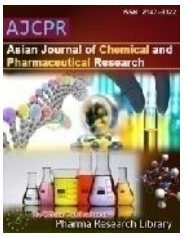
Asian Journal of Chemical and Pharmaceutical Research

Journal Home Page: www.pharmaresearchlibrary.com/ajcpr



Research Article Open Access

# Enhancement of Solubility and Dissolution Rate of Nelfinavir Mesylate using Complexing Agents

**M. Kiranmai[1*], M. Divya[1], G. Vijaya Reddy[1], G. Kalpana Devi[2]**

[1]*Sai Pranavi College of Pharmacy, Keesara, R.R. Dist., Telangana, India*
[2]*Assistant Professor, Sai Pranavi College of Pharmacy, Keesara, R.R. Dist., Telangana, India*

**A B S T R A C T**

In the present work, an attempt has been made to develop improvement of bioavailability tablets of nelfinavir mesylate**.** In the present work to enhance the solubility and dissolution rate of selected drug molecule. All the formulations were prepared by direct compression method using 6mm punch on 8 station rotary tablet punching machine. The blend of all the formulations showed god flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations, F1 formulation showed maximum % drug release i.e., 94.95% in 50 min hence it is considered as optimized formulation. The F1 formulation contains PEG 6000 as polymer in the concentration of 50 mg.

**Keywords:** nelfinavir, PEG 4000, PEG 6000,bioavailabilityenhances.

**A R T I C L E I N F O**

**CONTENTS**



**Article History: Received**18December 2015, **Accepted**21January 2015, **Available Online** 12April 2016

***Corresponding Author**
M.Kiranmai
Sai Pranavi College of Pharmacy,
Keesara, R.R. Dist., Telangana, India
Manuscript ID: AJCPR2848

**Citation:** M.Kiranmai, *et al*. Enhancement of Solubility and Dissolution Rate of Nelfinavir Mesylate using Complexing Agents.*A. J. Chem.Pharm, Res.*, 2016, 4(1): 36-42.



## 1. Introduction

The oral route is most common and preferred route for drug delivery system, it is convenient and easy ingestion. Moreover, patient compliance and drug treatment is more effective with oral administration than other routes of administration. Oral drug absorption from solid dosage forms depends on the release of the drug substance from the delivery system, mainly dissolution rate of the drug under the physiological conditions and permeability of the drug

across the gastrointestinal tract. Poorly water-soluble drugs are expected to have dissolution-limited absorption. Increasing the drug solubility may substantially improved drug absorption, and consequently drug bioavailability. Solid dispersion techniques have been used to enhance the dissolution and oral bioavailability of many poorly soluble drugs .Hence the researchers focused on two areas i) to enhance solubility and dissolution ii) to increase the permeability of poorly water soluble drugs. The main use of solid dispersion technique is to improve the dissolution rate and bioavailability of poorly water-soluble drugs. Many researches denoted that drugs are poor water solubility and high permeability for solid dispersion systems (BCS classification, this type of drugs shown dissolution rate is limited and categorized class-II drugs. Therefore for oral route of administration to increase the dissolution and bio availability by using solid dispersion systems for class-II drugs.About 40% of new chemical molecules are poorly water soluble. Most of the potential drugs are abandoned in initial stages of development due to solubility to overcome this problems by using the various techniques and methods to enhance the solubility and dissolution of poorly water soluble drugs.A poorly soluble drug represents a problem for their bioavailability related to their low dissolution rate. The major drawback of low aqueous solubility is delays its absorption from the gastrointestinal tract (GIT).Solubility behavior of a drug is one of the key factor of its oral bioavailability.

**Solid Dispersion**[1]

Solid dispersion is containing at least two different components one is hydrophilic matrix and another is hydrophobic drug, the matrix may be either amorphous or crystalline, the drug can be dispersed either amorphous or crystalline particles.Solid dispersion systems illustrated in literature to enhance the dissolution properties of poorly water-soluble drugs. Such as solubilization of drugs in solvents, salt formation, complex forms with cyclodextrin and sometimes particle size reduction also utilized to improve the dissolution of poorly water-soluble drugs. On other hand, solid dispersion system offers variety of formulations by using excipients to enhance dissolution of poorly water-soluble drugs for oral administration. When the solid dispersion exposed to aqueous media the carrier can be dissolves the solid dispersion is exposed to aqueous media,the carrier will dissolves and the drug releases as fine colloidal particles in the media.

The resulting enhanced surface area shows higher dissolution rate and bioavailability of poorly water-soluble drugs. In solid dispersion drug dissolves immediately to saturate the gastrointestinal tract (GIT) fluid, and excess drug precipitates as fine colloidal particles or oily globules of submicron to nano size. Solid dispersion technique was demonstrated by Sekiguchi and Obi. They investigated the faster absorption of poorly water-soluble drugs such as sulfathiazole by the formation of eutectic mixture with a water-soluble and physiologically inert carriers like urea.

In solid dispersions, molecular dispersions represents on particle size reduction, after carrier dissolution the drug is molecularly dispersed in dissolution medium. Solid dispersions apply this principle for solid dispersions to drug release by creating a mixture of poorly water soluble drug and highly soluble carriers, if higher surface area is formed, resulting enhanced dissolution rate and bioavailability. The drug solubility is mainly related to drug wettability to enhance the dissolution in solid dispersions,even without any surface activity also observed such as urea,anyhow carriers will influence the dissolution rate by co-solvents effect and direct dissolution particles shown in solid dispersion particles shown a high degree of porosity, increase the porosity also depends on carrier properties, more porous particles result higher dissolution rate. Poorly water-soluble crystalline drugs, at amorphous state drugs were shows higher solubility.Enhancement of drug release can be increased by using the drug in its amorphous state, no energy is required in the dissolution process to break up the crystal lattice.In solid dispersions(SD's) drugs are presented as supersaturated solutions after system dissolution; if drugs are precipitate,it is as a metastable polymorphic form with higher solubility than the most stable crystal form.For drugs with low crystal energy (low melting temperature or heat of fusion), the amorphous composition is dictated by the difference in melting temperature between the drug and the carrier,for drugs with high crystal energy shows a higher amorphous compositions can be obtained by choosing of carriers, which show specific interactions with them .

## 2. Materials and Methods

**Materials:**Nelfinavir, Poly ethylene glycol, Polyethylene, Magnesium stearate, Aerosil, Micro crystalline cellulose.

**Methodology**

**Pre-formulation Studies**

Pre-formulation involves the application of bio-pharmaceutical principles to the physicochemical parameters of drug substance are characterized with the goal of designing optimum drug delivery system.

**Analytical method development for Nelfinavir mesylate:**

**Determination of absorption maxima**

A spectrum of the working standards was obtained by scanning from 200-400nm against the reagent blank to fix absorption maxima. The λmaxwas found to be 235nm. Hence all further investigations were carried out at the same wavelength.

**Preparation of standard graph in pH 7.4 medium**

100 mg of Nelfinavir mesylate was dissolved in methanol 5 ml, volumetric flask make upto 100 ml of Phosphate buffer of pH 7.4 , from this primary stock 10 ml was transferred to another volumetric flask made up to 100ml with Phosphate buffer of pH 7.4, from this secondary stock was taken separately and made up to 10 ml with Phosphate buffer of pH 7.4, to produce 10,20,30,40 and 50 µg/ml respectively. The absorbance was measured at 235 nm by using a UV spectrophotometer.

**Formulation Development:**

Solid dispersions were prepared by solvent evaporation method. Methanol was used as solvent. Nelfinavir mesylate dose was taken as 200mg.Water soluble polymers such as PEG 4000 and PEG 6000 were selected as carriers. Drug and polymers were taken in different ratios stated in the

formulation chart (Table 2). The prepared solid dispersions were passed through the sieve no 20 to get uniform sized particles. The solid dispersions were mixed with required quantities of diluent, lubricant and glidant. The blend was evaluated for pre-compression parameters.

Total weight of tablets = 550 mg

The tablets were prepared by using 8 mm flat surfaced punch. The hardness of the tablets was maintained as 4.5 $kg/cm^2$.

**Evaluation of tablets**:

**Pre compression parameters:**

Measurement of Micromeritic Properties of Powders

**1. Angle of repose**

The angle of repose of API powder is determined by the funnel method. The accurately weight powder blend are taken in the funnel. The height of the funnel is adjusted in a way that, the tip of the funnel just touched the apex of the powder blend.

**2. Bulk density**

The powder sample under test is screened through sieve No.18 and the sample equivalent to 25 gm is weighed and filled in a 100 ml graduated cylinder and the power is leveled and the unsettled volume, $V_0$ is noted.

**3. Tapped density**

The powder sample under test is screened through sieve No.18 and the weight of the sample equivalent to 25 gm filled in 100 ml graduated cylinder. The mechanical tapping of cylinder is carried out using tapped density tester at a nominal rate for 500 times initially and the tapped volume $V_0$ is noted. Tappings are proceeded further for an additional tapping 750 times and tapped volume, $V_b$ is noted.

**4. Compressibility Index**

The Compressibility Index of the powder blend is determined by Carr's compressibility index to know the flow character of a powder. The formula for Carr's Index is as below:

**5. Hausner's ratio**

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. The ratio of tapped density to bulk density of the powders is called the Hasner's ratio. **Post compression parameters:**

**a) Thickness**

The thickness of tablets was determined by using Digital micrometer. Ten individual tablets from each batch were used and the results averaged.

**b) Weight variation**

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation three batches were calculated. It passes the test for weight variation test if not more than two of the individual tablet weights deviate from the average weight by more than the allowed percentage deviation and none deviate by more than twice the percentage shown. It was calculated on an electronic weighing balance.

**c) Friability**

The friability values of the tablets were determined using a Roche-type friabilator. Accurately weighed six tablets were placed in Roche friabilator and rotated at 25 rpm for 4 min.

**d) Assay**

The content of drug in five randomly selected tablets of each formulation. The five tablets were grinded in mortar to get powder; this powder was dissolved in 0.1 N HCl by sonication for 30 min and filtered through filter paper.The drug content was analyzed spectro-photometrically at 284 nm using UV sectrophotometer. Each measurement was carried out in triplicate and the average drug content was calculated.

**e) Disintegration test**

Six tablets were taken randomly from each batch and placed in USP disintegration apparatus baskets. Apparatus was run for 10 minutes and the basket was lift from the fluid, observe whether all of the tablets have disintegrated.

**f) Dissolution test of nelfinavir mesylate tablets**

Drug release from nelfinavir mesylate tablets was determined by using dissolution test United States Pharmacopoeia (USP) 24 type II (paddle). The parameters used for performing the dissolution were pH 7.4 medium as the dissolution medium of quantity 900ml. The whole study is being carried out at a temperature of $37^0$ C and at a speed of 50rpm. 5ml aliquots of dissolution media were withdrawn each time at suitable time intervals (5, 10, 20 mimutes.) and replaced with fresh medium. After withdrawing, samples were filtered and analyzed after appropriate dilution by UV spectrophotometer. The concentration was calculated using standard calibration curve.

## 3. Results and discussion

**Determination of λ max:**The prepared stock solution was scanned between 200-400 nm to determine the absorption maxima. It was found to be 235 nm.

**Calibration curve of Nelfinavir mesylate:**

The standard curve of Nelfinavir mesylate was obtained and good correlation was obtained with $R^2$ value of 0.999. The medium selected was pH 7.4 phosphate buffer. The standard graph values of Nelfinavir mesylate are tabulated as below-

**Table 2:**Standard Graph values of Nelfinavir mesylate at 235 nm in pH 7.4 phosphate buffer

| Concentration (µg/ml) | Absorbance |
|---|---|
| 0 | 0 |
| 10 | 0.198 |
| 20 | 0.396 |
| 30 | 0.601 |
| 40 | 0.804 |
| 50 | 0.998 |

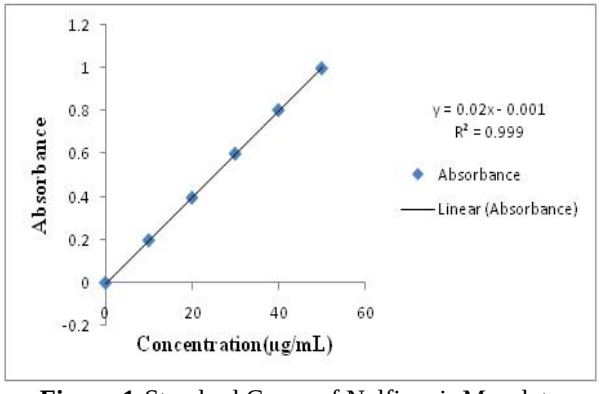



**Figure 1:**Standard Curve of Nelfinavir Mesylate

**Evaluation:**

**Characterization of Pre-compression Blend:**

The pre-compression blend of Etodalascsoilddispersions were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. Angle of repose was less than 280, Carr's index values were less than 11 for the pre-compression blend of all the batches indicating good to fair flowability and compressibility. Hausner's ratio was less than 1.25 for all the batches indicating good flow properties.

**Evaluation of Tablets:**

**Physical Evaluation of Nelfinavir mesylate solid dispersion tablets:** All the tablets of different batches complied with the official requirement of weight variation as their weight variation passes the limits. The hardness of the tablets ranged from 4.6 to 5 kg/cm$^2$ and the friability values were less than 0.561% indicating that the tablets were compact and hard. The thickness of the tablets ranged from 4.71-4.91cm. All the formulations satisfied the content of the drug as they contained 98-100% of Nelfinavir mesylate and good uniformity in drug content was observed. Thus, all the physical attributes of the prepared tablets were found to be practically within control limits.

***In vitro* release studies:** The drug release rate from buccal tablets was studied using the USP type II dissolution test apparatus. The dissolution medium was 900 ml of pH 7.4 phosphate buffer at 50 rpm at a temperature of 37 ± 0.5 °C. Samples of 5 ml were collected at different time intervals up to 1 hrs and analyzed after appropriate dilution by using UV Spectrophotometer at 235nm.

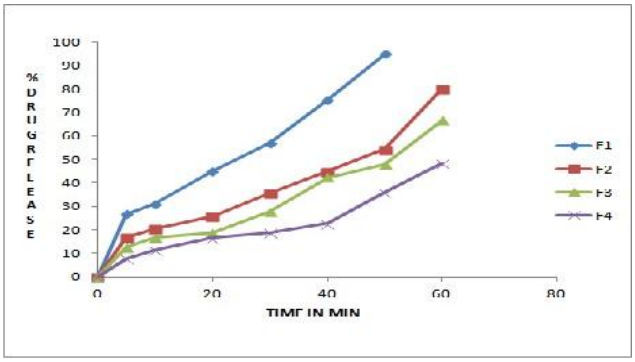



**Figure 2:***In-vitro* dissolution data for formulations F1 – F4 by using PEG 4000 Polymer

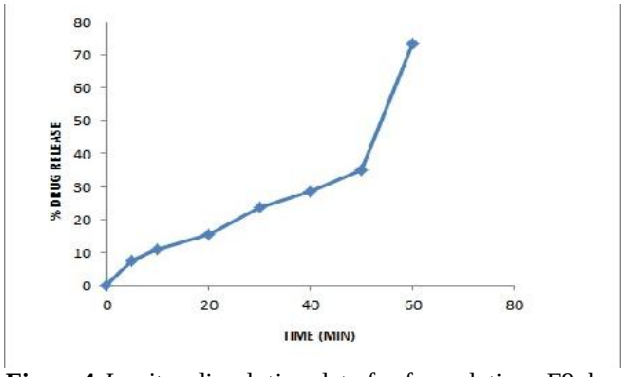



**Figure4:***In-vitro* dissolution data for formulations F9 by using PEG 4000 & 6000 Polymer.

Among all the formulations F1 formulation containing, Drug and Peg 4000 in the ratio of 1:0.25 showed good result that is 94.95 % in 50 minutes. As the concentration of polymer increases, the drug release was decreased. While the formulations containing PEG 6000 showed less release. Hence from the dissolution data it was evident that F1 formulation is the better formulation. The formulation containing combination of PEG 4000& 6000 was also not producing desired percentage drug release. The formulation is following zero order release kinetics.

***In-vitro* release studies:** The drug release rate from buccal tablets was studied using the USP type II dissolution test apparatus. The dissolution medium was 900 ml of pH 7.4 phosphate buffer at 50 rpm at a temperature of 37 ± 0.5 °C. Samples of 5 ml were collected at different time intervals up to 1 hrs and analyzed after appropriate dilution by using UV Spectrophotometer at 235nm.

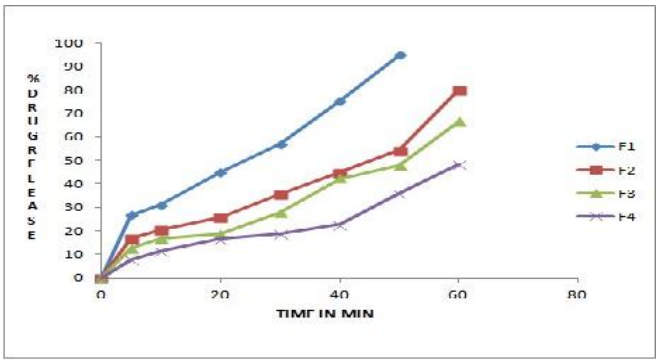



Figure 2:*In-vitro* dissolution data for formulations F1–F4 by using PEG 4000 Polymer

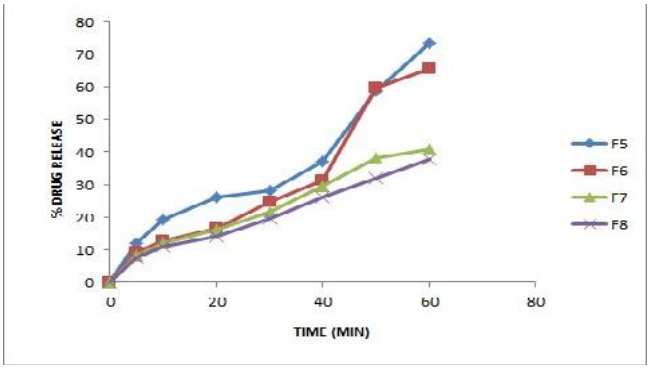



**Figure 3:** *In-vitro* dissolution data for formulations F5– F8 by using PEG 4000 Polymer

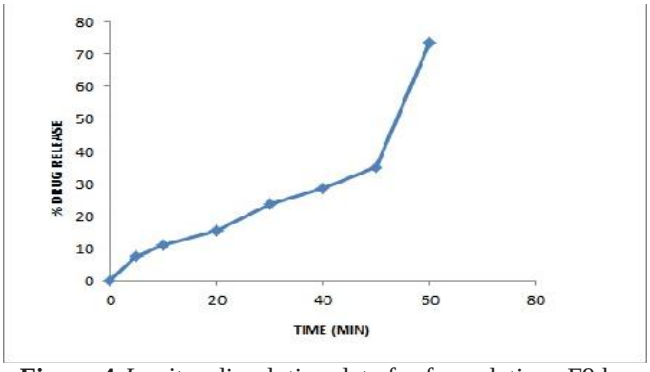



**Figure 4:***In-vitro* dissolution data for formulations F9 by using PEG 4000 & 6000 Polymer

Among all the formulations F1 formulation containing, Drug and Peg 4000 in the ratio of 1:0.25 showed good result that is 94.95 % in 50 minutes. As the concentration of polymer increases the drug release was decreased. While the formulations containing PEG 6000 showed less release. Hence from the dissolution data it was evident that F1 formulation is the better formulation. The formulation containing combination of PEG 4000& 6000 was also not producing desired percentage drug release. The formulation is following zero order release kinetics.

**Table 1:** Formulation table showing various compositions

| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| **Drug** | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 |
| **PEG 4000** | 50 | 100 | 150 | 200 | | | | | 100 |
| **PE 6000** | | | | | 50 | 100 | 150 | 200 | 100 |
| **MCC** | 290 | 240 | 190 | 140 | 290 | 240 | 190 | 140 | 140 |
| **Aerosil** | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| **Manesium stearate** | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

**Table 3:**Physical properties of pre-compression blend

| Formulation Code | Angle of repose (Θ) | Bulk density ($gm/cm^3$) | Tapped density ($gm/cm^3$) | Carr's Index (%) | Hausner's ratio |
|---|---|---|---|---|---|
| F1 | 25.10° | 0.53±0.01 | 0.59±0.01 | 9.43±0.12 | 1.09±0.02 |
| F2 | 25.43° | 0.54±0.03 | 0.60±0.02 | 9.40±0.13 | 1.10±0.01 |
| F3 | 25.41° | 0.54±0.02 | 0.58±0.03 | 10.01±0.19 | 1.13±0.06 |
| F4 | 26.40° | 0.51±0.01 | 0.61±0.06 | 10.11±0.02 | 1.16±0.01 |
| F5 | 27.12° | 0.58±0.03 | 0.63±0.03 | 10.34±0.13 | 1.17±0.03 |
| F6 | 25.31° | 0.59±0.03 | 0.64±0.04 | 10.12±0.34 | 1.11±0.06 |
| F7 | 26.11° | 0.56±0.01 | 0.63±0.01 | 9.93±0.11 | 1.13±0.03 |
| F8 | 26.15° | 0.53±0.03 | 0.58±0.03 | 10.13±0.02 | 1.12±0.01 |
| F9 | 26.10° | 0.54±0.01 | 0.61±0.03 | 10.20±0.13 | 1.13±0.03 |

All the values represent mean ± Standard deviation (SD), n=3

**Table 4:** Physical Evaluation of Nelfinavir mesylate tablets

| Formulation code | Weight variation (mg) | Thickness (cm) | Diameter | Hardness ($Kg/cm^2$) | Friability (%) | Content uniformity(%) |
|---|---|---|---|---|---|---|
| F1 | 553±1 | 4.76±0.01 | 8.12±0.01 | 4.5±0.7 | 420 | 99±0.12 |
| F2 | 554±2 | 4.74±0.04 | 8.14±0.02 | 4.2±0.5 | 0.341 | 99±0.3 |
| F3 | 551±1 | 4.71±0.01 | 8.01±0.01 | 4.6±0.6 | 0.363 | 100±0.1 |
| F4 | 554±2 | 4.80±0.06 | 8.03±0.03 | 4.8±0.5 | 0.561 | 100±0.3 |
| F5 | 555±3 | 4.81±0.04 | 8.04±0.04 | 4.8±0.4 | 0.482 | 99±0.6 |
| F6 | 554±1 | 4.74±0.05 | 8.09±0.05 | 4.4±0.6 | 0.513 | 99±0.4 |
| F7 | 545±1 | 4.76±0.03 | 8.11±0.03 | 5 ± 0.1 | 0.412 | 98±0.9 |
| F9 | 558±3 | 4.73±0.03 | 8.03±0.02 | 4.5±0.3 | 0.512 | 100±0.1 |

**Table 5:***In-vitro* dissolution data for formulations F1 – F4 by using PEG 4000 Polymer

| Time(Min) | % Drug release | | | |
|---|---|---|---|---|
| | F1 | F2 | F3 | F4 |
| 0 | 0 | 0 | 0 | 0 |
| 5 | 26.73 | 16.73 | 12.56 | 7.73 |
| 10 | 31.06 | 20.4 | 16.57 | 11.56 |
| 20 | 44.9 | 25.9 | 18.9 | 16.56 |
| 30 | 57.06 | 35.56 | 27.73 | 18.9 |
| 40 | 75.56 | 44.9 | 42.4 | 22.73 |
| 50 | 94.9 | 54.4 | 47.9 | 36.06 |
| 60 | | 79.9 | 66.56 | 48.4 |

**Table 6:***In-vitro* dissolution data for formulations F5– F8 by using PEG 6000 Polymer

| Time(MIN) | % Drug release | | | |
|---|---|---|---|---|
| | F5 | F6 | F7 | F8 |
| 0 | 0 | 0 | 0 | 0 |
| 5 | 11.86 | 8.18 | 9.21 | 7.51 |
| 10 | 19.01 | 11.86 | 12.60 | 10.90 |
| 20 | 26.16 | 16.06 | 16.43 | 15.55 |
| 30 | 28.22 | 21.44 | 24.83 | 23.80 |
| 40 | 36.99 | 29.62 | 31.32 | 30.29 |
| 50 | 58.81 | 59.77 | 37.95 | 31.98 |
| 60 | 73.55 | 65.59 | 40.90 | 37.58 |

**Table 7:***In-vitro*dissolution data for formulations F9 by using PEG 4000 & 6000 Polymer

| Time(MIN) | % Drug release |
|---|---|
| | F9 |
| 0 | 0 |
| 5 | 7.51 |
| 10 | 10.90 |
| 20 | 15.55 |
| 30 | 23.80 |
| 40 | 28.29 |
| 50 | 34.98 |
| 60 | 39.58 |

## 4. Conclusion

To enhance the aqueous solubility of Nelfinavir mesylate by suitable solid dispersion technique and study the influence of various water soluble polymers on the dissolution enhancement of the solid dispersions.In the present work to enhance the solubility and dissolution rate of selected drug molecule. All the formulations were prepared by direct compression method using 6mm punch on 8 station rotary tablet punching machine. The blend of all the formulations showed god flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F1 formulation showed maximum % drug release i.e., 94.95% in 50 min hence it is considered as optimized formulation. The F1 formulation contains PEG 6000 as polymer in the concentration of 50 mg.

## 5. Acknowledgement

The authors sincerely acknowledge the KP Labs (A Division of Karthikeya Drugs & Pharmaceuticals Private Limited), Kotahpet, Hyderabad, for providing Drugs and support to carry out this research work.

## 6. References

[1] Sarode Ashish,Wang Peng,Cote Catherine, Worthen David R. Low-Viscosity hydroxyl propylcellulose(HPC) grades SL and SSL: versatile pharmaceutical polymers for dissolution enhancement, controlled release, and pharmaceutical processing.AAPS Pharm Sci Tech.**2013**;14(1):151-159.

[2] Dr.K.L.Senthilkumar and Y.sirisha. Enhancement of dissolution rate studies on solid dispersion of Aceclofenac. International Journal of Pharma and Bio Sciences. **2011;** 2 (2):70-76.

[3] Anjan K. Mahapatra and P. N. Murthy Solubility and dissolution rate enhancement of efavirenz by inclusion complexation and liquid anti-solvent precipitation technique Journal of Chemical and Pharmaceutical Research, **2014**, 6(4):1099-1106

**[4]** Vyas Pooja R* and Patel Ketan J. Enhancement Of Solubility Of Itraconazole Using Novel Liquisolid Technique Pharma Science Monitor 6(2), Apr-Jun **2015**

[5] Ashis Kumar Mehatha, VidyadharaSuryadevara, Sasidhar R Lankapalli, Abhijit M Deshmukh, Laxmana P Sambath. Formulation and optimization of pioglitazone solid Dispersions prepared by hot melt extrusion Technique. Indonesian J. Pharm.,**2013**;24( 3): 206 – 214.

[6] P.Kumar, S.Kumar, A.kumar, M.Chander.Physicochemical Characterization of Solid Dispersion of Cefdinir with PVP K-30 and PEG 4000.International journal of pharmaceutical sciences and nanotechnology. **2010**; 3(2):948-956.

[7] Tantishaiyaku V, Kaewnopparat N, Ingkatawornwong S. Properties of solid dispersions of piroxicam in poly vinyl pyrrolidone Int J Pharm.,**1999**;30(2):143-51.

[8] Newa M,Bhandari KH,Lee DX,Sung JH,Kim JA,Yoo BK,Woo JS,Choi HG,Yong CS.Drug.Dev Ind.Enhanced dissolution of ibuprofen using solid dispersion with polyethylene glycol 20000. Pharm.**2008**; 34(10):1013-21.

[9] Jiang YR,Zhang ZH,Xia HJ,Jia XB.Study on solid

dispersion -based tanshinoneII(A). ZhongguoZhong, Yao ZaZhi .**2013**; 38(2):174-8.

[10] Ashish L.Sarode,Harpreet Sandhu,Navnit Shah, Waseem Malick,Hossein Zia. Hot melt extrusion (HME) for amorphous solid dispersions: Predictive tools for processing and impact of drug–polymer interactions on supersaturation. Europian Journal of Pharmaceutical Sciences. **2013**; 48(3):371-384.

[11] Abhay N. Padalkar,Sadhana R. Shahi , Abhijit G. Kale ,Mahesh Tube .Formulation and Characterization of Novel Solid Dispersions of Hydrochlorothiazide by Hot Melt Extrusion Technique.Journal of Biomedical and Pharmaceutical Research.**2012;**1 (2): 38-*45*.

[12] Andrews GP,AbuDiak OA,Jones DS, Physico-chemical characterization of hot melt extruded bicalutamide-polyvinylpyrrolidone solid dispersions. Pharm Sci**., 2010**; 99(3):1322-35.

[13] Noorullah Naqvi Mohammed, Soumyajit Majumdar, AbhilashaSingh , Weibin Deng , Narasimha S. Murthy,Elanor Pinto, Divya Tewari, Thomas Durig ,Michael A. Repka KlucelEF and ELF polymers for immediate-release oral dosage forms prepared by melt extrusion technology. AAPS Pharm.Sci Tech., **2012**, 13(4):1158-1169.

[14] Alazar N. Ghebremeskel , Chandra Vemavarapu , MayurLodaya . Use of surfactantsas plasticizers in preparing solid dispersions of poorly soluble API: stability testingof selected solid dispersions. Pharm. Research, **2006**; 23(8):1928-1936.

[15] Raja rajeswari K, Abbulu K, Sudhakar M Development, characterization and solubility study of solid dispersion of Valsartan. J. Chem. Pharm. Res**., 2011**, 3(1):180-187.

[16] Mohammed Maniruzzamana, Joshua S. Boateng a, Marion Bonnefille b, Attila Aranyos b, John C. Mitchell a, Dennis Douroumis. Taste masking of paracetamol by hot-melt extrusion: An in vitro and in vivo evaluation. European Journal of Pharmaceutics and Biopharmaceutics **(2011).**

[17] Jae Soon Ahn, Kang Min Kim, Chan Young Ko and Jae Seon Kang Absorption Enhancer and Polymer (Vitamin E TPGS and PVP K29) by Solid Dispersion Improve Dissolution and Bioavailability of Eprosartan Mesylate. Bull. Korean Chem. Soc., **2011**; 32(5): 1587-1592.

[18] Kulthe V.V and Chaudhari P.D Solubility Enhancement of Etoricoxib by Solid Dispersions Prepared by Spray Drying Technique. Ind J Pharm Edu Res., **2011**; 45(3):248-258.

[19] Shady A. Swidan, Hassan M. Ghonaim, Mamdouh M. Ghorab and Ahmed M. Samy.Formulation and Evaluation of Piroxicam Capsules Prepared by Solid Dispersion Technique. British Journal of Pharmaceutical Research.**2013**; 3(1): 108-134.

[20] R. B. Desi Reddy, P. Sivanarayana, T. Madhu Mounica, N. Prathibha, G. Sandhya and P. Alekhya. Solid dispersion–an approach to enhance the dissolution rate of amlodipine. Int J Pharm., **2013**; 3(1): 170-172.

[21] Badry M, G. Fetihb and M. Fathy. Improvement of solubility and dissolution rate of indomethacin by solid dispersions in Gelucire 50/13 andPEG4000. Saudi Pharmaceutical Journal.**2009**; 17(3): 217-225.

[22] Janssens S,H N de Armmas and J P Remon. The use of a new hydrophilic polymer, Kollicoat IR, in the formulation of solid dispersion of Itrconazole. European. J. Pharmaceutical Sci., **2007**; 30(3-4): 288-94.