPLC method for estimation of NLF in rabbit plasma

A new reverse phase HPLC method with UV detection was developed for the estimation of NLF in plasma samples. For this purpose a calibration curve was constructed by analyzing plasma samples containing different amounts of NLF. The experiment was conducted to develop a liquid chromatographic method for the determination of NLF using Waters Alliance 2695, HPLC system with Auto Sampler and 2487 UV-Visible detector. The chromatographic studies were performed using Hypersil ODS C_{18} column (4.6 ID X 150 mm, 5µm) at ambient temperature. Data acquisition was done by using Empower 2 software.

Mobile phase consisting of 15 Mm phosphate buffer(pH 3.0) : Acetonitrile(40:60v/v) was used in isocratic mode and the mobile phase was filtered through nylon filter of 0.45µm (millipore) and sonicated for 3 min before use. The flow rate was 1.0 ml/min and the injection volume was 20µl. Ultraviolet detection was performed at 230nm and the separation was achieved at ambient temperature. Under these conditions the NLF was eluted at 5.91 min with out any interference peaks. This method is used for the estimation of NLF in rabbit plasma obtained in pharmacokinetic evaluation of NLF mucoadhesive tablets.

Characterization of NLF CR formulation Powder Blends

Fourier Transmittance Infrared Spectroscopic (FT-IR) Studies

The FT-IR spectra of pure NLF and NLF with selected excipients like Chitosan, Carbopol, HPMCK4M, HP-β-CD, Avicel PH 200, Talc, Magnesium stearate were measured using ATR-FTIR spectrophotometer(Bruker, Germany). Samples were analyzed using an ATR-FTIR spectrometer (Bruker, Germany). ATR spectra were measured over the wave number range of 4000-500 cm^{-1} at a resolution of 1.0 cm^{-1}. The powder sample is simply placed onto the ATR crystal and the sample spectrum is collected.

Preparation of NLF Mucoadhesive tablets

NLF mucoadhesive tablets were prepared by direct compression method, as per the formulae given in Table 1. HPMC K4M, chitosan, carbopol were used as release retardant materials and as mucoadhesive polymers. Sufficient quantity of MCC (Avicel PH 200) was used to raise the bulk volume of the tablets to a weight of 1000mg each. Talc and magnesium stearate at 0.5% w/w levels were used as glidant and lubricants.

NLF which is equivalent to 700 mg of NLF base was weighed accurately and taken into a mortar. All the ingredients were passed through sieve # 80 seperately and collected before mixing. Initially drug and polymers were mixed thoroughly and then required quantities of fillers were added and finally the blend was mixed with talc, mixed thoroughly for 5min in a poly bag and then the required amount of magnesium stearate was added and was mixed for another 5 min. Powder blends (for 50 tablets each) of all the above formulations were compressed on single punch tablet press (Cadmach, India) using 12 mm punches (round shape) to a hardness of 4-6 kg/cm^2.

Evaluation of Flow properties of powder blend

The powder blends were evaluated for parameters like bulk density, tapped density, Carr's index, Angle of repose and Hausner's ratio.[14]

Evaluation of Post-compression Parameters of NLF Mucoadhesive Tablets

The compressed NLF Mucoadhesive Tablets were evaluated for properties like drug content, uniformity of weight, friability, hardness, swelling index, mucoadhesive strength, *in vitro* drug release studies and *in vivo* drug release studies.[15]

DSC studies

Thermal analysis of NLF and NLF in optimized formulation was performed using DSC studies (Mettler star sw 8.10, USA). The sample was sealed in a crimped aluminium pan and heated at a rate of 10° C/min from 25-400° C in nitrogen atmosphere. An empty aluminium pan was utilized as the reference pan.

Mucoadhesive Strength

Mucoadhesive strength of the tablet was measured on the modified physical balance. The apparatus consist of a modified double beam physical balance in which the right pan was replaced by a glass slide with copper wire and additional weight, to make the right side weight equal with left side pan. A teflone block of 3.8 cm diameter and 2 cm height was fabricated with an upward portion of 2 cm height and 1.5 cm diameter on one side. This was kept in a beaker filled with buffer media 0.1N HCl of pH 1.2, which was then placed below right side of the balance. Goat or rat stomach mucosa was used as a model membrane and buffer media 0.1N HCl of pH 1.2 was used as moistening fluid. The goat or rat stomach mucosa was obtained from local slaughter house and kept in a Krebs buffer during transportation. The underlying mucous membrane was separated using surgical blade and was washed thoroughly with buffer media 0.1N HCl of pH 1.2. It was then tied over the protrusion in the Teflon block using a thread. The block was then kept in a glass beaker. The beaker was filled with phosphate buffer media 0.1N HCl of pH 1.2 up to the upper surface of the goat stomach mucosa to maintain stomach mucosa viability during the experiments. One side of the tablet was attached to the glass slide of the right arm of the balance and then the beaker was raised slowly until contact between goat mucosa and mucoadhesive tablet was established. A preload of 10 mg was placed on the slide for 5 min (preload time) to establish adhesion bonding between mucoadesive tablet and goat or rat stomach mucosa. The preload and preload time were kept constant for all formulations. After the completion of preload time, preload was removed from the glass slide and water was then added in the plastic bottle in left side arm by peristaltic pump at a constant rate of 100 drops per min. The addition of water was stopped when mucoadhesive tablet was detached from the goat or rat stomach mucosa. The weight of water required to detach mucoadhesive tablet from stomach mucosa was noted as mucoadhesive strength in grams. From the mucoadhesive strength following parameter was calculated.

Force of adhesion (N) = (Mucoadhesive strength/1000) × 9.81

Bond strength (N/m2) = Force of adhesion (N)/Surface area(m2)

Swelling index

Swelling of tablet excipients particles involves the absorption of a liquid resulting in an increase in weight and volume. Liquid uptake by the particle may be due to saturation of capillary spaces within the particles or hydration of macromolecule. The liquid enters the particles through pores and binds to large molecules, breaking the hydrogen bonds and resulting in the swelling of the particles. The extent of swelling can be measured in terms of % weight gain by the tablet.

Method

For each formulation batch, one tablet was weighed and placed in a beaker containing 200 ml of buffer media. After each time interval the tablet was removed from beaker and weighed again up to 8 hours. The swelling index was calculated using following formula.

Swelling Index (S.I.) = (Wt-Wo)/Wo

Where, S.I. = Swelling index

Wt = Weight of tablet at time t

Wo = Weight of tablet before placing in the beaker

***In vitro* Drug Release Studies**

In vitro drug release studies of NLF from mucoadhesive tablet formulations were carried in 900 mL of 0.1N HCl as dissolution medium using USP XXI type II (Paddle method) Dissolution Rate Test Apparatus (DISSO 8000, LABINDIA, Mumbai, India) with agitation speed of 50 rpm and a temperature of 37 ± 0.5°C was maintained. Aliquots of 5 mL were withdrawn at predetermined different time intervals and filtered using a 0.45µ nylon disc filters and replaced with 5mL of fresh dissolution medium. The filtered samples were suitably diluted and analyzed at 252nm using UV-Visible Elico SL150 spectrophotometer. The drug release experiments were conducted in triplicate.

Release Kinetics and Mechanisms

Different kinetic models i.e., zero-order, first-order, Higuchi's and release mechanism model Korsmeyer Peppas were applied to interpret the release profile of NLF from mucoadhesive tablets.[16,19]

Stability Studies on NLF Mucoadhesive Tablets

The stability of optimized NLF mucoadhesive tablets developed in the present study were evaluated (as per ICH and WHO) at 40 ± 2^0 C and 75 ± 5% RH for 6 months. These studies were carried out at 3rd and 6th months. During storage, the products were monitored for appearance, hardness, friability, drug content, *in vitro* disintegration time, wetting time and drug release studies which were carried out at 3 and 6 months.

RESULTS AND DISCUSSION

Characterization of NLF Tablet Powder Blends

Fourier Transmittance Infrared Spectroscopic (FT-IR) Studies

The characteristic absorption bands of NLF were all retained in the FTIR spectra of 1:1 w/w physical mixtures of the NLF and selected excipients. The results indicated that there was no *in situ* interaction between NLF and the selected excipients in the formulations (Table 2).

Evaluation of Flow properties of powder blend

The powder blends of the formulations were evaluated for the flow properties. The results were in good agreement with specified values. These results indicated that the powder blends of all formulations were suitable to compress tablets by direct compression method.

Evaluation of Post-compression Parameters of NLF Mucoadhesive Tablets

***In vitro* Drug Release Studies**

The NLF mucoadhesive tablets prepared by direct compression using chitosan, carbopol, HPMCK4M as mucoadhesive and release retardant polymers and MCC Avicel PH 200) as filler were evaluated in paddle type apparatus using 900 ml of 0.1 HCl with agitation speed of 50 rpm.

In the present study, initially the effect of different concentrations (10%, 15%, 20% w/w) of mucoadhesive polymers as release retardants on NLF release from NLF mucoadhesive tablets was studied. F1,F2 and F3 containing chitosan at a level of 10%w/w, 15%w/w and 20%w/w of total tablet weight gave 99.99±0.22, 94.91±0.46 and 90.43±0.12 percent NLF releases respectively at the end of 10 h. The tablets in case of F1, F2 and F3 remained intact for 10 h. Higher concentration of chitosan in F3 showed slow swelling rate followed by slower erosion/disintegration of tablet and hence more retarding capacity. Lower concentration of chitosan in F1 induced faster swelling of the tablet, leading to more drug release along with maintaining tablet integrity. Hence, keeping in view of drug release profiles, 10% chitosan was selected as optimum release retarding concentration.

Later the effect of different concentrations of carbopol (10%,15%,20%) and HPMCK4M (10%,15%,20%) on NLF release from NLF mucoadhesive tablets was studied. Considering drug release profiles and maintainence of tablet integrity F4(10% carbopol) and F7(10% HPMCK4M) were selected for further studies along with F1(10% chitosan). All the formulations of HPMCK4M [F7(10%), F8(15%), F9(20%)] could not maintain tablet integrity upto 10 h due to low viscosity of HPMCK4M compared to carbopol and chitosan. The percent drug release of F4(98.19±1.85) at the end of 10 h was significantly higher when compared to F5(90.18±0.42) and F6(85.17±0.22) which may be due to lower concentration of the hydrogel, carbopol in F4(10%). Increase in carbopol concentration increased swelling pattern. Rheological properties of gels, gel network structure and their erosion rates affect the rate of poorly soluble drug release. The gel formed of carbopol was capable of preventing matrix disintegration and controlling additional water penetration. The drug release was in the order of HPMCK4M>chitosan>carbopol. Among the same polymer containing formulations the drug release was in the order of 10%>15%>20%.

Since NLF is poorly water soluble drug, its release from NLF mucoadhesive tablet is incomplete and therapeutically effective drug levels may not be achieved. Hence, in the present investigation HP-β-CD at a level of 10% w/w of total tablet weight (F10,F11,F12) were included in the formulations and their effect on the NLF release was studied in order to achieve therapeutically affective levels of NLF. A 99.99±0.14% NLF release was observed at the end of 10 h with F10 containing 10% chitosan and 10% HP-β-CD. The addition of cyclodextrins significantly increased the initial burst release of NLF from the formulations. The NLF release was more with chitosan(F10) than carbopol(F11) which may be due to more swelling behaviour of carbopol. Formulation, F12 having HPMCK4M could not maintain tablet integrity up to 10 h. This is because of low viscosity of HPMCK4M compared to hydrogels such as chitosan and carbopol leading to faster disruption and erosion of F12.Based on the MDT values it can be further confirmed that carbopol showed slow swelling rate followed by slower erosion/disintegration of tablet.

Among all the formulations, F10 containing 10%w/w HP-β-CD and 10%w/w chitosan gave superior and required NLF release of 99.99±0.14% at the end of 10 h and fulfilled the regulatory requirements in terms of percent drug release. (Fig 1).

Mean dissolution time is a parameter that indicates the efficiency of the formulation to release the drug. In this also F11, F10 and F12 stand in decreasing order. It is observed that at every time point the values of swelling index for F10, F11 and F12 are less than those corresponding values of F1, F4 and F7. So it is again confirmed that the increase in drug release rate is being associated with decreased bioadhesion and decreased swelling. (Table 5).

Release Kinetics and Mechanisms

Formulations F10, F11, F12 were evaluated for release kinetics and mechanisms. For the formulations F11 and F12, it was found that the coefficient of determination(R^2), which is the square of coefficient of correlation was more for first order plots. To find the mechanism of drug release, coefficient of determination values were calculated for Higuchi and Korsmeyer Peppas plots. The high values of R^2 indicate that diffusion is the mechanism of drug release from the NLF mucoadhesive tablets. The n values in Peppas plots were calculated which were in the range of 0.320 to 0.775 and this indicated that the diffusion may be of fickian to anamolous variety(both diffusion and erosion).

DSC studies

Analysis by differential scanning calorimetry was carried out to study the possibility of a physical interaction between the drug and the excipients. DSC thermogram of the pure NLF showed a sharp endothermic peak at around 158°C which was retained in the DSC thermogram of optimized formulation. These results indicated that the NLF was compatible with all the selected excipients in the formulations.

The compressed NLF mucoadhesive tablets were evaluated for properties like drug content, uniformity of weight, friability and hardness. The percent drug content of NLF mucoadhesive tablets was between 98.29± 0.046

to 99.01± 0.017 of labelled claim. A good degree of uniformity in weight of tablets was achieved for all batches of tablet formulations prepared. The % deviation was within 3, which indicates excellent uniformity in weight of all batches of tablet formulations. The friability values of all batches of tablet formulations prepared were less than 1%. The hardness of all batches of tablet formulations compressed ranged between 4-4.3 kg/cm^2. (Fig 2,3).

Stability Studies on NLF Mucoadhesive Tablets

The mucoadhesive tablets prepared by the optimized formulation F10 were charged on accelerated stability and monitored for appearance, hardness, friability, drug content, wetting time and dissolution profile studies, at 40 ± 2°C / 75 ± 5% RH for 6 months. Physical observation and drug release studies were conducted after 3 months of storage and after 6 months of storage. The stability study reveals no significant variation in appearance, hardness, friability, drug content, swelling index, mucoadhesive strength, and *in-vitro* dissolution study up to three and six months. Statistical analysis was done by paired t-test, to verify whether the differences observed between the physical parameters before and after during storage at 40 ± 2°C and at 75±5% relative humidity (RH), for in 6 months period, were significant or not. No significant difference was observed in any one of all the cases (P>0.05). The results are shown in Table 6.12. The drug release profiles of the formulations containing nelfinavir mesylate before and after storage are shown in Tables 6.13 and in Figures 6.21 and 6.22. The results thus indicated that the formulation was stable under accelerated conditions of temperature and humidity.

***In vivo* studies**

As per *in vivo* study protocol, nelfinavir mesylate products were administered per orally to healthy rabbits at a dose equivalent to 9 mg of nelfinavir/kg of body weight of rabbit and the plasma concentrations were determined by HPLC method.

Pharmacokinetic parameters were determined, after the oral administration of pure drug (N) suspension, elimination rate constant k_{el} was found to be 0.203 hr^{-1} and the corresponding biological half-life ($t_{1/2}$) was found to be 3.412 hours. The MRT was found to be 5.39 hours. A peak plasma concentration of 290 ng/ml was observed at 1.5 hours after administration of pure drug suspension (N).

When the experimental Mucoadhesive tablet formulation was administered orally, peak concentration of 790 ng/ml was observed at 4 hours. The elimination rate constant k_{el} for nelfinavir was found to be 0.1062 hr^{-1}, and the corresponding biological half life ($t_{1/2}$) was found to be 6.5 hours. The MRT was found to be 11.96 hr. Very high C_{max}, AUC0-∞ (extent of absorption) and $AUMC_{0-\infty}$ were observed with Mucoadhesive tablet, when compared to N.

Table 1: Formulation of Mucoadhesive Tablets of Nelfinavir Mesylate.

Ingredients (mg/Tab)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
NLF	700	700	700	700	700	700	700	700	700	700	700	700
Chitosan	100	150	200	-	-	-	-	-	-	100	-	-
Carbopol	-	-	-	100	150	200	-	-	-	-	100	-
HPMCK4M	-	-	-	-	-	-	100	150	200	-	-	100
HP-β-CD	-	-	-	-	-	-	-	-	-	100	100	100
MCC	190	140	90	190	140	90	190	140	90	90	90	90
Mg. Stearate	5	5	5	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5	5	5	5
Total weight	**1000**	**1000**	**1000**	**1000**	**1000**	**1000**	**1000**	**1000**	**1000**	**1000**	**1000**	**1000**

Table 2: Fourier Transmittance Infrared Spectroscopic (Ft-Ir) Studies.

Characteristic peaks	Vibration	Frequency range (cm^{-1})	Frequency (cm^{-1}) observed for NLF	Frequency (cm^{-1}) observed for NLF Mucoadhesive Tablet
OH	bending	1750-1680	1659.48	1659
N-H	Stretching	3400-3000	3361.88	3360
C-H	bending	900-660	836.56	837.45
S=O	Stretching	1380-1200	1375.44	1375
C-O	Stretching	1420-1350	1358.14	1358
N-H	bending	1580-1580	1540.59	1539

Table 3: Coeeficient of Determination ($R^{2)}$ Values In The Analysis of Release Data of Nelfinavir Mesylate Mucoadhesive Tablets Prepared As Per Various Kinetic Models.

FORMULATION	Zero order	First order	Higuchi plot	Peppas plot
F1	0.7808	0.935	0.9506	0.9711
F2	0.7628	0.879	0.9207	0.8251
F3	0.846	0.819	0.8915	0.9259
F4	0.6626	0.753	0.7947	0.4964
F5	0.535	0.645	0.8681	0.9936
F6	0.8326	0.950	0.9627	0.9534
F7	0.6568	0.877	0.9079	0.9632
F8	0.708	0.887	0.9003	0.8876
F9	0.8242	0.918	0.9604	0.9514
F10	**0.924**	**0.885**	**0.9949**	**0.9868**
F11	0.7614	0.920	0.9263	0.91
F12	0.8194	0.917	0.9735	0.9873

Table 4: Bioadhesive Strength and Bioadhesive Force of Mucoadhesive Formulations.

Formulation	Bioadhesive strength(gm) *	Bioadhesive force(dynes) *
F1	27.21 ± 0.01	2.68 ± 0.08
F2	27.82 ± 0.46	2.72±0.06
F3	28.19 ± 0.17	2.78 ± 0.15
F4	32.33 ± 0.34	3.23 ± 0.09
F5	34.56 ± 0.05	3.45 ± 0.08
F6	35.19 ± 0.91	3.51 ± 0.01
F7	14.51 ± 0.11	1.44 ± 0.15
F8	14.72 ± 0.46	1.45 ± 0.11
F9	14.98 ± 0.07	1.48 ± 0.09
F10	27.44 ± 0.34	2.71 ± 0.27
F11	32.62 ± 0.65	3.25 ± 0.28
F12	14.99 ± 0.91	1.42 ± 0.13

*All values are expressed as mean± SE, n=3.

Table 5: Mean Dissolution Time of Formulations F10, F11 and F12.

FORMULATION	MDT(Seconds)
F10	289
F11	329
F12	256

Figures

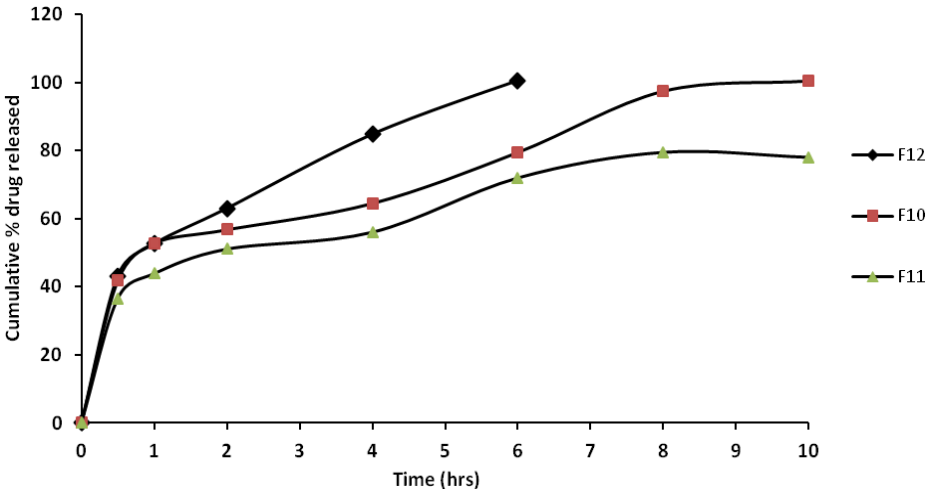

Figure 1: Comparitive Dissolution Profile of F10, F11, F12 Mucoadhesive Tablets of Nelfinavir Mesylate.

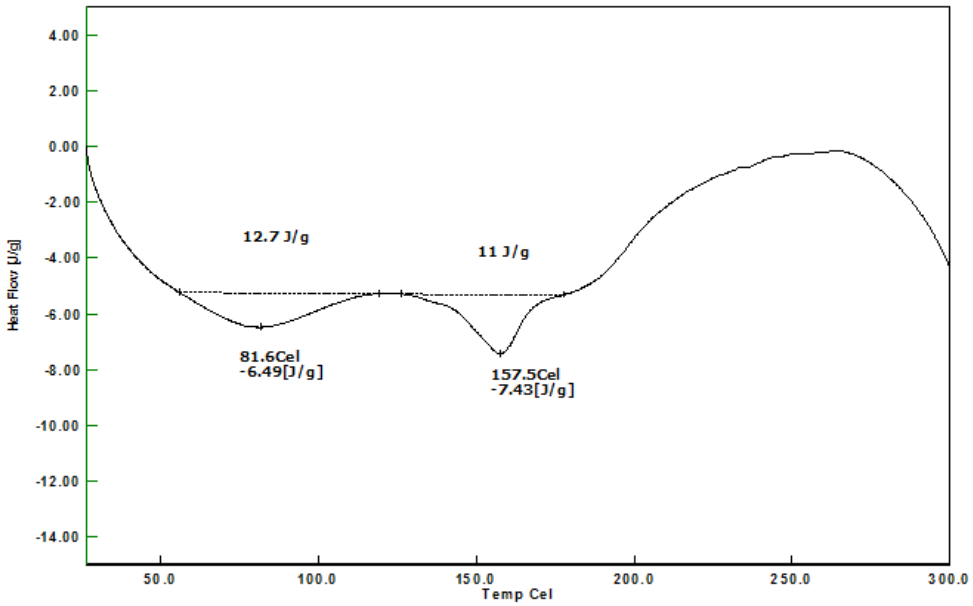

Figure 2: Dsc Thermogram of Pure Drug.

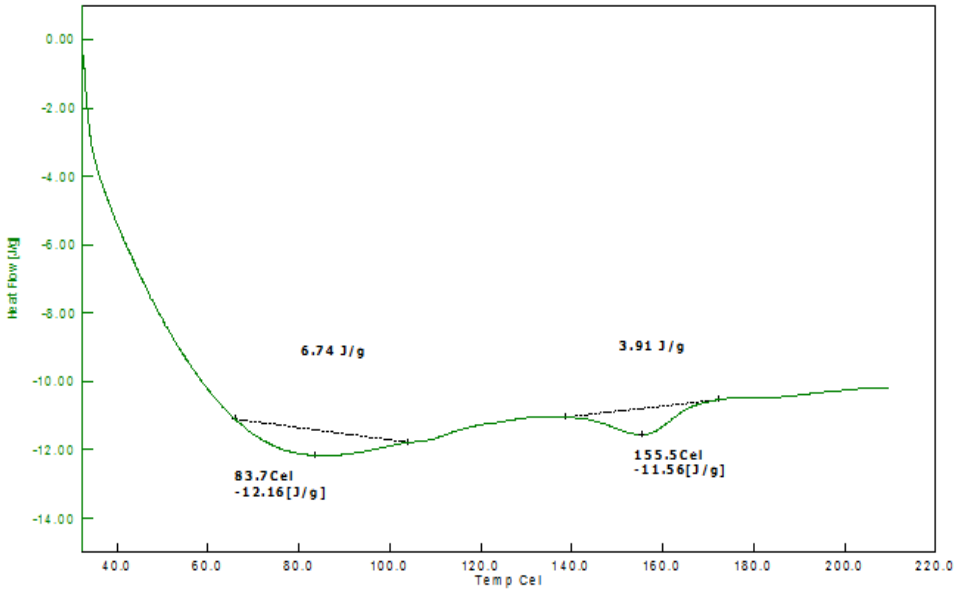

Figure 3: Dsc Thermogram of F10 Mucoadhesive Tablet of Nlf.

REFERENCES

1. Marc L, Sabine K, Jennifer B, Dressman. Classification of orally administered drugs on the world health organization model list of essential medicines according to the biopharmaceutics classification system. European Journal of Pharmaceutics and Biopharmaceutics, 2004; 58: 265–278.
2. Wu C, Benet LZ. Predicting drug disposition via application of BCS: transport/absorption/elimination interplay and development of a biopharmaceutics drug disposition classification system. Pharmaceutical Research, 2005; 22: 11–23.
3. World Health Organization. Proposal to waive *in vivo* bioequivalence requirements for the WHO model list of essential medicines immediate release, solid oral dosage forms. Geneva, October 2005.
4. Takagi T, Ramachandran C, Bermejo M, Yamashita S, Yu LX, Amidon GL. A provisional biopharmaceutical classification of the top 200 oral drug products in the united states, great britain, spain and japan. Molecular Pharmaceutics, 2006; 3: 631–643.
5. Bret Berner, Jenny Louie-Helm. Tablet shapes to enhance gastric retention of swellable controlled release oral dosage forms. US patent 6, 88, 962B1-2002.
6. John W Shell, Jenny Louie-Helm, Micheline Markey. Extending the duration of drug release with

in the stomach during the fed mode. US patent 6, 340, 475 B2-2002.
7. Joseph J. Eron, Jr. HIV-I protease inhibitors. Clinical infectious diseases, 2000; 3(1): 160-170.
8. Jennifer F, David C, Patrick G, H, Zoe C, Rhiannon M, Ian W, Margaret J. Intracellular and plasma pharmacokinetics of nelfinavir and M8 in HIV-infected patients: relationship with P-glycoprotein expression. Antiviral therapy, 2000; 9: 77–84.
9. Torne S.J, Torne J. S. Cyclodextrin based drug delivery system of protease inhibitor-NLF. Journal of inclusion phenomena and macro cyclic chemistry, 2007; (57): 689-697.
10. Ranjit M, Sayon P, Somasree R, Sabyasachi M. Polymeric nanocarriers: A promising research avenue for the delivery of anti-HIV drugs. International Journal of applied pharmaceutics, 2012; 2(2).
11. Hiremath. S.N, Godge G. R, Kharia A. A., Vaisya V. R. Studies on the preparation, characterisation and solubility of β-Cyclodextrin-NLF inclusion complexes. Journal of pharmaceutical research and health care, 2007; 2(3): 279-284.
12. Pheeba M, Ganesh Shankar arya. Formulation and in-vitro evaluation of NLF using cellulose acetate. International Journal of pharmacy and pharmaceutical sciences, 2010; 2(3).
13. Khanna B, Kedar B, Kumar K. Formulation development and Dissolution rate enhancement of NLF. International journal of pharmaceutical innovations, 2011; 1(4): 88-99.
14. The United State Pharmacopoeia, USP30-NF-25, Asian edition. Rockville M, United State Pharmacopoeial Convention Inc, 2007; 643-645.
15. Leon Lachman, Herbert A. Lieberman, Joseph L.Kanig, The Theory and Practice of Industrial pharmacy, 3rd Edition, Varghese publishing house, 1987; 296-300.
16. Brazel CS, Peppas NA. Modeling of drug release from swellable polymers. European journal of Pharmaceutics and Biopharmaceutics, 2000; 49(1): 47-58.
17. Lapidus H, Lordi NG. Drug release from compressed hydrophilic matrices, Journal of Pharmaceutical Sciences, 1966; 55(8): 840-843.
18. Higuchi T. Mechanism of sustained action medication, theoretical analysis of rate of release of solid drugs dispersed in solid matrices. Journal of Pharmaceutical Sciences, 1963; 52(12): 1145-1153.
19. Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA. Mechanism of solute release from porous hydrophilic polymers. International Journal Of Pharmaceutical Sciences, 1983; 15(1): 25-35.