Contents lists available at UGC-CARE

International Journal of Pharmaceutical Sciences and Drug Research

[ISSN: 0975-248X; CODEN (USA): IJPSPP]

Available online at www.ijpsdronline.com

Research Article

Fluidized Hot Melt Granulation Technique: An Approach to Improve Micromeritics Properties and Dissolution Rate of Efavirenz

Deval J. Modi*, Pragna K. Shelat, Divyesh H. Shastri

Department of Pharmaceutical Sciences, K. B. Institute of Pharmaceutical Education and Research, Kadi Sarva Vishwavidyalaya, Sector-23, GH-6 Circle, Gandhinagar-382023, Gujarat, India

ARTICLE INFO

Article history:

Received: 29 June, 2020

Revised: 22 August, 2020

Accepted: 30 August, 2020

Published: 30 September, 2020

Keywords:

Efavirenz,
Fluidized bed granulation,
Fluidized hot melt granulation,
Meltable binder,
Top spray.

DOI:

10.25004/IJPSDR.2020.120518

ABSTRACT

The fluidized hot melt granulation technique is a process by which pharmaceutical powders are efficiently agglomerated using a low melting binder. The effect of the binder properties and concentrations on agglomerate growth mechanisms were studied in this research paper, using this technique with the primary objective of improvement in the solubility and dissolution rate of efavirenz by melt-dispersion granulation employing meltable hydrophilic carrier, and then to convert the melt dispersion into flowable and compressible dispersion granules to yield a rapidly dissolving tablet formulation. The optimized concentrations of co-polymers, like polyethylene glycol (PEG) 6000, PEG 4000, gelucire 50/13, gelucire 44/14, poloxamer 188, and poloxamer 407 in different ratios (i.e., 1:1, 1:2, 1:3, and 1:4) as meltable binder along with the drug were sprayed dropwise over lactose as diluent loaded into fluid bed chamber for the preparation of the granules of efavirenz and characterized for its micromeritical properties, differential scanning calorimetry (DSC), X-ray diffraction (XRD), etc. The tablets prepared from the granules were evaluated for drug dissolution rate. The prepared granules were found to have excellent flow properties indicated by mean diameter D50:138 µm, Carr's index 13.92%, and the drug content uniformity of 98.10%. XRD data exhibited a partial loss of crystallinity as indicated by significantly less intensity of efavirenz peak in the sample than pure efavirenz. Drug release from the tablet was fast found 99.12 %w/v within 30 minutes. The absence of efavirenz endothermic peak at higher proportions of meltable binder reported by DSC data exhibited an amorphous form of efavirenz that led to complete solubilization, and thus, the faster dissolution rate of efavirenz.

Introduction

In the last two decades, there has been an increasing interest in the solubility enhancement of active pharmaceutical ingredients, particularly on those belonging to class II of the Biopharmaceutics Classification System (BCS). Hence, the enhancement of the aqueous solubility in such a case shall lead to increased therapeutic efficacy and bioavailability.[6] Numerous techniques and methods have been reported on how the solubility of efavirenz (EFZ) can be enhanced. Enhancement of the dissolution rate is attaining a suitable blood concentration for therapeutic effect, their dissolution rates are typically the rate-limiting step for bioavailability. Efavirenz is established in anti-HIV with poor water solubility.

Fluidized hot melt granulation (FHMG) has received considerable attention in recent years with most of these processes involving the spraying of the molten binder onto a bed of fluidized particles. In this method, the granule growth mechanism is dependent on the ratio of binder droplet size to powder particle size. Using a lower ratio led to nucleation, which then gave rise to coalescence and further granule growth (Schaefer's group). The increased granule size was influenced by the viscosity of the binder melt and by utilizing the binder properties

***Corresponding Author:** Deval J. Modi

Address: K. B. Institute of Pharmaceutical Education and Research, Kadi Sarva Vishwavidyalaya, Sector-23, GH-6 Circle, Gandhinagar-382023, Gujarat, India

Email ✉**:** modideval80@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

improved the physical properties of tablets pressed from the hot melted granules.[9]

The main objective of the present research work was to improve the solubility and dissolution rate of efavirenz by melt-dispersion granulation employing meltable hydrophilic carrier and then to convert the melt dispersion into flowable and compressible dispersion granules to yield a rapidly dissolving tablet formulation.

Materials and Methods

Materials

Efavirenz was procured from Piramal Pharma Solution, India. Lactose monohydrate (Flowlac 100) was purchased from Meggle and extra-granular avicel PH 102 was purchased from FMC, polyplasdone XL 10 was purchased from Ashland and magnesium stearate was purchased from Ferro Synpro. The materials used were Gelucire® 50/13 or 44/14 (Gattefosse Ltd., France), PEG 6000 or 4000 (Synth Ltda., Brazil), poloxamer 407 or 188 (Synth Ltda., Brazil).

Method

Solubility Study in Different Binders

Phase solubility studies, in which excess amount of efavirenz was added to conical flasks containing different meltable binders and stirred in a water bath for one hour using a magnetic stirrer (model: 1MLH, company: Remi, country: India). Then, the content of each flask was filtered through a 0.45 µm membrane and the filtrate was suitably diluted and analyzed at 247 nm by ultraviolet (UV) spectrophotometer.

Screening of Drug to Binder Ratio

For fluid bed processing (FBP) (Glatt®-GPCP); mixtures of meltable binders in different ratios shown in Table 1, along with efavirenz were prepared and kept in a jacketed vessel to obtain the desired temperature of near melting point with continuous heating and stirring. The molten mixture was sprayed dropwise from the top over the 40# sifted lactose monohydrate (Flowlac 100) powder loaded in a fluidized bed chamber to prepare granules. The formed granules were then rapidly cooled down to room temperature by fluidization and collected for subsequent micromeritical characterizations.

Table 1: Drug:binder ratio

S. No.	*Drug*	*Binder*	*Drug:binder ratio*
1	Efavirenz	Gelucire 50/13	1:1, 1:2, 1:3, 1:4
2	Efavirenz	Gelucire 44/14	1:1, 1:2, 1:3, 1:4
3	Efavirenz	PEG 6000	1:1, 1:2, 1:3, 1:4
4	Efavirenz	PEG 4000	1:1, 1:2, 1:3, 1:4
5	Efavirenz	Poloxamer 407	1:1, 1:2, 1:3, 1:4
6	Efavirenz	Poloxamer 188	1:1, 1:2, 1:3

Preparation of Tablets

Dried granules were sifted through 30# screen using a mechanical sifter and mixed with avicel PH102 (40#), polyplasdone XL100 (40#) in a double cone blender for 5 minutes at 10 ± 2 rpm, and lubricated with magnesium stearate (60#). The lubricated granules were compressed using a tablet compression machine (RIMEK®) and evaluated for drug release and dissolution profile.

Selection of appropriate Process Parameters of Fluid Bed Processing (FBP)

The effect of critical process parameters (CPPs) on product quality (e.g., average granule size) was analyzed and control manufacturing through timely measurements of critical quality and performance attributes of in-process materials, which were modeled out with the goal of ensuring product quality as revealed, is shown in Table 2.

Characterization

Micromeritical Properties

Various micromeritical properties of granules were evaluated, i.e., bulk density (BD), tapped density (TD), compressibility index (% CI), and Hausner's ratio.

Size Analysis and Drug Content Uniformity

The granule size distribution study carried out using a particle size analyzer (model: Mastersizer 3000 and make: Malvern) in the range of 65 to 1,200 µm. 10 milligrams of melt granules were added to 10 mL of distilled water, heated to 60 to 70°C, and allowed to cool at room temperature. The lipid was solidified, and the drug solution was filtered through Whatman filter paper no. 1. The samples were analyzed for drug content by UV spectrophotometer (model: UV 1800 and make: Shimadzu) at 247 nm after suitable dilution.

DSC Analysis

DSC scans of the powdered samples were recorded using DSC (822e, Mettler Toledo) with the STARe software. All the samples were weighed (4–5 mg) and heated for a total time of 40 minutes at a scanning rate of 5°C/minutes under dry air (N_2) flow (50 mL/min) at a pressure of 25 psi between 50 and 250°C (furnace temperature). Aluminum pans and lids (40 µL capacity) were used in this study.

X-Ray Diffraction (XRD) Study

The XRD patterns were recorded on an X-diffractometer

Table 2: FBP limit parameter

No.	*FBP parameter*	*Limit*
1	Inlet temperature	50 ± 10°C
2	Outlet temperature	40 ± 10°C
3	Product temperature	30 ± 10°C
4	Spraying rate	3 gm/mL
5	Atomization air pressure	2.5 bar

(Phillip PW 1130/00 diffractometer, Netherlands), employing CuK_{∞} radiation source operating at 30 mA and 40 kV. Samples were scanned from 6 to 40° 2θ at a scanning rate of 0.02° 2θ S^{-1}.

Fourier Transform Infraradiation (FTIR) Study

The FTIR spectra of the prepared formulation were recorded on Shimadzu FTIR (8400 spectrophotometer). The potassium bromide pellet method was employed, and the background spectrum was collected under an identical situation. Each spectrum was derived from single average scans collected in the region 400 to 4,000 cm^{-1}. Spectra were analyzed by software supplied by Shimadzu.

In vitro Dissolution Study

In vitro dissolution study of efavirenz was performed on United States Pharmacopoeia (USP) type-II dissolution test apparatus in 900 mL of 2 %w/v sodium lauryl sulfate (SLS) solution with constant temperature 37 ± 0.2°C and speed 50 ± 2 rpm. Aliquots were withdrawn at 10, 20, and 30 minutes time intervals and analyzed by UV-visible spectrophotometric, and the percentage release of the drug was recorded.

Physical Parameters of Tablet

The hardness and thickness of tablets were determined using a tablet hardness tester (TBH 300 MP Erweka, Germany). The friability of tablets was determined in Roche friabilator tester on 20 tablets, in the apparatus running for 4 minutes at a speed of 25 rpm. Disintegration time was determined in the water at 37°C by means of disintegration test apparatus with disks (ZT 74, Erweka, Germany). The time recorded was the time required for the last tablet (out of six) to disintegrate.

Stability Study

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors, such as, temperature, humidity, and enables recommended storage condition, re-test periods, and shelf life to be established. Stability studies were carried out for optimized formulations. A formulation was stored at accelerated stability condition 40 ± 2°C/ 75 ± 5% RH and 25 ± 2°C/ 60 ± 5% RH for an interval of 1, 3, and 6 months. Samples were withdrawn and tested with regards to the parameters, i.e., drug content and *in vitro* drug release.

Table 3: Solubility study in different binders

Binders	*Solubility (mg)*
PEG 6000	28.19 ± 0.12
PEG 4000	17.12 ± 0.26
Gelucire 50/13	25.49 ± 0.1
Gelucire 44/14	14.56 ± 0.31
Poloxamer 407	30.39 ± 0.15
Poloxamer 188	34.19 ± 0.28

Results and Discussion

Solubility Study in Different Binders

The saturated solubility of efavirenz was determined by UV spectrophotometry at 247 nm and yielded a value of efavirenz found to be more soluble in poloxamer 188, as shown in Table 3.

Screening of Binder Concentration

Micromeritical Characterization

All tested formulations had a Carr's index ranging from 13.92 ± 0.17% to 25.7 ± 0.58% and the granules obtained from batch F23 showed good micromeritical properties, i.e., Carr's index 13.92 ± 0.17, Hausner's ratio 1.16 ± 0.02, bulk density 0.439 ± 0.05, and tapped density 0.51 ± 0.04. Results of the characterization of the granules are shown in Table 4. The granulation using poloxamer 407 as a binder was not possible for two of the experimental conditions chosen for the experimental design. This was due to the high viscosity of poloxamer (POL) in the molten state.

Granules Size Analysis and Drug Content Uniformity Studies

The amount of fine powder (< 70 µm) and big lumps (size > 1,200 µm) are less than 2 and 6%, respectively, which confirmed that the parameters selected were correct. The majority of the fraction of the granules was between the size range of 150 to 400 µm and more than 50% of the granules had a size in the range of 120 to 249 µm. The drug content in the prepared melt granules of batches F1 to F19 was determined and found to have 98.1 ± 1.63 %w/v, showed no or less wastage or deterioration of the drug in the melt granules formulation. The results are shown in Table 5.

DSC Analysis

The DSC curves are shown in Fig. 1. Efavirenz shows a sharp melting peak of 137.27°C. DSC curve of dispersion at higher proportions of poloxamer 188 exhibited no drug endothermic peak. The absence of efavirenz melting endothermic in these samples due to the solubility of the drug in poloxamer 188.

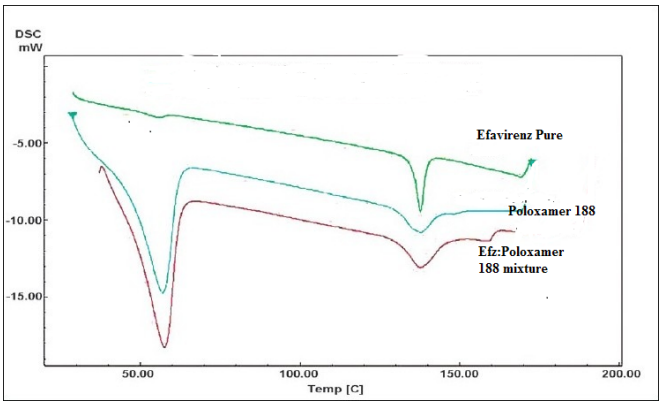

Fig. 1: DSC thermogram of A) pure drug, B) poloxamer 188, and C) physical mixture blend

Table 4: Screening of different binder ratio

Meltable binder	*Batch code*	*Drug:binder ratio*	*Bulk density (g/mL)*	*Tapped density (g/mL)*	*Hausner's ratio*	*Carr's index (%)*
PEG 6000	F1	1:1	0.352 ± 0.05	0.453 ± 0.05	1.28 ± 0.04	22.29 ± 1.68
	F2	1:2	0.41 ± 0.04	0.503 ± 0.03	1.22 ± 0.09	18.48 ± 0.58
	F3	1:3	0.411 ± 0.04	0.595 ± 0.03	1.2 ± 0.05	16.96 ± 0.64
	F4	1:4	0.406 ± 0.04	0.478 ± 0.03	1.17 ± 0.06	15.06 ± 0.29
PEG 4000	F5	1:1	0.419 ± 0.05	0.564 ± 0.01	1.34 ± 0.08	25.7 ± 0.58
	F6	1:2	0.412 ± 0.01	0.533 ± 0.02	1.29 ± 0.1	22.71 ± 0.89
	F7	1:3	0.398 ± 0.02	0.487 ± 0.03	1.22 ± 0.09	18.27 ± 0.84
	F8	1:4	0.403 ± 0.04	0.479 ± 0.05	1.18 ± 0.04	15.86 ± 0.18
Gelucire 50/13	F9	1:1	0.42 ± 0.04	0.506 ± 0.02	1.20 ± 0.03	16.99 ± 1.01
	F10	1:2	0.49 ± 0.04	0.575 ± 0.04	1.17 ± 0.01	14.78 ± 1.88
	F11	1:3	0.557 ± 0.02	0.653 ± 0.01	1.17 ± 0.05	14.7 ± 0.18
	F12	1:4	0.501 ± 0.3	0.586 ± 0.02	1.17 ± 0.06	14.5 ± 0.31
Gelucire 44/14	F13	1:1	0.514 ± 0.04	0.684 ± 0.02	1.33 ± 0.01	24.85 ± 0.98
	F14	1:2	0.482 ± 0.02	0.619 ± 0.03	1.28 ± 0.08	22.13 ± 1.2
	F15	1:3	0.516 ± 0.03	0.654 ± 0.02	1.26 ± 0.09	21.1 ± 0.18
	F16	1:4	0.504 ± 0.05	0.623 ± 0.04	1.23 ± 0.08	19.1 ± 1.18
Poloxamer 407	F17	1:1	Due to high viscosity of molten mixture, does not spray; experiment failed			
	F18	1:2				
	F19	1:3				
	F20	1:4				
Poloxamer 188	F21	1:1	0.552 ± 0.02	0.652 ± 0.03	1.18 ± 0.01	15.33 ± 0.13
	F22	1:2	0.46 ± 0.03	0.55 ± 0.04	1.19 ± 0.02	16.36 ± 1.04
	F23	1:3	0.439 ± 0.05	0.51 ± 0.04	1.16 ± 0.02	13.92 ± 0.17

Table 5: Granules size analysis and % drug content

Meltable binder	*Batch code*	*Drug:binder ratio*	*Granules size distribution D50 (µm)*	*% drug content*
PEG 6000	F1	1:1	212	96.37 ± 0.98
	F2	1:2	189	97.31 ± 1.87
	F3	1:3	158	98.5 ± 0.42
	F4	1:4	152	97.73 ± 2.1
PEG 4000	F5	1:1	249	95.31 ± 2.15
	F6	1:2	214	98.45 ± 1.48
	F7	1:3	194	97.23 ± 2.36
	F8	1:4	171	98.73 ± 1.45
Gelucire 50/13	F9	1:1	201	97.31 ± 2.48
	F10	1:2	184	98.5 ± 1.64
	F11	1:3	178	98.5 ± 2.33
	F12	1:4	154	95.73 ± 1.98
Gelucire 44/14	F13	1:1	195	96.85 ± 0.41
	F14	1:2	187	97.09 ± 1.33
	F15	1:3	185	97.31 ± 1.98
	F16	1:4	170	96.26 ± 2.1
Poloxamer 188	F17	1:1	120	96.09 ± 1.57
	F18	1:2	149	97.31 ± 1.49
	F19	1:3	138	98.1 ± 1.63

X-Ray Diffraction Analysis

The intensity of the peak efavirenz in the physical mixture (PM) dispersion sample (Fig. 2) was significantly less than of the pure drug due to partial loss of crystallinity. This suggested that the drug in PM dispersion is amorphous as compared to the pure drug. Increase dissolution of the drug was observed an amorphous form dissolve at a faster rate than crystalline materials.

FTIR Studies

All major peaks of EFZ and poloxamer 188 were observed in Fig. 3 and were retained in drug:POL 188 (1:3) meltable mixture, which clearly indicated that no interaction occurred between pure drug and poloxamer 188.

In vitro Dissolution Studies

The dissolution profile of all formulations are shown in Table 6 and Fig. 4. Fig. 4 indicated that the melt granules formulation 1:3 of efavirenz:poloxamer 188 gives a fast dissolution rate of 99.12 ± 1.63% in 30 minutes, as compared to other meltable binders. The melt granulation technique has improved the dissolution rate of efavirenz to a greater extent.

Physical Parameters of Tablet

Tablets obtained from granules prepared by the FHMG technique have shown faster disintegration time, as shown in Table 7. Faster disintegration corresponded to the lower hardness of the tablet. Disintegration time (DT) of formulation batch F19 containing drug:poloxamer 188 ratio of 1:3 have shown less than 4 minutes.

The hardness of the tablets was in the range of 8 to 14 kg/cm^2. This reveals that the required compressibility was imparted by avicel PH102. Poloxamer 188 is a waxy material and tends to stick to the punches during compression. This problem was resolved by incorporating magnesium stearate. Despite the corresponding lower hardness, these tablets were more resistant to mechanical stress as demonstrated in the friability test. Friability values were in the range of 0.12 to 0.28%, which ensured no loss of materials from the surface or edge of tablets. This may be attributed to the waxy nature of poloxamer 188. All the formulations passed the weight variation test, which was an indication of good flowability.

Stability Studies

The optimized formulation batch F19 was evaluated for stability studies as per International Council for

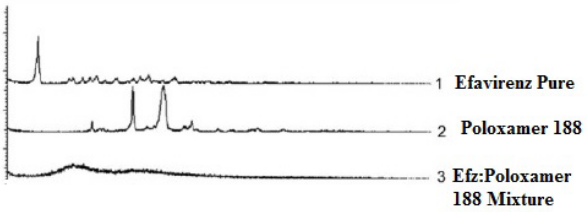

Fig. 2: X-ray diffraction spectra of efavirenz pure (1), poloxamer 188 (2), and 1:3 ratio dispersion (3)

Table 6: % drug release of formulation

			Dissolution (%) in minutes		
Meltable binder	*Batch code*	*Drug:binder ratio*	*10*	*20*	*30*
PEG 6000	F1	1:1	10.15 ± 1.25	21.59 ± 1.19	32.15 ± 1.47
	F2	1:2	22.15 ± 1.72	36.52 ± 1.87	49.1 ± 1.17
	F3	1:3	30.18 ± 1.08	41.26 ± 2.09	52.16 ± 0.18
	F4	1:4	36.58 ± 1.29	58.12 ± 1.44	71.59 ± 2.12
PEG 4000	F5	1:1	10.21 ± 2.41	20.78 ± 1.4	23.13 ± 1.5
	F6	1:2	14.78 ± 1.45	29.84 ± 1.51	35.85 ± 2.13
	F7	1:3	16.87 ± 1.79	33.52 ± 1.25	51.19 ± 2.45
	F8	1:4	23.69 ± 1.49	46.98 ± 1.11	70.79 ± 1.84
Gelucire 50/13	F9	1:1	21.58 ± 1.14	36.98 ± 1.41	57.1 ± 1.78
	F10	1:2	28.56 ± 1.52	41.25 ± 1.94	62.58 ± 2.03
	F11	1:3	31.29 ± 1.04	49.82 ± 1.74	69.48 ± 2.51
	F12	1:4	39.62 ± 1.56	59.84 ± 1.58	84.15 ± 2.14
Gelucire 44/14	F13	1:1	17.51 ± 2.1	25.31 ± 1.45	35.89 ± 1.23
	F14	1:2	19.2 ± 2.13	35.18 ± 1.56	49.04 ± 1.44
	F15	1:3	23.51 ± 1.87	46.62 ± 1.48	68.25 ± 2.15
	F16	1:4	27.19 ± 1.48	51.89 ± 1.94	74.85 ± 1.64
Poloxamer 188	F17	1:1	39.65 ± 1.36	51.12 ± 1.32	59.23 ± 1.54
	F18	1:2	52.18 ± 1.68	65.25 ± 1.92	74.69 ± 2.86
	F19	1:3	59.23 ± 1.97	74.69 ± 1.91	99.12 ± 1.63

Table 7: Physical parameter of tablet

Meltable binder	*Batch code*	*Drug:binder ratio*	*Hardness (kg/cm^2)*	*Weight (mg)*	*Friability (%)*	*Disintegration time (minute)*
PEG 6000	F1	1:1	11 ± 1.2	512 ± 0.9	0.181	7.1
	F2	1:2	10 ± 1.6	514 ± 1.1	0.185	6.9
	F3	1:3	10 ± 1.8	511 ± 0.4	0.211	6.4
	F4	1:4	9 ± 1.1	512 ± 0.6	0.139	6.6
PEG 4000	F5	1:1	14 ± 1.3	514 ± 1.2	0.218	9.8
	F6	1:2	13 ± 1	516 ± 1	0.211	8.1
	F7	1:3	11 ± 1.4	513 ± 0.8	0.214	8.6
	F8	1:4	10 ± 1	514 ± 0.1	0.218	6.2
Gelucire 50/13	F9	1:1	10 ± 1.1	510 ± 0.6	0.135	5.3
	F10	1:2	9 ± 1.3	512 ± 0.8	0.132	5
	F11	1:3	9 ± 1.2	514 ± 1.2	0.119	4.9
	F12	1:4	8 ± 1.7	516 ± 1	0.127	4.5
Gelucire 44/14	F13	1:1	11 ± 1.3	513 ± 0.6	0.214	5.3
	F14	1:2	9 ± 1	515 ± 0.9	0.225	6.1
	F15	1:3	9 ± 1.7	513 ± 0.5	0.286	5.9
	F16	1:4	9 ± 1.9	513 ± 0.9	0.245	7.2
Poloxamer 188	F17	1:1	9 ± 1.1	515 ± 0.9	0.131	4.5
	F18	1:2	8 ± 1.6	517 ± 1.1	0.128	4.3
	F19	1:3	8 ± 1.2	514 ± 0.5	0.125	4

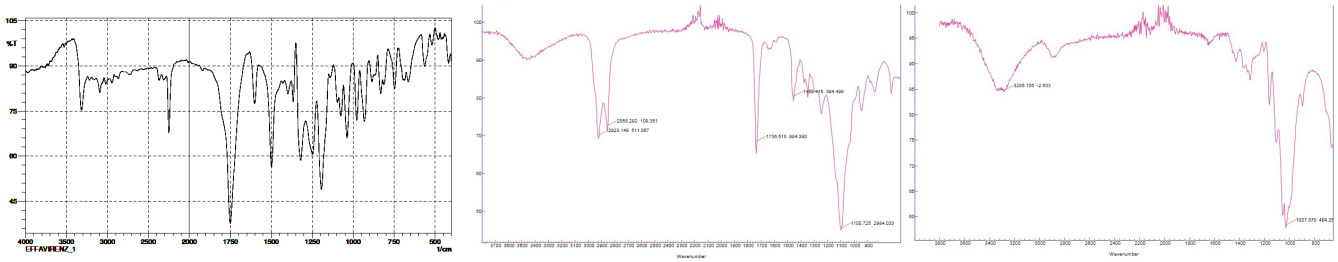

Fig. 3: FTIR of pure drug efavirenz (A), poloxamer 188 (B), and drug:poloxamer 188 (1:3) meltable mixture (C)

Harmonisation (ICH) guidelines at 40 ± 2°C/ 75 ± 5% RH and 25 ± 2°C/ 60 ± 5% RH conditions and monitored for drug content and *in vitro* drug release study at 1, 3, and 6 months. Table 8 indicated the results of the stability studies revealed no significant variation in drug content uniformity and *in vitro* drug release profile up to 6 months.

Comparative In vitro Drug Release Profile Study

The optimized formulation batch F19 prepared through the FHMG technique, using poloxamer 188 in the drug:binder ratio of 1:3 evaluated for *in vitro* drug release profile study and compared with the generic marketed formulation of a tablet containing 50 mg efavirenz, using 900 mL of 2% SLS solution for 30 minutes. The drug release rate of efavirenz from optimized formulation batch F19 was 99.12 % w/v, as compared with 88.46 % w/v efavirenz release from marketed 50 mg tablet at the end of 30 minutes, as shown in Fig. 5, which clearly indicated that the optimized formulation could be used to improve the therapeutic effect of efavirenz.

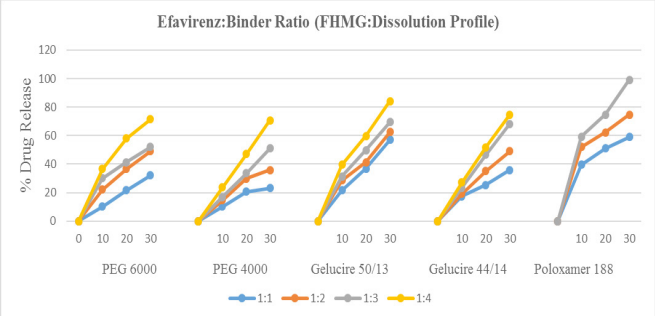

Fig. 4: Dissolution profile of drug:binder ratio

Discussion

The granules obtained in all experimental conditions have shown adequate flow properties. The granule size (D50) showed moderate size enlargement indicating binder coating predominated over agglomeration. Dispersions granules of efavirenz prepared with different ratios of melted binders, i.e., gelucire 50/13 or 44/14, PEG6000 or 4000, and poloxamer PF188 or

Table 8: Stability studies

	Optimized formulation: F19							
Parameters	*40 ± 2ºC/ 75 ± 5% RH*				*25 ± 2ºC/ 60 ± 5% RH*			
Duration	*Initial*	*1 M*	*3 M*	*6 M*	*Initial*	*1 M*	*3 M*	*6 M*
Assay	98.01 ± 1.53	97.15 ± 1.48	98.11 ± 1.15	98.09 ± 1.05	98.01 ± 1.53	98.22 ± 1.08	97.46 ± 1.6	97.33 ± 1.12
Dissolution	*% drug release*							
10 minutes	59.23 ± 1.97	58.12 ± 1.71	57.36 ± 1.15	58.16 ± 1.03	59.23 ± 1.97	55.11 ± 1.78	56.76 ± 1.46	55.33 ± 1.05
20 minutes	74.69 ± 1.91	75.34 ± 1.04	73.01 ± 1.84	74.66 ± 1.14	74.69 ± 1.91	75.17 ± 1.41	74.02 ± 1.3	75.19 ± 1.01
30 minutes	99.12 ± 1.63	98.19 ± 1.16	97.31 ± 2.1	98.56 ± 1.21	99.12 ± 1.63	97.99 ± 1.78	98.08 ± 1.4	98.14 ± 1.16

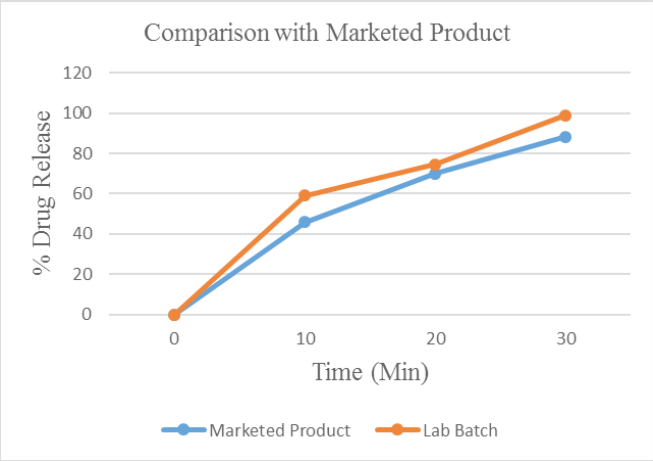

Fig. 5: Comparative *in vitro* drug dissolution study lab batch (orange line) and marketed sample (blue line)

PF407, by melting method shown to have good flow properties, increased saturation solubility of the drug, and *in vitro* dissolution rates and based on micromeritical properties and drug release profile studies. Formulation batch F19 containing drug:poloxamer 188 in the ratio of 1:3 was selected for preparation of the tablet formulation and further studies. After characterization of dispersion granules by DSC, XRD, and FTIR study, a decreased crystallinity, as well as, the surface morphology of the polymeric particles explained the enhanced solubility and improved dissolution rate of efavirenz. Thus, the dispersion granules can be utilized successfully to enhance the water solubility of poorly water-soluble drugs.

Conclusion

The granulation process in a fluidized bed using the FHMG technique proved to be an excellent option for pharmaceutical granulation for the solubility improvement and dissolution enhancement of poorly soluble drugs.

Acknowledgement

The authors are highly thankful to the K. B. Institute of Pharmaceutical Education and Research, KSV, for providing facilities and guidance for the research.

References

1. Sruti J, Patra CN, Swain S, Panigrahi KC, Patro AP, Beg S, *et al*. Improvement in the dissolution rate and tableting properties of cefuroxime Axetil by melt-granulated dispersion and surface adsorption. Acta Pharma Sinica B. 2013;3(2):113-122.
2. Kalra K, Sharma S, Jain DA. Enhancement of solubility and dissolution rate of rifapentine by melt granulation technique. Int. J Pharm Life Sci. 2012;3(3):1503-1506.
3. Shimpi S, Chauhan B, Mahadik KR, Paradkar A. Preparation and evaluation of diltiazem hydrochloride-Gelucire 43/01 floating granules prepared by melt granulation. AAPS Pharm Sci Tech. 2004 Jul 12;5(3):e43.
4. Tayel SA, Soliman II, Louis D. Formulation of ketotifen fumarate fast-melt granulation sublingual tablet. AAPS PharmSciTech. 2010 Jun;11(2):679-685.
5. Kraciuk R, Sznitowska M. Effect of different excipients on the physical characteristics of granules and tablets with carbamazepine prepared with polyethylene glycol 6000 by fluidized hot-melt granulation (FHMG). AAPS PharmSciTech. 2011 Dec;12(4):1241-1247.
6. Mukharya A. Development and scale-up of SD-FBP formulation technology in line with parametric QbD. Res J Pharm Sci 2012; 1(1):1-21.
7. Patel K, Prasad RK, Bajpai M. Enhancement of dissolution rate of domperidone using melt granulation technique. Scholar Res Lib. 2011;3(2):25-33.
8. Tandel H, Shah D, Vanza J, Jani P. Formulation development and *in vitro/ex vivo* assessment of mucoadhesive microemulsion for nasal delivery of centrally acting drug modafinil. Ind. Journal Novel Drug Delivery. 2016;8(2):72-92.
9. Mothilal M, Harish Kumar A, V Manasa, V Manimaran. Formulation and evaluation of modafinil fast dissolving tablets by sublimation technique. J Chem Pharm Sci. 2013;6(3):147-154.
10. Avachat AM, Parpani SS. formulation and development of bicontinuous nanostructured liquid crystalline particles of efavirenz. Colloids surf Bio interfaces. 2015;126:87-97.
11. Gaur PK, Mishra S, Bajpai M, Mishra A. Enhanced oral bioavailability of efavirenz by solid lipid nanoparticles: *in vitro* drug release and pharmacokinetics studies. Biomed Res Int. 2014;2014:363404.
12. Kotta S, Khan AW, Ansari SH, Sharma RK, Ali J. Anti HIV nanoemulsion formulation: optimization and *in vitro-in vivo* evaluation. Int J Pharm. 2014 Feb 28;462(1-2):129-134.
13. Patel GV, Patel VB, Pathak A, Rajput SJ. Nanosuspension of efavirenz for improved oral bioavailability: formulation optimization, *in vitro*, *in situ,* and *in vivo* evaluation. Drug Dev Ind Pharm. 2014 Jan;40(1):80-91.
14. Singh A, Majumdar S, Deng W, Mohammed NN, Chittiboyina AG, Raman V, *et al*. Development and characterization of taste masked efavirenz pellets utilizing hot melt extrusion. J Drug Deliv Sci Technol. 2013;23(2):157–163.
15. Koh PT, Chuah JN, Talekar M, Gorajana A, Garg S. Formulation development and dissolution rate enhancement of efavirenz by solid dispersion systems. Indian J Pharm Sci. 2013 May;75(3):291-301.

HOW TO CITE THIS ARTICLE: Modi DJ, Shelat PK, Shastri DH. Fluidized hot melt granulation technique: an approach to improve micromeritics properties and dissolution rate of efavirenz. Int. J. Pharm. Sci. Drug Res. 2020;12(5):554-560. **DOI:** 10.25004/IJPSDR.2020.120518