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Polymeric recrystallized spherical agglomerates of felodipine by quasi-emulsion solvent diffusion method

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ABSTRACT

The objective of the present work was to study the effect of different polymers on the solubility and dissolution rate of Felodipine (FL) a poorly water soluble antihypertensive, by spherically agglomeration using acetone, water and dichloromethane as good solvent, poor solvent and bridging liquid, respectively. The quasi-emulsion solvent diffusion technique was used as a method for spherical agglomeration. The hydrophilic polymers like polyvinyl pyrrolidone, polyvinyl alcohol, and polyethylene glycol were used in agglomeration process. The pure drug (FL) and its agglomerates with different polymers were characterize by differential scanning calorimetry (DSC), Powder X-ray diffraction (PXRD), IR spectroscopic studies and scanning electron microscopy (SEM). The DSC results indicated that decrease in melting enthalpy related to disorder in the crystalline content. PXRD studies also showed changes in crystallanity, IR spectroscopy revealed that there were no chemical changes in the recrystallized agglomerates. The spherical agglomerates with different polymers exhibited marked increase in solubility (41.01 µg mL^{-1}) and dissolution rate (98.83% in 120 mins) as compared with FL. The SEM studies showed that the agglomerates posseeses a good spherical shape. The recrystallized agglomerates also exhibited higher micromeritic properties (bulk density, tapped density and angle of repose).

Key words: Felodipine, Spherical Agglomerates, Solubility, Dissolution, Micromeritic Properties.

INTRODUCTION

Combinatorial chemistry and high throughput screening are modern techniques in drug research. Many of the drugs, evolving from these techniques, can be categorized as class II drugs according to Biopharmaceutical classification system [1]. These drugs are poorly water soluble, but once they are dissolved they easily absorbed through the gastro-intestinal membrane. Therefore, bioavailability after oral administration can be improved by enhancement of the dissolution rate. One of the approaches to enhance the dissolution rate is use of spherical crystallization technique [2]. Spherical crystallization has been developed by Yoshiaki Kawashima and co-workers as a novel particulate design technique to improve processibility such as mixing, filling, tableting characteristics and dissolution rate of pharmaceuticals [3]. The resultant crystals can be designated as spherical agglomerates [4]. Spherical crystallization is an effective alternative to improve dissolution rate of drugs [5, 6]. This can be achieved by various methods such as spherical agglomeration, quasi-emulsion solvent diffusion and neutralization methods [7]. Felodipine (FL) (Fig. 1), a second-generation calcium antagonist of the 1,4-dihydropyridine (DHP) type, lowers blood pressure by selective dilation of arterial smooth muscles in peripheral resistance vessels [8]. Clinical studies have demonstrated that felodipine, which is approved for marketing in several countries, is an effective, well tolerated antihypertensive drug [9]. The major problem of felodipine is its very low water solubility, which results into poor dissolution rate [10]. The purpose of the present work was to improve the solubility, dissolution rate and micromeritic properties of felodipine through spherical crystallization by quasi-emusion solvent diffusion technique.

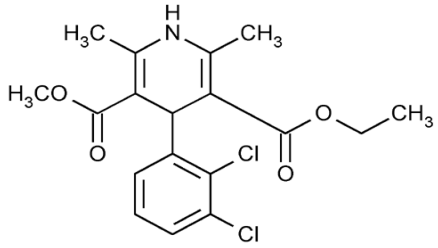


Fig. 1. Chemical structure of Felodipine

MATERIALS AND METHODS

Felodipine USP was generously provided as a gift sample from Cipla Ltd., Mumbai Central, Mumbai, India. Polyvinyl pyrrolidone K-30 (PVP K-30), Polyethylene glycol 6000 was obtained as a gift sample from Signetchem, Mumbai, India. Glyceryl monosterate, polyvinyl alcohol (PVA), acetone, and dichloromethane were purchased from Lobachemie, Mumbai, India. All other chemicals used were of analytical grade.

Preparation of spherically agglomerated solid dispersion

All spherical agglomerates were obtained by the quasi emulsion solvent diffusion method. Spherical agglomerates were prepared with and without stabilizers by spherical crystallization technique. The stabilizers composition was given in Table 1. Felodipine (1.0 g) was dissolved in good solvent acetone (5.0 mL). The bridging liquid dichloromethane (1.0 mL) was added to it.

The resulting solution was then poured dropwise in to the poor solvent distilled water (75 mL) containing different stabilizers like PVP K-30, PEG-6000, PVA with a stirring rate of 800 rpm using propeller type agitator (Remi Motors Ltd., Mumbai, India) at room temperature. After agitating the system for 0.5 h, the prepared agglomerates were collected by filtration through whatmann filter paper no. 42. The spherical crystals were washed with distilled water and dried in desiccator at room temperature.

Table 1. Composition of Spherical Agglomerates

Ingredients	F-0	F-1	F-2	F-3
Felodipine (g)	1	1	1	1
Acetome (mL)	5	5	5	5
DCM (mL)	1	1	1	1
PVP K-30 (g)	--	0.75	--	--
PVA (g)	--	--	0.75	--
PEG 6000 (g)	--	--	--	0.75
Water (mL)	75	75	75	75
Stirring Speed (rpm)	800	800	800	800

Infrared spectroscopy, differential scanning calorimetry (DSC) and Powder X-ray diffraction studies (PXRD)

The infrared (IR) spectra of powder FL, and the agglomerates were recorded on an IR-spectrophotometer (IRAFFINITY-1, Shimadzu, Japan). Differential scanning calorimetry (DSC) analysis was performed using a DSC 823 calorimeter (Mettler Toledo model) operated by star e software. Samples of FL and its agglomerates were sealed in an aluminium crucible and heated at the rate of 10 ^{0}C min^{-1} up to 300 ^{0}C under a nitrogen atmosphere (40 mL min^{-1}). Powder X-ray diffraction patterns (XRD) of the pure drug and spherical agglomerates were monitored with an x-ray diffractometer (Panalytical Xpert pro MPD xrd machine) using copper as x-ray target, a voltage of 40 KV, a current of 30 mA and with 1.5404 Angstorm wavelength. Xcelerator RTMS with secondary monochromator was used as a detector. The samples were analyzed over 2θ range of 7.02-59.98^0 with scanning step size of 0.02^0 (2θ) and scan step time of one second.

Micromeritic properties

The loose bulk density (LBD) and tapped bulk density (TBD) of plain felodipine and its spherical agglomerates were determined. Carr's index and Hausner's ratio were calculated using LBD and TBD values [11]. The angle of repose was accessed by the fixed funnel method [12].

Scanning Electron Microscopy

The surface morphology of the agglomerates was accessed by scanning electron microscopy (SEM). The crystals were splutter coated with gold before scanning.

Drug Loading

The drug loading efficiency of agglomerates was determined by dissolving 100 mg of crystals in 5 mL methanol and diluting further with distilled water (100 mL), followed by measuring the absorbance of appropriately diluted solution spectrophotometrically (PharmaSpec UV-1700, UV-Vis spectrophotometer, Shimadzu) at 362 nm.

Solubility studies

A quantity of crystals (about 100 mg) was shaken with 10 mL distilled water in stoppered conical flask at incubator shaker for 24 h at room temperature. The solution was then passed through a whatmann filter paper (No. 42) and amount of drug dissolved was analyzed spectrophotometrically.

***In vitro* dissolution studies**

The *in vitro* dissolution studies were carried out using an 8 station USP 23 dissolution testing apparatus (Electrolab, India). The dissolution medium used was 900 mL of Phosphate buffer pH 6.8 containing 1.8 % Tween 80 [13-15]. The dissolution medium was kept at in a thermostatically controlled water bath at 37±0.5 ^{0}C. The agglomerates and pure drug containing 10 mg of Felodipine were weighed and introduced into the dissolution medium. The medium was stirred at 75 rpm using paddle. The dissolution tests were carried out for 120 min. At predetermined time intervals 5 mL of samples were withdrawn and analyzed spectrophotometrically. At each time of withdrawal, 5 mL of fresh corresponding medium was replaced into the dissolution flask. The cumulative amount of drug release was calculated and plotted versus time.

Dissolution efficiency studies

The dissolution efficiency of the batches was calculated by the method mentioned by Khan [16]. It is defined as the area under the dissolution curve between time points t_1 and t_2 expressed as a percentage of the curve at maximum dissolution, y100, over the same time period or the area under the dissolution curve up to a certain time, t, (measured using trapezoidal rule) expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time equation (01) [17].

$$\text{Dissolution efficiency} = \frac{\int_0^t y\,dt}{y100\ (t_2 - t_1)} \times 100\% \qquad (1)$$

DE_{60} values were calculated from dissolution data and used to evaluate the dissolution rate.

Statistical Analysis

The results were analyzed by two tailed Student's t-test using Graph Pad Instat software (GPIS; version 5.0), and Microsoft Excel 2007. The results obtained from the dissolution studies were statistically validated using ANOVA (Dunnett Multiple Comparisons Test).

RESULTS AND DISCUSSION

Quasi Emulsion Solvent Diffusion Method

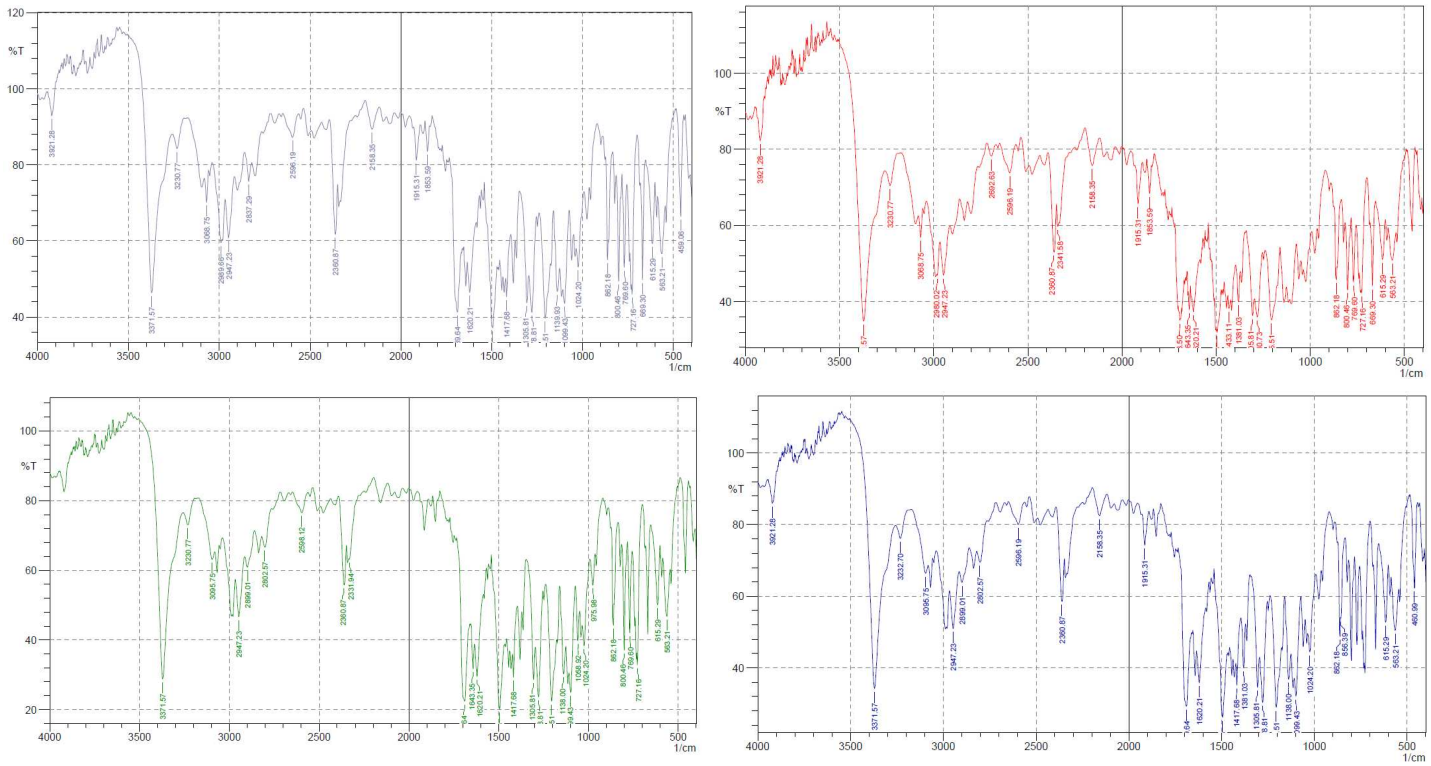
Spherical agglomerates of Felodipine were prepared by quasi emulsion solvent diffusion method (QESD) using a three solvent system. It involves good solvent, poor solvent and a bridging liquid. The selection of these solvents depends on the miscibility of the solvents and the solubility of drug in individual solvent. Accordingly acetone, dichloromethane, water were selected as a good solvent, bridging liquid, and poor solvent, respectively. Felodipine is highly soluble in acetone, but poorly soluble in water. Also it is soluble in dichloromethane which is

immiscible in water. Hence, this solvent system was used in the present study. In QESD method, when good solvent solution of drug plus bridging liquid were poured in the poor solvent (containing different stabilizers) under agitation, quasi emulsion droplets of bridging liquid and good solvent were produced. Then the good solvent diffuses gradually out of the emulsion droplet into the outer poor solvent phase. The counter-diffusion of the poor solvent into the droplets induces the crystallization of the drug within the droplet due to the decrease in solubility of the drug in the droplet containing the poor solvent. The bridging liquid wets the crystal surface to cause binding and promotes the formation of liquid bridges between the drug crystals to form spherical agglomerates. The spherically agglomerated crystals are formed by coalescence of these dispersed crystals. In the present study effect of different stabilizes on solubility and dissolution rate of spherical agglomerates of felodipine were studied.

IR, DSC, and PXRD studies

The possible interaction between the drug and the carrier was studied by IR spectroscopy and DSC. Infrared spectra of Felodipine as well as its spherical agglomerates are presented in Fig. 2. The IR spectra of spherical agglomerates showed that no changes occurred in chemical structure and did not present a great fingerprint difference. This was further supported by DSC results.

a) **b)**



c) **d)**

Fig. 2. IR spectra of a) Felodipine b) Spherical agglomerates F-1, c) Spherical agglomerates F-2, d) Spherical agglomerates F-3

The DSC thermograms of pure Felodipine and its spherical agglomerates are presented in Fig. 3. The DSC thermogram of Felodipine showed a single endotherm at 146.28^{0}C, which was ascribed to drug melting. There was a negligible change in the melting endotherms of prepared spherical agglomerates compared to pure drug (F1 = 145.95^{0}C, F2 = 146.14^{0}C, F3 = 146.12^{0}C). This observation further supports the IR spectroscopy results, which indicated the absence of any interactions between the drug and additives used in the preparation. However, there was a decrease, although very small, in the melting point of the drug in the spherical agglomerates compared to that of pure felodipine. This indicates the little amorphization of felodipine when prepared in the form of agglomerates.

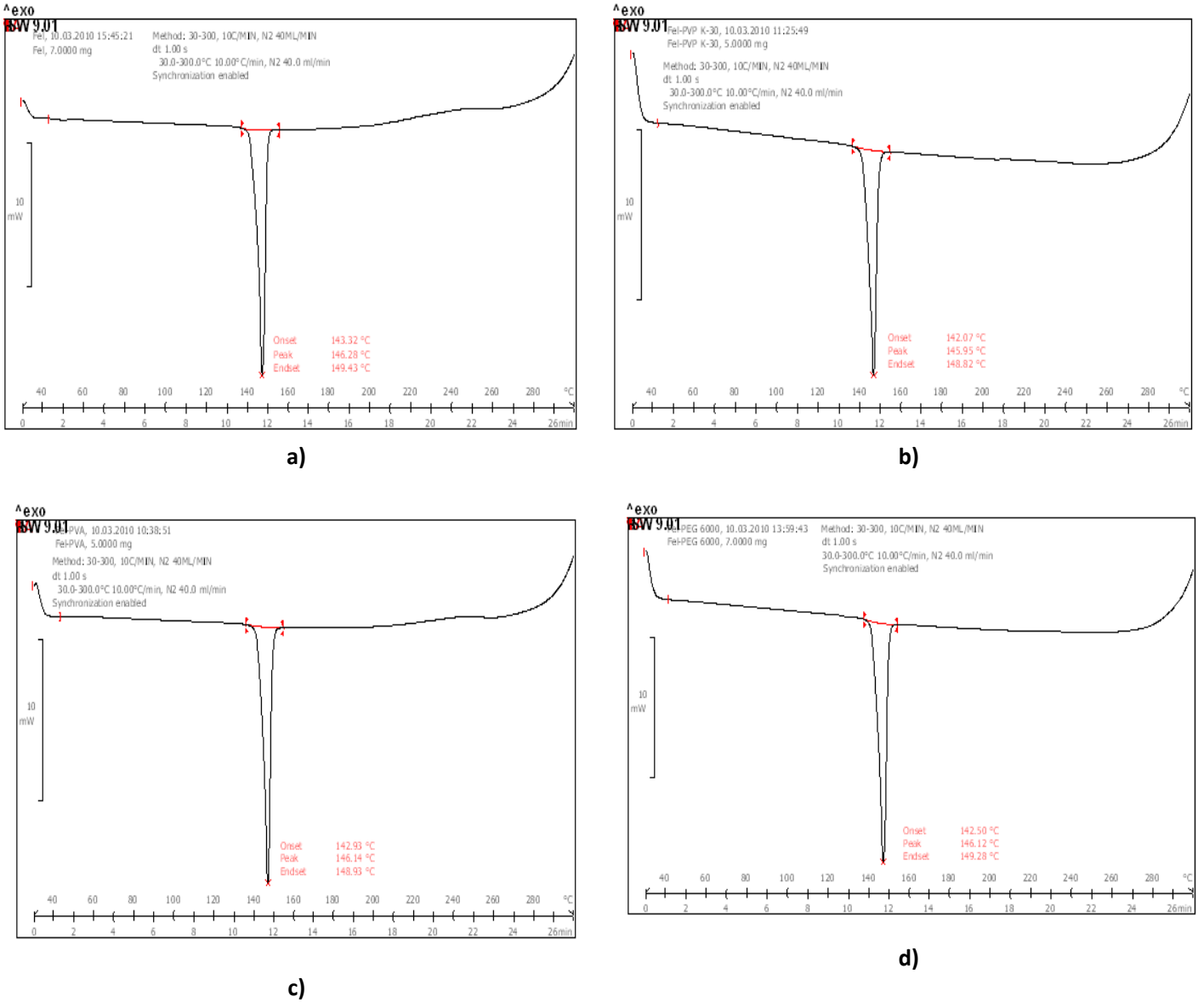


Figure 3. DSC Patterns of a) Felodipine b) Spherical agglomerates F-1, c) Spherical agglomerates F-2, d) Spherical agglomerates F-3

The results of powder X-ray diffraction pattern of felodipine and spherical agglomerates are shown in Fig. 4. Pure drug exhibited intense and long peaks whereas spherical agglomerates showed a halo pattern with less intense peaks, which indicate a considerable decrease in crystallinity or partial amorphization of the drug in its agglomerated form. This further supports the DSC results which demonstrated partial amorphization of the drug agglomerates.

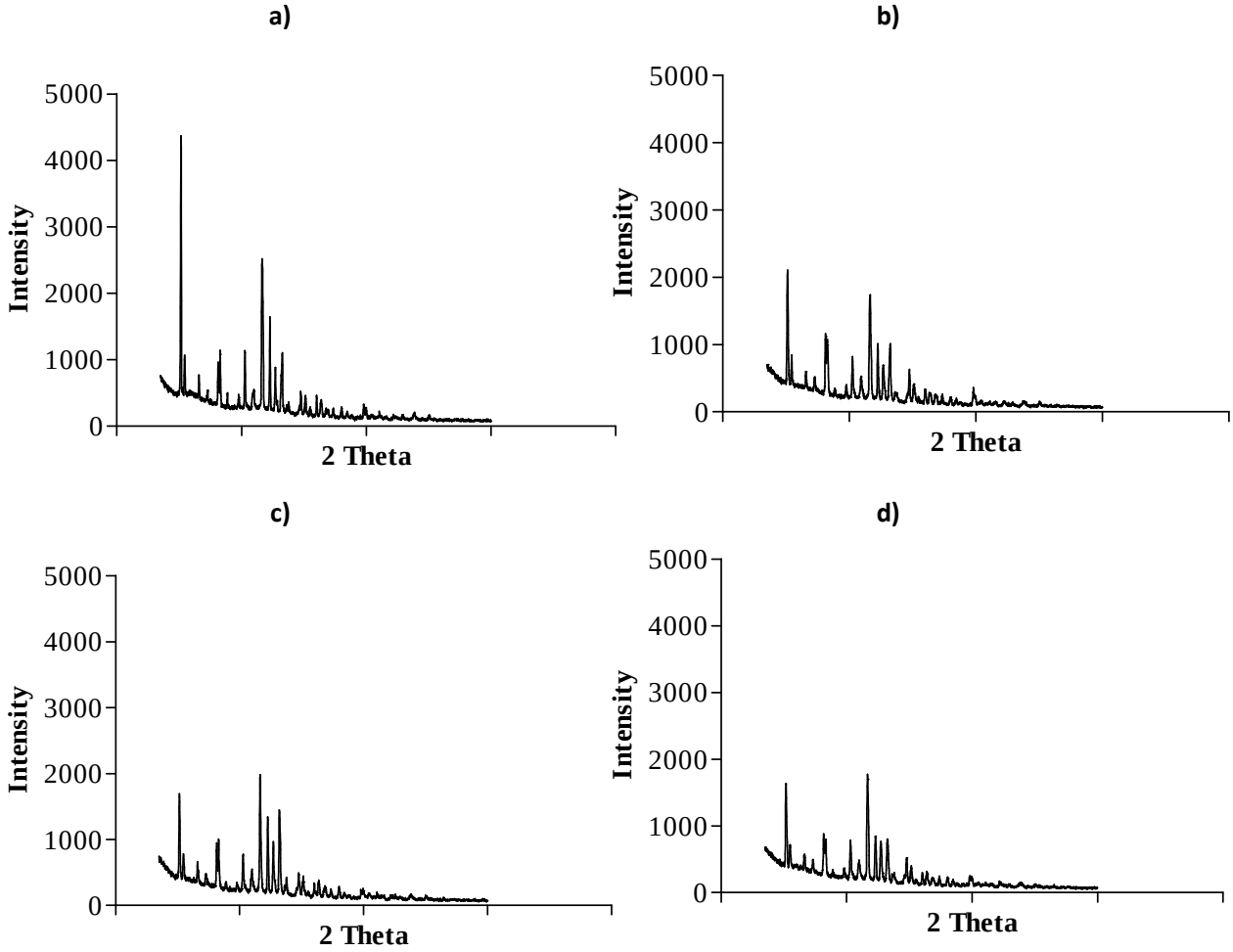


Fig. 4. X-ray diffraction spectra a) Felodipine b) Spherical agglomerates F-1, c) Spherical agglomerates F-2, d) Spherical agglomerates F-3

Micromeritic Properties

The results of loose bulk density (LBD), tapped bulk density (TBD), Carr's index, Hausner's ratio, angle of repose are presented in Table 2. These parameters were used to assess the packability, flow and compressibility properties of the agglomerates. The LBD, TBD, Carr's index, Hausner's ratio and angle of repose values for pure drug Felodipine were 0.390 ± 0.02 g mL^{-1}, 0.625 ± 0.01 g mL^{-1}, 37.60 ± 0.50 %, 1.60 ± 0.03, 51.34 ± 0.32^0 respectively, indicating poor flow and packability properties. On the other hand, all prepared spherical agglomerates exhibited higher LBD (0.408 ± 0.02 g mL^{-1} to 0.454 ± 0.03, n = 3) and TBD (0.465 ± 0.01 to 0.526 ± 0.01, n = 3) values which indicate good packability. Also all the prepared agglomerates

exhibited low Carr's index, Hausner's ratio and angle of repose values, indicating excellent flow properties and compressibility (Carr's index: 12.60 ± 0.42 to 14.96 ± 1.51 % , n = 3; Hausner's ratio: 1.14 ± 0.02 to 1.18 ± 0.01; angle of repose: 14.03 ± 1.20^0 to 18.43 ± 0.31^0, n = 3). The improved flowability and compressibility of spherical agglomerates may be due to the sphericity, regular and larger size of crystals.

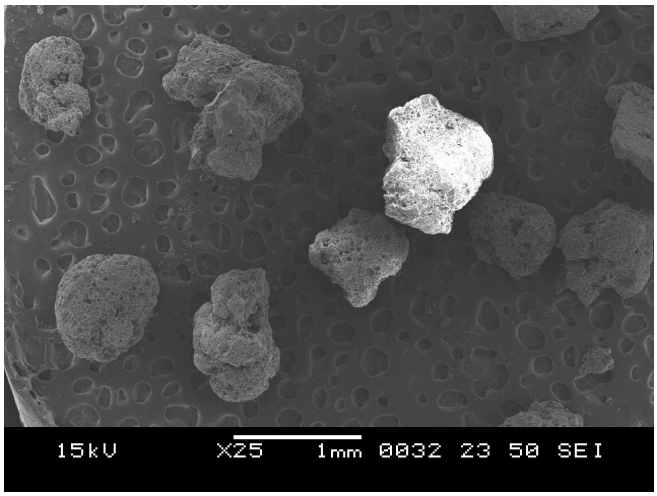
Table 2. Micromeritics, solubility and drug loading efficiency data for the agglomerates and pure drug[a]

Samples	Loose Bulk Density (LBD) (g mL^{-1})	Tapped Bulk Density (TBD) (g mL^{-1})	Carr's index (%)	Hausner's Ratio	Angle of Repose (^{0})	Solubility in Water (µg mL^{-1})	Drug Loading (%)
FEL	0.390 ± 0.02	0.625 ± 0.01	37.60 ± 0.50	1.60 ± 0.03	51.34 ± 0.32	19.47 ± 0.03	100.0 ± 0.0
F-0	0.408 ± 0.02[b]	0.465 ± 0.01[b]	14.96 ± 1.51[b]	1.18 ± 0.01[b]	18.43 ± 0.31[b]	22.10 ± 0.01[b]	100.0 ± 0.0
F-1	0.416 ± 0.01[b]	0.476 ± 0.02[b]	12.60 ± 0.42[b]	1.14 ± 0.02[b]	14.30 ± 0.22[b]	41.01 ± 0.02[b]	98.34 ± 1.4
F-2	0.454 ± 0.03[b]	0.526 ± 0.01[b]	13.68 ± 0.53[b]	1.15 ± 0.01[b]	14.03 ± 1.20[b]	40.83 ± 0.02[b]	98.17 ± 1.3
F-3	0.434 ± 0.01[b]	0.500 ± 0.01[b]	13.20 ± 2.15[b]	1.15 ± 0.01[b]	14.93 ± 1.29[b]	40.37 ± 0.03[b]	98.03 ± 1.3

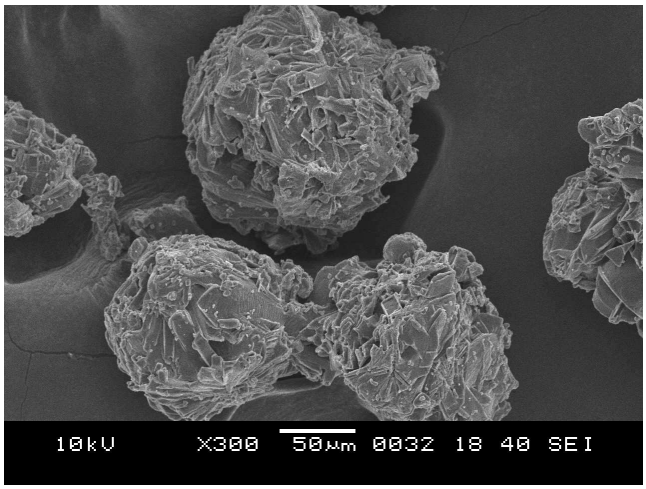
[a]Mean ±SD, n=3, [b]Significantly different compared to pure felodipine (p < 0.05)

Scanning electron microscopy

The results of surface morphology studies are shown in Fig. 5. The SEM results revealed the spherical structure of agglomerates. The surface morphology studies also revealed that the agglomerates were formed by very small crystals, which were closely compacted into spherical form. These photo-micrographs show that the prepared agglomerates were spherical in shape which enabled them to flow very easily.



a)



b)

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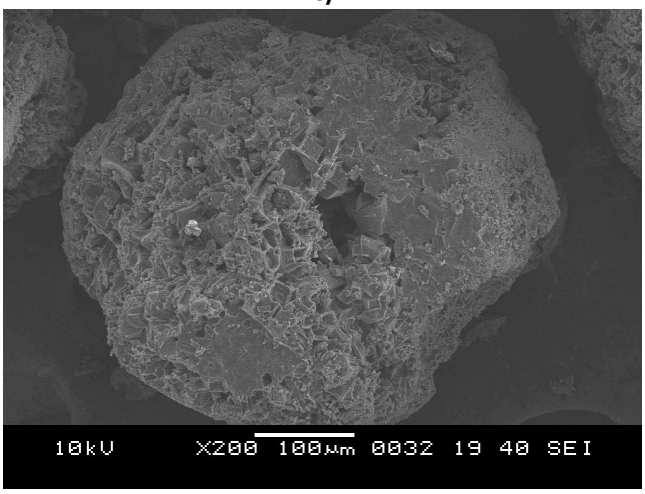

Fig. 5. Scanning electron micrographs of: a) spherical agglomerates containing PVP K-30 (F-1) at 25x, b) spherical agglomerates containing PVA (F-2) at 300x, c) spherical agglomerates containing PEG 6000 (F-3) at 200x

Drug Loading and Solubility Studies

The results of drug loading efficiency and aqueous solubility are shown in Table 2. The drug loading of agglomerates was uniform among the different spherical agglomerates prepared and range from 98.03 ± 1.3 to 100.0 ± 0.0 % (n = 3), indicating negligible loss of drug during agglomeration process. The result of solubility studies indicate that pure Felodipine possesses a very low solubility in water (19.47 ± 0.03 µg mL^{-1}, n = 3); the drug solubility from crystals increased significantly ($p < 0.05$), demonstrating that the incorporation of hydrophilic polymers enhances the drug solubility. Amongst the hydrophilic polymers used PVP K-30 spherical agglomerates shows maximum solubility (41.01 ± 0.02 µg mL^{-1}, n = 3).

In vitro dissolution studies

The results of *in vitro* dissolution studies are shown in Fig. 6 and Table 3. Pure Felodipine exhibited less release at the end of 120 min (21.01 ± 1.22 %, n = 3) while spherical agglomerates with hydrophilic stabilizers improved the dissolution rate of Felodipine. The agglomerates (F-1) released 98.83 ± 2.55 % (n = 3) drug at the end of 120 min. The dissolution efficiency at 60 min (DE_{60}) for pure drug was 7.11 ± 0.65 % (n = 3), whereas for agglomerates (F-1) was 68.80 ± 0.43 % (n = 3). The results revealed that the spherical agglomerates with stabilizers showed significant increase ($p < 0.05$) in drug release compared to the pure drug. Among the different hydrophilic polymer tested, PVP K-30 showed better effect on solubility and dissolution rate compared to other polymers. The increase in the dissolution rate of agglomerates could be attributed to deposition of polymer onto the recrystallized drug surface and better wettability of the spherical agglomerates. The percent drug release from different agglomerates was increased in the following order: PVP-K30>PEG 6000>PVA.

Table 3. Drug Release and Dissolution Efficiency

Spherical Agglomerates	Phosphate Buffer pH 6.8 with 1.8 % Tween 80	
	DP_{120} (%)	DE_{60} (%)
FEL	21.01 ± 1.22	7.11 ± 0.65
F-0	24.50 ± 2.12[b]	11.97 ± 0.29[b]
F-1	98.83 ± 2.55[b]	68.80 ± 0.43[b]
F-2	68.90 ± 2.79[b]	44.81 ± 0.80[b]
F-3	86.38 ± 1.22[b]	55.16 ± 1.19[b]

DP_{120} – Percent drug release at 120 min, DE_{60} – Dissolution Efficiency at 60 min, [a] Mean ±SD, n = 3, [b]Significantly different compared to pure felodipine ($p < 0.05$)

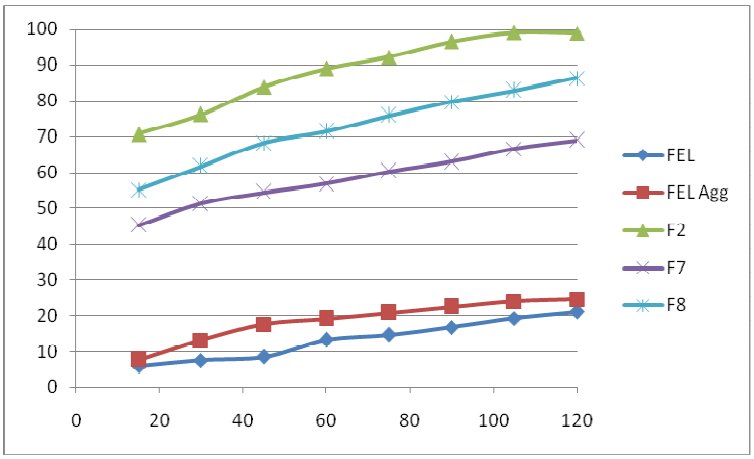

Fig. 6. Dissolution profile of pure drug and agglomerates in Phosphate buffer 6.8 with 1.8 % Tween 80

CONCLUSION

The present study shows that spherical agglomerates of Felodipine prepared with PVP K-30, PEG 6000 and PVA exhibited improved solubility and dissolution rate in addition to improving the micromeritics properties. This technique may be applicable for producing oral solid dosage forms of FL with improved dissolution rate with improving physicochemical and micromeritic properties.

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