

Class II drugs; a dissolution / bioavailability challenge: Flutamide-loaded spray dried lactose for dissolution control

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Abstract

Flutamide (FL) is the only presently recommended drug for monotherapy of benign prostatic hypertrophy. Five FL-loaded powdered formulations were prepared by spray drying. Aerosil was used with PEG 400 or PEG 6000 to improve powder flow and FL dissolution, respectively. Differential Scanning Calorimetry (DSC) studies revealed no interactions as evidenced by the persisting FL peak at 113°C. SEM pictures showed changes in powder morphology with F3 and F5 giving spongy-appearing particles with intra-particle channels. Wettability of the formulations was strongly increased as evidenced by the fast water rise through the powder bed (1.5- 44 min) compared with native FL (> 3 hr). The powders were tested for their angle of repose, Carr's index and Hausner's ratio. The results showed improved flow compared to both native FL and lactose. The best angle of repose (27.4°) was seen with F3. This formulation also showed "fair" compressibility index and Hausner's ratio of 16.7 and 12.0, respectively. Compressed into tablets, all formulations showed significant improvement of FL release ($p < 0.05$) compared to commercial tablets. The highest drug release was seen with F3 showing 37% of FL released after 120 minutes compared with 11% FL released from commercial tablet after the same interval.

Key words:

Flutamide; DSC; powder wettability; angle of repose; Carr's index; Hausner's ratio.

How to Cite this Paper:

Wael M. Samy "Class II drugs; a dissolution / bioavailability challenge: Flutamide-loaded spray dried lactose for dissolution control", Int. J. Drug Dev. & Res., April-June 2012, 4(2): 195-204

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Article History:-----

Date of Submission: 09-03-2012

Date of Acceptance: 07-04-2012

Conflict of Interest: NIL

Source of Support: NONE

Introduction:

The solubility and dissolution rate of a poorly water-soluble drug will substantially influence its bioavailability since an orally administered drug must first dissolve in digestive fluids in order to be absorbed through the biological membranes of the gastrointestinal tract (GI tract).

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Class II and Class IV drugs in the biopharmaceutics classification system (BCS) are defined as having low aqueous solubility. Particularly for Class II drugs, an increase in the solubility and dissolution rate will result in more efficient drug absorption, since Class II drugs are well absorbed from the GI tract once in solution due to their relatively high lipophilicity. Many techniques have been reported in the scientific literature to improve the solubility and dissolution properties of poorly water-soluble drugs. Increasing the available surface area for dissolution via particle size reduction is one of the oldest methods for improving the dissolution rates of poorly water-soluble drugs (1). Solid dispersion systems have also been widely studied and repeatedly shown to improve the dissolution properties of poorly water-soluble drugs (2, 3). In addition, the inclusion Complexation of drug with cyclodextrins by kneading (4), steam-granulating (5), coprecipitating (6), freeze-drying (7) and spray-drying (8) has also been shown to dramatically increase drug solubility and dissolution rate. Also hot melt extrusion was used as a method to enhance dissolution rate of poorly soluble drugs (9).

Nanosuspensions were also used to improve dissolution of naproxen, an anti-inflammatory drug with very poor water solubility (10).

Flutamide (FL), a nonsteroidal antiandrogen, is therapeutically effective for the treatment of benign prostatic hypertrophy and androgen dependent prostate cancer. It is the only one presently recommended for monotherapy (11). Flutamide is used increasingly as part of total androgen ablation therapy and in neoadjuvant treatment before radical prostatectomy (12). The low bioavailability of FL after oral administration may be due to poor wettability, low aqueous solubility, poor permeability,

rapid first pass hepatic metabolism, and low concentration at the absorption surface (13). Therefore, developing novel formulations that increase solubility and dissolution rate of FL will produce higher concentrations of the drug in solution at the absorption site and hence may overcome the solubility-mediated poor bioavailability. Few studies have been performed to improve the solubility of FL and enhance its dissolution rate by preparing its high energy solid dispersions with polyethylene glycol 6000 and PVP (14). Co-precipitates prepared using different ratios of FL with α - and β - cyclodextrins via solvent technique revealed that β - cyclodextrin was more efficient than α -cyclodextrin in enhancing the drug dissolution rate (15). In another study, FL-HP β CD (hydroxypropyl- β -cyclodextrin) inclusion complex was prepared using solvent freeze-drying technique in a completely aqueous solution. Results showed that the complex substantially increased the aqueous FL solubility and improved its oral bioavailability in rats (13, 16). Lyophilization monophasic solution technique was also used to prepare FL-CD complexes at different molar ratios for improving the solubility and dissolution performance of the drug (17). Another approach to improve FL solubility was by the preparation of liquid FL systems that showed improved drug dissolution (18).

Also solid dispersions of drugs with PEG 6000 were useful in solving various problems such as stability, solubility, dissolution and bioavailability (19).

In this study the preparation of FL-loaded lactose in a directly compressible form was discussed. Drug - loaded spray dried lactose was used as a method of improving the flow properties, compressibility as well as dissolution rate of FL. Having the ability to solubilize some compounds and improve wettability (20), the effect of PEGs on FL dissolution was also tested.

Materials and Methods:

Materials:

Flutamide (FL) was kindly donated by Archimica (Origgio, Italy). Lactose was kindly donated by Pharco Pharm., Co, Egypt. Both colloidal silicone dioxide (Aerosil® 200) and sodium starch glycolate (Explotab) were supplied by FMC Co. (Philadelphia, PA, USA). All other reagents and chemicals were of analytical grade.

Method:

Preparation of FL-loaded lactose:

Flutamide (15 gm) was dissolved in 50 ml isopropanol (solution A), while lactose was dissolved in distilled water to get a 30% w/w solution (solution B). The prepared formulations were prepared by mixing the two solutions together with the addition

of water, isopropanol, PEG 400, PEG 6000 and/or Aerosil according to table I. The mixed volumes were selected to obtain a FL load of 50 % w/w in the final powders, whereas Aerosil and PEGs were added in the maximum amounts applicable to the used conditions of spray drying as estimated in a preliminary study. Higher Aerosil resulted in blockage of the device connections and nozzle, while higher PEG concentration resulted in a sticky not well-dried product. The mixtures were stirred with a magnetic stirrer during feeding to a Minispray Dryer B 290 (Buchi, Switzerland). Inlet temperature was adjusted at 150°C and the outlet at 90 - 92 °C with an air flow rate of 439 L/hr. The prepared powders were stored in a desiccator till further testing.

Table I: Composition of different FL powdered formulations

Formula	Solution A (ml)	Solution B (ml)	Water (ml)	Isopropanol (ml)	Aerosil (mg)	PEG 400 (ml)	PEG 6000 (gm)
F1	50	50	--	--	--	--	--
F2	25	25	25	25	--	--	--
F3	25	25	25	25	75	--	--
F4	25	25	25	25	75	0.375	--
F5	25	25	25	25	75	--	0.375

Differential Scanning Calorimetry:

Differential Scanning Calorimetry was performed using Shimadzu differential scanning calorimeter, DSC-50 (Shimadzu, Kyoto, Japan) in order to assess the thermotropic properties and the thermal behavior of FL, lactose, as well as the prepared powders. Samples of 3-4 mg of the pure drug or the above mentioned samples were sealed in a 50- µl aluminum pans at a constant heating rate of 5°C/min. in the scanning temperature range of 25 to 250 °C. Empty pans were used as references and the whole thermal behaviors were studied under a nitrogen purge.

Morphology observation:

The surface topography of the prepared powders was examined using a JEM-100S scanning electron

microscope (JOEL, Japan). Samples were mounted on metal stabs using double-sided adhesive tape, coated with approximately 10-20 nm gold film for 20 s under vacuum using a sputter coater and then examined. Scans were performed at an acceleration voltage of 10 kV.

Flowability studies:

In order to ensure good flow properties of the powders, tapped and bulk densities, angle of repose measurements (fixed height cone method), Carr's index and Hausner's ratio were adopted (21, 22). The flow properties of the powders were measured using a Flowability Tester, BEP2 (Copley, UK). The bulk volume was obtained by pouring an amount of 10 grams of the powder in a 25 mL graduated cylinder, the volume of powder was recorded and the bulk

density was calculated. Tapped density was measured using a Tapped Density Tester, JV1000 (Copley, UK). The experiments and calculations were done in triplicate and the results were recorded (Table II).

Wettability/ powder bed hydrophilicity study:

The native drug, its physical mixture with lactose, or the prepared granules (about 1 gm) were placed on a sintered glass disk forming the bottom of a glass tube. Methylene blue crystals were placed on the top of the powder surface. The whole device was brought into contact with water and the time taken for the capillary rising of water to the surface so as to dissolve methylene blue crystals was measured (23).

Preparation of Flutamide tablets:

Explotab® (2%w/w) and magnesium stearate/talc (2%) were added to each formula and then compressed using a single punch tablet press machine with 12 mm punch and die (Single punch tablet press, Model CP-501, Vanguard Pharmaceutical Machinery Inc., USA) at a pressure of 6-7 Kg.

Evaluation of the prepared tablets:

- **Flutamide content** of each formulation or the commercial tablets was determined by accurately weighing 10 tablets of each formula individually. Tablets were then crushed and a weight equivalent to one table was dissolved in 250 ml 0.1 N HCl, then the solution was filtered, properly diluted, and measured spectrophotometrically (T80, UV/VIS Spectrometer, PG Instruments Ltd, UK) at λ_{max} of 302 nm, thereafter, the flutamide content of each tablet was determined.

- **Friability** of the prepared formulations was performed using tablet friability tester (Roch friabilator), and the percentage loss in weights were calculated and taken as a measure of the tablet friability.

- **Hardness** of the prepared tablets was evaluated using Erweka hardness tester. Six tablets of each

formulation were tested and the mean hardness of each formula was then determined.

- **Disintegration time** was performed using USP disintegration tester (Copley DTG 3000, Copley, UK). Six tablets of each formulation was tested (one placed in each tube) using distilled water at 35 ± 0.5 °C. Time till disintegration was measured and the average was calculated.

- **In-vitro dissolution studies:** The dissolution rate of flutamide from the prepared tablets was determined using USP XXIV dissolution rate apparatus II (Pharma Test, Germany) the jars were filled with 900 ml of PBS (pH 7.4) containing 0.2% w/w Tween 80 at 37 ± 0.5 °C at a stirring rate of 100 ± 2 rpm.

One tablet of each formula, containing an equivalent to 125 mg (FLT) was placed in each jar of the dissolution rate apparatus. At predetermined time intervals, 5-ml aliquots from the dissolution medium were withdrawn and replaced with an equal volume of pre-warmed buffer. The aliquots withdrawn were filtered through 0.45 μ m Millipore membrane filter, diluted and analyzed spectrophotometrically for their flutamide content at λ_{max} 302 nm. The experiments were done in triplicates and the average was recorded.

Results:

DSC study:

Figure 1 reveals that the thermal behaviors of the pure components together with the thermal behavior of the prepared powders. Flutamide peak was clear in its DSC thermogram demonstrating a sharp characteristic peak at 113 °C indicating its melting temperature. Lactose showed two peaks at 142 and 212°C, which may correspond to vaporization of adsorbed water and its melting point, respectively. The peaks of both FL and lactose persisted in F1with broadening of the first lactose peak. In case of F4 the

FL peak was broadened with disappearance of the first lactose peak.

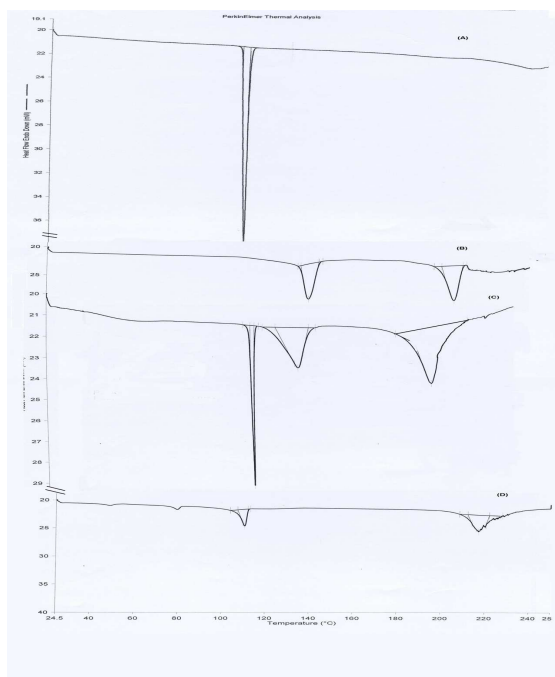
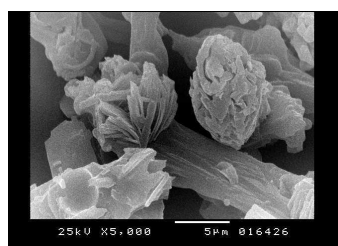


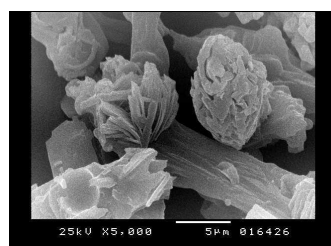
Figure 1: DSC analysis of (A) FL, (B) lactose, (C) F1 and (D) F4.

Morphology observation:

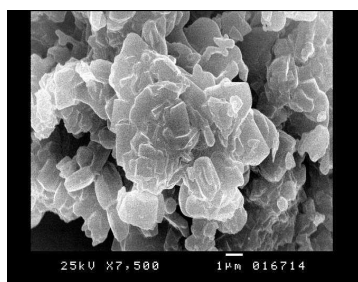
Native FL powder showed rectangular flaky-appearing particles (figure 2-a). On the application of spray drying, with high FL concentration in the feed solution (F1), the powder showed partial disappearance of the rectangular drug particles with



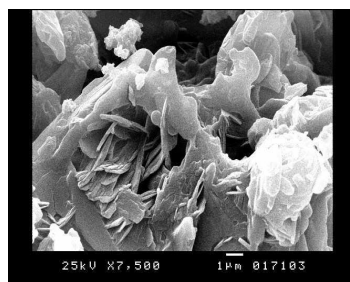
(a) Flutamide



(b) F1



(c) F2



(d) F3

the formation of a rosette-shaped particles and increased void spaces (figure 2-b). The decrease in FL and lactose concentrations of the solution to be dried (7.5 % w/w each) in F2 gave rise to more homogenously looking particles with complete absence of the FL particle shape (figure 2-c). The incorporation of Aerosil in the feed solution (F3) gave rise to spongy, scaly appearing particles with relatively blunt margins (Figure 2- d). This spongy appearance could be due to adsorption of the molten FL; at the entrance temperature; on the finely divided Aerosil, and may account for the slightly lower density of F2 (0.16 g.cm-3) compared to F1

Incorporation of either PEGs gave waxy appearing particles with the disappearance of the FL particle shape with F5 particles showing spongier appearance and higher void spaces (Figure 2- e, f). The presence of the liquid PEG 400 in F4 gave rise to less spongy-appearing particles with relatively higher inter-particle adherence and bad flow (figure 2-e).

Flowability studies:

All the tested parameters for both lactose and native FL showed poor flow properties with lactose showing a θ value of 39° and FL a value of 47° (Table II).

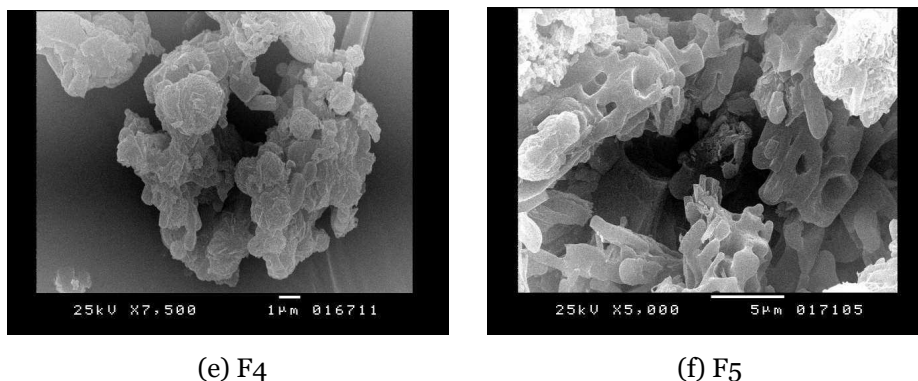


Figure 2: Scanning electron micrographs for different FL-loaded powder formulations. Lactose had a compressibility index and Hausner's ratio of 24.7 and 1.33, respectively. On the other hand, the prepared powdered formulations showed an angle of repose ranging from 27 to 40° for F3 and F1, respectively.

Table II Physical parameters of the prepared FL powders (values are mean ± SD, n=3).

Formula	Angle of repose	Bulk density g.cm ⁻³	Tapped density g.cm ⁻³	Carr's Index	Hausner's ratio
Lactose	39.2 ± 1.0	0.61 ± 0.020	0.81 ± 0.020	24.69 ± 1.03	1.33 ± 0.03
Flutamide	47.3 ± 1.1	0.18 ± 0.220	0.22 ± 0.029	20.46 ± 3.96	1.29 ± 0.03
Formula F1	39.9 ± 0.8	0.18 ± 0.004	0.22 ± 0.004	18.18 ± 0.92	1.22 ± 0.02
Formula F2	37.2 ± 0.9	0.16 ± 0.005	0.19 ± 0.002	16.77 ± 1.97	1.20 ± 0.03
Formula F3	27.4 ± 0.7	0.17 ± 0.010	0.21 ± 0.007	16.85 ± 1.94	1.20 ± 0.03
Formula F4	38.7 ± 0.6	0.17 ± 0.007	0.20 ± 0.008	18.85 ± 1.23	1.23 ± 0.04
Formula F5	32.0 ± 0.5	0.18 ± 0.005	0.27 ± 0.010	33.92 ± 0.81	1.52 ± 0.02

The best flow parameters were seen with F3 having a θ value of 27.4, compressibility index of 16.8 and a Hausner's ratio of 1.2.

Wettability/ powder bed hydrophilicity study:

All the prepared powders showed significantly short rising time (P<0.01) of water to its surface as compared to native FL indicating high wettability of the prepared powdered formulations. Physical mixture of FL/lactose showed a rise time of more than 3 hours, whereas FL did not show dissolution of the methylene blue even after 48 hours indicating its poor wettability (table III).

Table III: Wettability of the prepared FL powdered formulations.

Formula	Water rising time (min)
Flutamide	> 360
Physical mixture	> 360
F1	44
F2	42
F3	1.5
F4	36
F5	20

The application of spray drying showed high reduction in the water rising time to less than one hour for F1 and F2 indicating improvement in drug wettability. The fastest water rise was 90 seconds with F3. Presence of PEGs also resulted in good wettability with water rising time of 36 and 20 minutes for F4 and F5, respectively (table III).

Evaluation of the prepared tablets: Flutamide content, hardness, disintegration and friability

All the prepared tablets; as well as the commercial ones; showed 100 ± 5% of the claimed drug content

Tablets prepared from all the tested formulations had tablet hardness ranging from 5.5 to 8 Kg, disintegration time of 12-15 minutes and percentage loss in tablets' weight on friability testing that did not

exceed 1%. These results comply with the pharmacopeial requirements of tablet testing.

In-vitro dissolution studies:

The dissolution profiles of the tested tablets showed significant increase ($p < 0.05$) in FL release compared with the marketed tablet (figure 3).

The maximum release rate was observed with tablets prepared from F3 powdered formula with 14% of the drug released after 45 minutes compared with 6% in case of commercial tablet. The percentage FL release from F3 tablets was 37% after 2 hours compared with 11% in case of commercial tablets. The increase in FL concentration in the spray drying feed mixture (F1 and F2) did not show significant difference in drug release ($p > 0.01$).

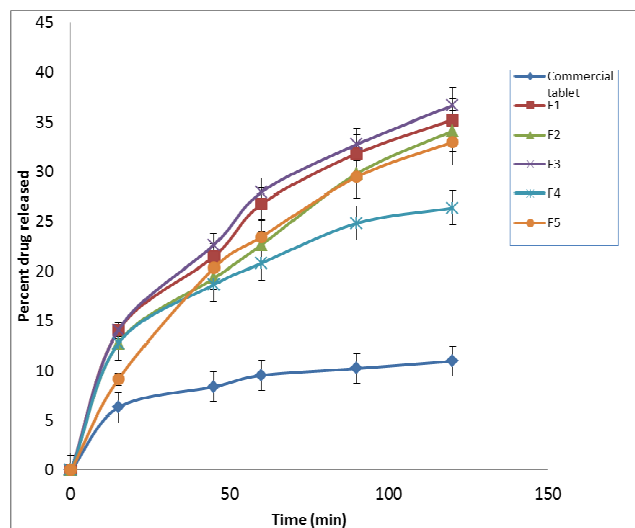


Figure 3: In-vitro FL release from compressed tablets of different powdered formulations.

Incorporation of PEG 400 in the formula with Aerosil (F4) gave rise to a slight change in FL release with 21% released after the first hour compared with 28% for F3. The use of PEG 6000 gave rise to a FL release of about 33% after 2 hours.

Discussion:

DSC study:

One of the most classical applications of DSC analysis is the determination of the possible interactions between a drug entity and the excipients in its formulation. It is very important to establish the existence of any incompatibilities during the pre-

formulation stage to ensure the success of the subsequent stability studies (24). The persistence of FL peaks at 113 °C in F1 indicates no interaction with lactose during the spray drying procedures (figure 1). In case of F4 the presence of the liquid PEG 400 may have led to decreased FL crystallinity and presence of the drug in an amorphous solubilized form (25) as seen from the broadening and decreased peak sharpness. Also the disappearance of the first lactose peak at 142 °C may be due to absence of the adsorbed water which could be replaced with the liquid PEG 400.

Morphology and Flowability studies:

Native FL powder showed a rectangular flaky-appearing particles (figure 2-a) which may account for its relatively "poor" flow parameters as defined by the USP 29 (26).

Spry drying of lactose/FL mixture at concentration of 15%w/w each resulted in the partial disappearance of the flaky drug particles and appearance of the new rosette-shaped particles (figure 2-b). This change in particle morphology could be due to melting of FL at the entrance temperature (150 °C) and subsequent solidification at the exit temperature.

The decrease in FL concentration of the solution to be dried (7.5 % w/w) in F2 gave rise to more homogenously looking particles with complete absence of the FL particle shape (figure 2-c). This variation in particle shape between F1 and F2 can be attributed to the lower isopropanol/water content of the sprayed droplet in case of F1 (70%) compared with the other formulations (85%). This low solvent content causes an abrupt increase in solids concentration upon exposure to the hot air current thus rapid transformation to the original FL shape. The improvement of powder flow upon spray drying can be attributed to the change in particle shape and powder porosity. The calculated compressibility index and Hausner's ratio (table II) indicate that F3 has "fair" flow properties with "aid not needed" (26),

this would make F3 a potential candidate allowing proper tableting of such formulation. F5, containing the waxy PEG 6000 and showing marked spongy appearance had the highest difference between its bulk and tapped density (table II).

Wettability/ powder bed hydrophilicity:

As expected from its marked porosity, F3 gave the highest wettability of the prepared powders. The improved powder wettability on PEGs addition can be attributed to the channels formed in these spongy-appearing powder aggrigation in addition to the hygroscopicity of PEGs. Also the modification of the particle surface properties seen in the SEM pictures may led to a reduction of the value of its contact angle which improves the powder wettability. Mooter et al (27) has also suggested that the improvement of wettability of the powder could result from the formation of a film of polyethylene glycol around the drug particles which modifies the hydrophobicity of the surfaces.

Flutamide content, hardness, disintegration and friability

The obtained results indicate that the prepared powdered formulations have good tableting potentials by converting FL into a directly compressible powder that gives tablets obeying the pharmacopeial requirements without the need for filler addition. These findings are of potential importance in tablet manufacture of poorly water soluble drugs.

In-vitro dissolution studies:

The increased FL release from F3 (figure 3) can be attributed to the porosity of the powder seen in the morphological findings as well as the relatively high wetability of the powder. The suggested reduction of the value of the contact angle; as evidenced by the increased powder wettability; could lead to this increase in dissolution kinetics. On the other hand the effect of PEGs in increasing FL release (F4 and F5) can be attributed to the increased

wettability of the drug in addition to their solubilizing effect on FL in the micro-environment around the particle (18). Possible mechanisms have been proposed to account for the increase in the dissolution kinetics of drugs from polyethylene glycol solid dispersions. The mechanisms include the carrier controlled dissolution (28, 29), the continuous drug layer formation (29) and that involving the release of intact particles with dissolution occurring over a large surface area (30). The last mechanism could be applicable to explain the improved FL dissolution after spray drying which gave rise to smaller particles with larger surface area.

In addition, PEG 400 was found to improve FL solubility to 0.747 mg/ml (31) compared with 0.4×10^{-3} mg/ml in water. It also improved FL dissolution from its liquisolid systems (18). These findings suggest that F4 could be some form of a liquisolid system containing FL partially dissolved in the liquid PEG 400 within a lactose matrix which is supported by the inter-particle adherence and bad flow of F4.

Comment:

The method of spray drying was suitable for preparing directly compressible FL-loaded powders with good drug distribution and fair flow properties that facilitates tablet preparation without the need for other granulation or mixing techniques. The prepared FL powdered formulations were able to significantly increase FL dissolution and wettability with F3 giving the best results. This increase can improve the reported low oral FL bioavailability which was strongly improved in rats upon the improvement of its in-vitro dissolution (16). This study may also pave the way for further studies on water-insoluble drugs to be prepared by this technique.

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