TO EXPLORE POTENTIAL OF FLUIDIZED HOT MELT GRANULATION TECHNIQUE TO IMPROVE MICROMERITICS PROPERTIES AND DISSOLUTION RATE OF MODAFINIL

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***ABSTRACT*:** Improvement of solubility and dissolution rate of Modafinil, the Fluidized hot melt granulation technique is a process by which pharmaceutical powders are efficiently agglomerated by the use of a low melting point binder which is added to the other components of the powder. The effect of the binder properties and concentration on agglomerate growth mechanisms studied using FHMG technique. Modafinil drug and Optimized concentrations of Low-melting point co-polymers of 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's mixture top sprayed dropwise over lactose as diluent which loaded into fluid bed chamber to prepare granules of Modafinil and evaluated for Micromeritical properties, DSC, XRD etc. The tablets prepared from the granules while other excipients added was evaluated for drug dissolution rate. The granules were found to have excellent flow properties indicated by mean diameter D50:122µm, Carr's index 13.89 ± 0.01% and 98.87 ± 1.03% drug content uniformity. XRD data exhibited partial loss of crystallinity indicated by significantly less intensity of the modafinil peak in sample than pure modafinil. Absence of modafinil endothermic peak at higher proportions of meltable binder reported by DSC data exhibited amorphous form of modafinil leads to complete solubilization and thus faster dissolution rate of modafinil. Drug release from tablet was fast found 98.52 ± 1.53% within 30 minutes. The Fluidized hot melt granulation technique is an easy and fast method to improve the dissolution rate of poorly water-soluble drug such as a modafinil, using new hydrophilic Meltable binder.

Index Terms: Fluidized Hot Melt Granulation, Fluidized bed granulation, Meltable Binder, Top Spray, Modafinil.

INTRODUCTION

Drugs of Biopharmaceutical Classification System (BCS) class IV are characterized by Low membrane permeability, slow dissolution rate (due to low aqueous solubility) [1-3]. The solubility or dissolution rate of a drug in this category is a major factor in determining the rate and amount of its absorption.

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. Modafinil is an established in CNS Stimulant with poor water solubility.

Improvement of solubility and dissolution rate of poorly water-soluble drugs, (1) Reducing particle size to increase surface area (2) Solubilization in surfactant systems (3) Formation of water soluble complexes (4) Use of prodrug and drug derivatization approaches such as strong electrolyte salt forms that usually have higher dissolution rates (5) Lyophilization utilizing skimmed milk as a carrier (6) Manipulation of the solid state of the drug substance to improve drug dissolution, i.e., by decreasing crystallinity of the drug substance through formation of solid dispersions. Solid dispersion can be defined as distribution of active ingredients in molecular, amorphous, and crystalline forms surrounded by an inert carrier. Formulation of poorly water-soluble drugs as solid dispersions improvement in their dissolution rates and is accompanied by an increase in their relative bioavailability.

The fluid bed granulation process is a combination of three steps: dry mixing, spray agglomeration and drying to desired granule size [4].

The Fluidized hot melt granulation technique is a process by which pharmaceutical powders are efficiently agglomerated by the use of a low melting point binder which is added to the other components of the powder. At molten state, the binder acts as a granulating liquid. Liquids containing melts binder and drug are sprayed into a fluidized bed system. The solids form small particles as starter cores. These are sprayed with other liquids which in turn, after form a hard coating around the starter core. On top spray method is a zone of liquid drops, and spraying is the act of breaking up a liquid into a multitude of these droplets.

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

MATERIALS AND METHODS

Materials

Modafinil was procured from Alembic Pharmaceuticals, 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), Polyethylene glycol 6000 or 4000 (Synth Ltda, Brazil), Poloxamer 407 or 188 (Synth Ltda, Brazil).

EXPERIMENTAL METHOD

1. Solubility Study in Different Binders

Phase solubility studies in that Excess amount of Modafinil was added to all different Meltable binders. Samples were maintained under magnetic stirring in water bath, after 1 hour, the content of each flask was filtered through 0.45 µm membrane and filtrate was suitably diluted and analyzed at 220 nm by UV Spectrophotometry.

2. Screening of Binder Ratio

For FBP (Glatt®-GPCP); Modafinil was added with melted binder (Different Ratio, Table 1), this mixture in Jacketed vessel to obtain the temp. of near melting point with continuous heating and stirring until a solution was obtained. To carry out Top spray fluidized bed granulation, 40# sifted Lactose Monohydrate (Flowlac 100) was loaded in fluidized bed processor. Molten mixture was sprayed dropwise over lactose which loaded into fluid bed chamber. After experiments, the granules were rapidly cooled down to room temperature by fluidization. collect for subsequent micromeritical characterization.

Table 1: Drug: Binder Ratio

Sr. No.	Drug	Binder	Drug:Binder Ratio
1	Modafinil	Gelucire 50/13	1:1, 1:2, 1:3, 1:4
2	Modafinil	Gelucire 44/14	1:1, 1:2, 1:3, 1:4
3	Modafinil	PEG 6000	1:1, 1:2, 1:3, 1:4
4	Modafinil	PEG 4000	1:1, 1:2, 1:3, 1:4
5	Modafinil	Poloxamer 407	1:1, 1:2, 1:3, 1:4
6	Modafinil	Poloxamer 188	1:1, 1:2, 1:3

3. Preparation of Tablets

Dried granules were sifted through 30# screen in mechanical sifter. Dried sifted granules were mixed in double cone blender for 5 minutes at 10±2 RPM with 40# Avicel PH 102, Polyplasdone XL 10 & lubricated with 60# pre-sifted magnesium stearate. Lubricated granules were compressed using tablet compression machine (RIMEK®) and Estimate the drug release profile.

4. Selection of appropriate process parameters of FBP

Process understanding experiments was developed for FBP. The effect of 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 in Table 2.

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

CHARACTERIZATION

1. Micromeritical characterization of Granules

The Micromeritical characterization of granules were evaluated using different parameter like bulk density (BD), tapped density (TD), Compressibility index (% CI), Hausner's ratio.

2. Determination of drug content & Granules size analysis

10 milligrams of melt granules were added to 10 ml of distilled water, heated to 60˚-70˚C and allowed to cool at room temperature. The lipid was solidified and the drug solution was filtered through whatman no. 1 paper. The sample was analyzed for drug content by UV spectrophotometer at 220 nm after suitable dilution.
The size distribution of granules was evaluated using particle size analyzer in the range of 65 – 1200 µm.

3. **Differential Scanning Calorimetry (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 total time of 40 minute at a scanning rate of 5° C/minute under dry air (N2) flow (50 ml/min) at pressure of 25 psi between 50 and 250° C (furnace temperature). Aluminium pans and lids (40µl capacity) were used for the study.

4. X-ray diffraction analysis

X-ray diffraction (XRD) patterns were recorded on an X-diffractometer (Phillip PW 1130/00 diffractometer, Natherland), 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}.

5. **Fourier Transform Infraradiation analysis**

FTIR spectra of prepared formulation was recorded on Shimadzu FTIR – 8400 spectrophotometer. Potassium bromide pellet method was employed and background spectrum was collected under identical situation. Each spectrum was derived from single average scans collected in the region 400 – 4000 cm^{-1}. Spectra was analyzed by software supplied by shimadzu.

6. In vitro dissolution study

In vitro dissolution study of Modafinil was performed on USP type II dissolution test apparatus in 900 ml of 0.1 N HCL Solution with constant temperature 37 ± 0.2°C and speed 50 rpm. Aliquots were withdrawn at 10,20 and 30 minutes predetermined time intervals, analyzed by UV-visible spectrophotometric method and percentage release of drug was recorded.

7. Physical Parameter of Tablet

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

8. Stability Studies

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 on optimized formulation. A Formulation was stored at accelerated stability condition 40ºC ± 2ºC / 75 ± 5 % RH and 25ºC ± 2ºC / 60 ± 5 % RH for interval of 1, 3 and 6 months. Samples were withdrawn and tested with regards to the parameters i.e. assay and *in-vitro* drug release.

RESULTS AND DISCUSSION

1. Solubility Study in Different Binders

The Saturated Solubility of Modafinil determined by UV Spectrophotometry at 220 nm, and yielded value at Modafinil more soluble in Poloxamer 188 shown in Table 3.

Table 3: Solubility Study in different binders

Binders	Solubility (mg)
PEG 6000	0.594 ± 0.45
PEG 4000	0.573 ± 0.59
Gelucire 50/13	1.162 ± 0.40
Gelucire 44/14	0.564 ± 0.63
Poloxamer 407	1.103 ± 0.11
Poloxamer 188	2.143 ± 0.54

2. Screening of Binder Concentration: Micromeritical Characterization

All tested formulations had a Carr's index ranging from 13.89 ± 0.01% to 25.56 ± 0.02% and optimized formulation drug with Poloxamer 188 (1:3) was showed good micromeritical properties of granules. Results of the characterization of the granules reported in Table 4. The granulation using Poloxamer 407 as binder was not possible for two of the experimental conditions chosen for the experimental design. This was due to the high viscosity of POL in the molten state.

Table 4: Screening of Different Binder Ratio

Meltable Binder	Drug:Binder Ratio	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Hausner's Ratio	Carr's index (%)
PEG 6000	1:1	0.59 ± 0.05	0.75 ± 0.02	1.27 ± 0.04	21.33 ± 0.02
	1:2	0.58 ± 0.03	0.73 ± 0.03	1.25 ± 0.01	20.54 ± 0.01
	1:3	0.56 ± 0.01	0.69 ± 0.02	1.23 ± 0.01	18.84 ± 0.04
	1:4	0.54 ± 0.01	0.66 ± 0.01	1.22 ± 0.06	18.18 ± 0.01
PEG 4000	1:1	0.67 ± 0.01	0.9 ± 0.01	1.34 ± 0.02	25.56 ± 0.02
	1:2	0.61 ± 0.03	0.79 ± 0.02	1.29 ± 0.01	22.78 ± 0.03
	1:3	0.58 ± 0.02	0.74 ± 0.03	1.27 ± 0.04	21.62 ± 0.02
	1:4	0.54 ± 0.01	0.67 ± 0.05	1.24 ± 0.03	19.40 ± 0.03
Gelucire 50/13	1:1	0.54 ± 0.04	0.65 ± 0.03	1.20 ± 0.03	16.92 ± 0.02
	1:2	0.54 ± 0.02	0.64 ± 0.02	1.19 ± 0.01	15.63 ± 0.01
	1:3	0.56 ± 0.03	0.69 ± 0.04	1.17 ± 0.03	15.15 ± 0.03
	1:4	0.58 ± 0.02	0.68 ± 0.02	1.17 ± 0.06	14.70 ± 0.31
Gelucire 44/14	1:1	0.55 ± 0.01	0.69 ± 0.01	1.25 ± 0.02	20.28 ± 0.02
	1:2	0.61 ± 0.03	0.76 ± 0.04	1.25 ± 0.04	19.74 ± 0.02
	1:3	0.50 ± 0.05	0.62 ± 0.02	1.23 ± 0.01	19.10 ± 0.01
	1:4	0.51 ± 0.01	0.63 ± 0.02	1.23 ± 0.02	19.04 ± 0.01
Poloxamer 407	1:1	Due to High Viscosity of Molten mixture, does not spray, Experiment was failed.			
	1:2				
	1:3				
	1:4				
Poloxamer 188	1:1	0.5 ± 0.02	0.6 ± 0.02	1.20 ± 0.05	16.67 ± 0.04
	1:2	0.67 ± 0.02	0.78 ± 0.01	1.16 ± 0.01	14.10 ± 0.04
	1:3	0.62 ± 0.01	0.72 ± 0.01	1.16 ± 0.01	13.89 ± 0.01

3. Drug Content & Granules size analysis

The drug content in the prepared melt granules were determined and found mean 98.87 ± 1.03% shows no or less wastage or deterioration of the drug in the melt granules formulation, results reported in table 5.
The amount of fine powder (< 70 µm) and amount of big lumps (size > 1200 µm) are less than 2% and 6% respectively. This finding confirms that the parameter was correct. The main fraction was 150 -400 µm and the more than 50% of the granules had a size in the range of 122 – 204 µm results are shown in Table 5.

Table 5: % Drug Content

Meltable Binder	Drug:Binder Ratio	Granules size Distribution D50 (µm)	% Drug Content
PEG 6000	1:1	202	97.49 ± 1.03
	1:2	198	98.61 ± 1.51
	1:3	184	98.16 ± 1.30
	1:4	178	97.06 ± 1.91
PEG 4000	1:1	204	97.91 ± 1.11
	1:2	185	98.73 ± 1.61
	1:3	176	98.80 ± 1.40
	1:4	168	98.44 ± 1.59
Gelucire 50/13	1:1	192	96.37 ± 1.66
	1:2	185	98.72 ± 1.08
	1:3	180	97.08 ± 1.33
	1:4	178	96.15 ± 1.15

Gelucire 44/14	1:1	195	98.58 ± 1.20
	1:2	188	98.90 ± 1.04
	1:3	173	96.13 ± 1.19
	1:4	169	97.62 ± 1.33
Poloxamer 188	1:1	142	97.27 ± 1.37
	1:2	134	98.48 ± 1.19
	1:3	122	98.87 ± 1.03

4. Differential Scanning Calorimetry (DSC) Analysis

DSC curves shown in Fig. 1 Modafinil shows sharp melting peak 171.5° C. DSC curve of dispersion at higher proportions of Poloxamer 188 exhibited no drug endothermic peak. The absence of Modafinil melting endothermic in these sample due to solubility of the drug in Poloxamer 188.

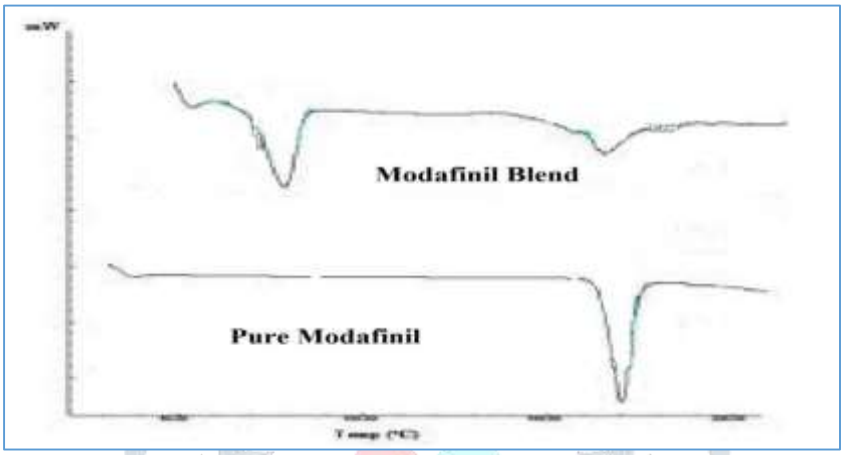

Fig. 1: DSC Thermogram of A) pure drug, B) Poloxamer 188 C) Physical mixture blend

5. X-ray diffraction analysis

The intensity of the peak Modafinil in 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 drug was observed an amorphous form dissolve at a faster rate than crystalline materials.

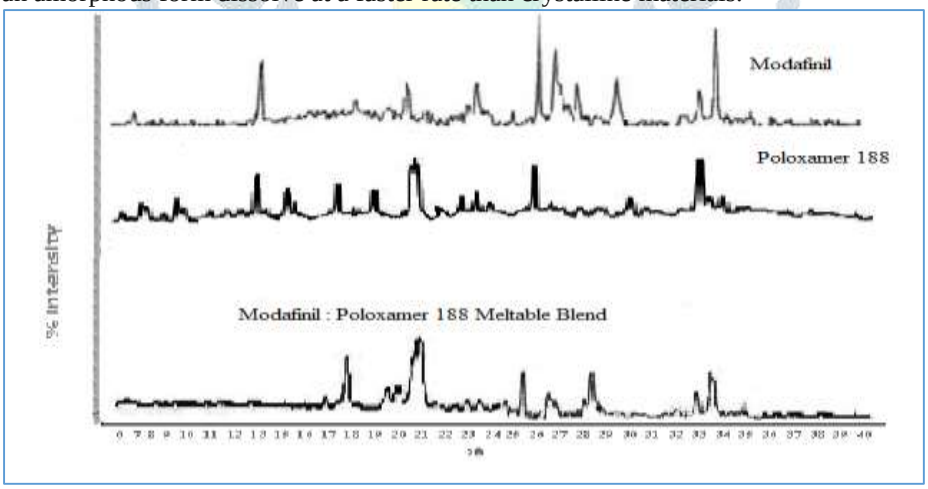

Fig. 2: X-ray diffraction spectra of Modafinil Pure (1), Poloxamer 188 (2), 1:3 Ratio Dispersion (3)

6. Fourier Transform Infraradiation (FTIR)

All Major Peaks of Modafinil and Poloxamer 188 observed (fig. 3) and were retained in Drug: Poloxamer 188 (1:3) Meltable Mixture, which clearly indicate that no interaction exits between Pure drug and Poloxamer 188.

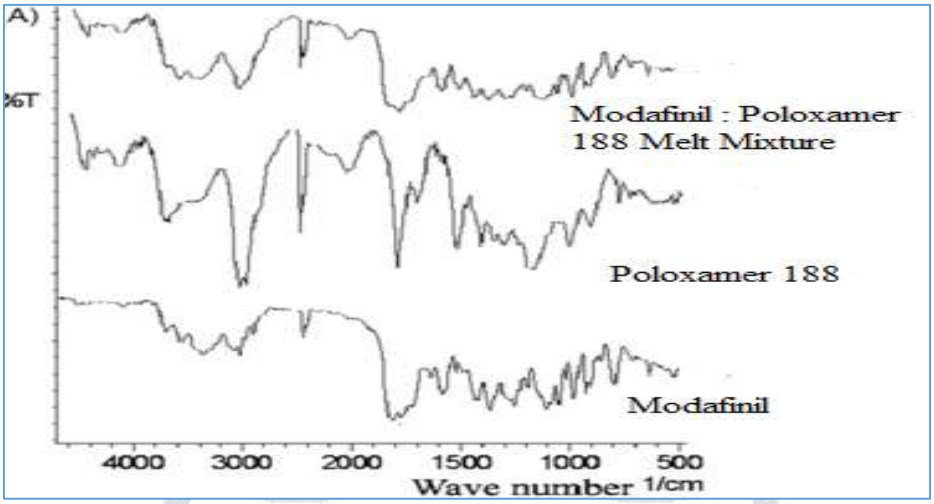

Fig. 3: FTIR of Pure Drug Modafinil (A), Poloxamer 188 (B), Drug: Poloxamer 188 (1:3) Meltable Mixture (C)

7. In vitro dissolution studies

Dissolution profile of all formulations is shown in table 6 and fig. 4. The figure indicated that the melt granules formulation 1:3 of Modafinil: Poloxamer 188 gives fast dissolution rate 98.52 ± 1.53% in 30 minutes of as compared to other Meltable binders. Melt granulation technique has improved the dissolution rate of modafinil to a greater extent.

Table 6: % Drug release of formulation

Meltable Binder	Drug:Binder Ratio	Dissolution (%) in minutes		
		10	20	30
PEG 6000	1:1	11.52 ± 1.84	23.84 ± 1.32	33.96 ± 2.10
	1:2	13.74 ± 1.35	29.35 ± 2.13	47.41 ± 2.73
	1:3	20.13 ± 2.42	35.42 ± 2.74	62.61 ± 1.89
	1:4	26.32 ± 1.41	48.98 ± 1.52	73.61 ± 1.25
PEG 4000	1:1	8.12 ± 1.29	19.87 ± 1.39	31.31 ± 1.48
	1:2	12.54 ± 1.42	27.48 ± 2.87	45.93 ± 2.87
	1:3	15.96 ± 2.98	31.25 ± 2.19	50.62 ± 1.98
	1:4	21.67 ± 1.19	45.89 ± 1.64	64.11 ± 1.42
Gelucire 50/13	1:1	11.52 ± 1.24	23.84 ± 1.51	33.96 ± 1.48
	1:2	13.74 ± 1.62	29.35 ± 1.05	47.41 ± 1.06
	1:3	20.13 ± 1.14	35.42 ± 1.84	62.61 ± 1.52
	1:4	26.32 ± 1.66	48.98 ± 1.68	93.61 ± 1.24
Gelucire 44/14	1:1	9.25 ± 1.11	20.31 ± 1.06	29.61 ± 1.59
	1:2	12.15 ± 1.64	26.91 ± 1.61	45.22 ± 1.17
	1:3	17.20 ± 1.05	31.03 ± 1.97	56.33 ± 1.63
	1:4	23.61 ± 1.54	43.20 ± 1.41	72.71 ± 1.35
Poloxamer 188	1:1	32.15 ± 1.26	43.89 ± 1.22	75.33 ± 1.44
	1:2	39.56 ± 1.58	62.14 ± 1.82	81.78 ± 1.76
	1:3	42.23 ± 1.87	69.35 ± 1.81	98.52 ± 1.53

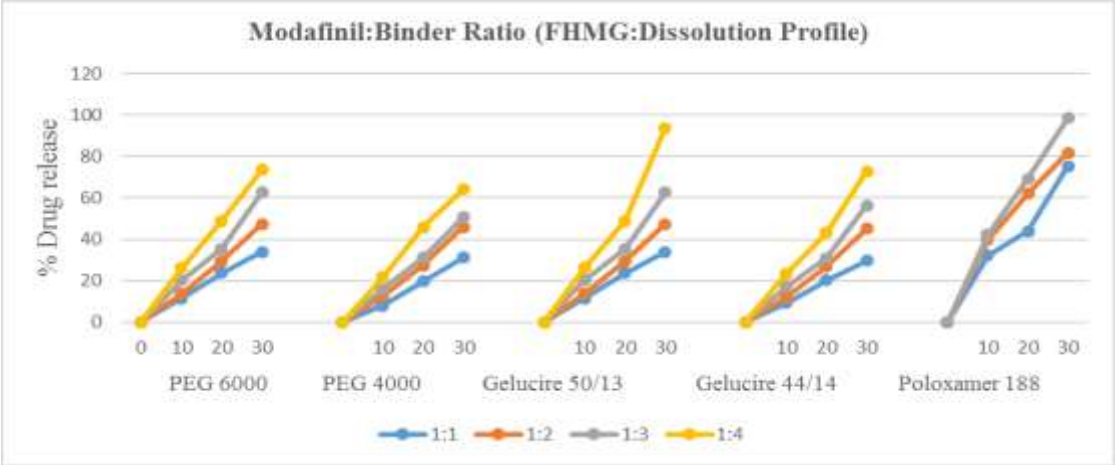

Fig. 4: Dissolution profile of Drug: Binder Ratio

8. Physical Parameter of Tablet

Tablets obtained from granules prepared by fluidized hot melt granulation have lower disintegration time. The evaluation results of the physical properties of these tablets are shown in table 7. Faster disintegration correspondence to lower hardness of tablet made from fluidized hot melt granulation granules. Drug: Poloxamer 188 (1:3) formulation showed a lower than 6 min of disintegration time.

Hardness of the tablets was in the range of 11 kg/cm^2 to 13 kg/cm^2. This reveals that the required compressibility was imparted by Avicel pH 102. Poloxamer 188 is a waxy materials and tends to stick to the punches during compression. This problem was resolved by incorporating magnesium stearate.

Inspite of the correspondence to lower hardness, these tablets were more resistant to the mechanical stress as demonstrated in the friability test. Friability value were in the range of 0.11 to 0.6%, which ensure no loss of materials from the surface or edge of tablets. This may be attributed to the waxy nature of Poloxamer 188. All the formulation passed the weight variation test which is an indication of good flowability.

Table 7: Physical Parameter of Tablet

Meltable Binder	Drug:Binder Ratio	Hardness (kg/cm^2)	Weight (mg)	Friability (%)	DT (min)	Assay (%)
PEG 6000	1:1	13 ± 0.4	699 ± 0.3	0.2	9.3	97.10 ± 0.93
	1:2	13 ± 0.8	700 ± 0.1	0.25	8.10	98.90 ± 1.81
	1:3	12 ± 0.10	708 ± 0.4	0.3	8.6	96.70 ± 0.35
	1:4	11 ± 0.3	699 ± 0.5	0.6	8.8	98.9 ± 1.15
PEG 4000	1:1	12 ± 0.5	705 ± 0.4	0.5	10.10	98.61 ± 1.14
	1:2	12 ± 0.2	702 ± 0.3	0.4	10.3	96.51 ± 1.11
	1:3	13 ± 0.6	698 ± 0.7	0.21	11.8	98.85 ± 1.64
	1:4	11 ± 0.2	700 ± 0.1	0.23	8.4	98.89 ± 1.36
Gelucire 50/13	1:1	12 ± 0.3	702 ± 0.6	0.15	7.5	98.80 ± 1.10
	1:2	12 ± 0.5	703 ± 0.3	0.17	7.3	97.61 ± 1.56
	1:3	12 ± 0.4	705 ± 0.4	0.13	6.10	98.45 ± 1.24
	1:4	11 ± 0.9	701 ± 0.6	0.15	6.7	99.06 ± 1.28
Gelucire 44/14	1:1	13 ± 0.5	698 ± 0.9	0.20	7.5	96.51 ± 1.10
	1:2	12 ± 0.10	699 ± 0.6	0.26	8.3	97.48 ± 1.24
	1:3	12 ± 0.9	705 ± 0.5	0.21	7.11	98.01 ± 1.19
	1:4	11 ± 0.10	709 ± 0.2	0.15	9.4	98.18 ± 1.4
Poloxamer 188	1:1	13 ± 0.2	704 ± 0.3	0.11	6.7	98.12 ± 1.84
	1:2	12 ± 0.8	701 ± 0.6	0.10	6.5	97.11 ± 1.44
	1:3	12 ± 0.4	706 ± 0.5	0.11	6.2	99.15 ± 1.11

9. Stability Studies

The optimized formulation drug: Poloxamer 188 (1:3) was charged on 40ºC ± 2ºC / 75 ± 5 % RH and 25ºC ± 2ºC / 60 ± 5 % RH stability condition and monitored for assay and in-vitro drug release study at 1,3 and 6 months. The obtained data were mentioned in table 8. The stability study reveals no significant variation in assay and in-vitro drug release of optimized formulation up to 6 months.

Table 8: Stability Studies

Parameters	Optimized Formulation : Modafinil : Poloxamer 188 (1:3)							
	40ºC ± 2ºC / 75 ± 5 % RH				25ºC ± 2ºC / 60 ± 5 % RH			
Duration	Initial	1M	3M	6M	Initial	1M	3M	6M
Assay	99.15 ± 1.11	98.27 ± 1.05	98.22 ± 1.29	98.11 ± 1.17	99.15 ± 1.11	98.34 ± 1.10	97.58 ± 1.91	97.45 ± 1.06
Dissolution	% Drug Release							
10 minute	42.23 ± 1.87	41.02 ± 1.18	42.55 ± 1.02	40.23 ± 1.33	42.23 ± 1.87	39.76 ± 2.10	41.02 ± 1.81	40.31 ± 1.15
20 minute	69.35 ± 1.81	65.31 ± 1.51	66.41 ± 1.05	65.76 ± 1.81	69.35 ± 1.81	65.41 ± 1.01	66.10 ± 1.54	67.12 ± 1.60
30 minute	98.52 ± 1.53	97.21 ± 1.18	98.19 ± 1.02	98.12 ± 1.61	98.52 ± 1.53	97.91 ± 1.24	98.16 ± 1.91	98.28 ± 1.08

COMPARATIVE IN VITRO DRUG DISSOLUTION STUDY PERFORMED LAB BATCH AND MARKETED FORMULATION

The percentage drug release from formulation was determined in 900 ml of 0.1 N HCL Solution for the period of 30 min. the release rate for Modafinil containing Poloxamer 188 was 98.52 ± 1.03% at the end of 30 min as seen in Fig. 5. Results showed that the as compared to marketed formulation, Generic Modafinil Tablet 100 mg showed 88.28 ± 2.1 % drug release at the end of 30 min. This clearly hot melt granulation formulation of the drug could be used for successful therapeutic effect of Modafinil.

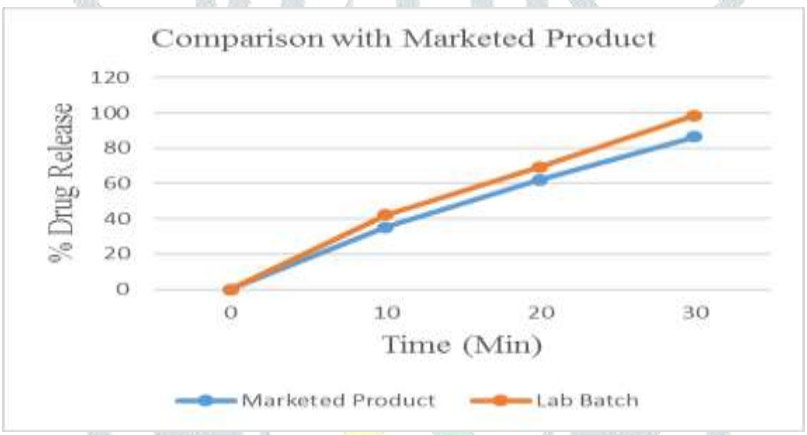

Fig. 5: Comparative in vitro drug dissolution study Lab batch (Orange Line) and marketed sample (Blue Line)

CONCLUSION

The fluidized hot melt granulation process in fluidized bed showed to be an excellent option for pharmaceutical granulation when solvents must be avoided, for protection of unstable drugs. The granules obtained in all experimental conditions showed adequate flow properties for pharmaceutical, as proven by micromeritical properties. The sizes of the granules, represented by their D50, showed moderate size enlargement which may be an indicator that coating predominated over agglomeration. Dispersions granules of Modafinil prepared with different Gelucire 50/13 or 44/14, PEG6000 or 4000 and Poloxamer 188 or 407 by melting method resulted in increased saturation solubility of drug, Flow properties and in vitro dissolution. Based on study of different dispersion granules and drug release, Poloxamer 188 was selected as it has shown better results, and formulated into tablet. characterization of dispersion granules by DSC, XRD and FTIR study, a decreased crystallinity of Modafinil as well as the surface morphology of the polymeric particles can explain the enhanced solubility and improved dissolution rate. It explains that dispersion granules can be utilized successfully to enhance the water solubility of poorly water soluble drug.

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