



INFLUENCE OF NOVEL 'DISPERSED FUSION TECHNIQUE' ON DISSOLUTION AND PHARMACOTECHNICAL PROPERTIES OF PHARMACEUTICAL SOLID DISPERSION

Sachin Gahoi^{*a,b}, Gaurav K Jain^c, Mayank Singhal^c, Mohammad Anwar^c, Farhan J Ahmad^c, Roop K Khar^c

^a School of Pharmacy and Medical Sciences, Singhania University, Rajasthan, India.

^b Formulation Development Services, R&D Centre, Matrix Labs Ltd., Andhra Pradesh, India.

^c Department of Pharmaceutics, Faculty of Pharmacy, Hamdard University, New Delhi, India.

*Corresponding author's E-mail: sachin.gahoi@matrixlabsindia.com

Accepted on: 17-05-2011; Finalized on: 15-06-2011.

ABSTRACT

This research compares two solid dispersion techniques; In-situ fusion (IF) and Dispersed fusion (DF) to improve the dissolution of lumefantrine, poorly water-soluble model drug, with particular attention to technological properties of granules. Solid dispersions having identical composition were produced using IF and DF techniques and their morphology, particle size, Lumefantrine (LMF) particle size in granules, flowability, dissolution behaviors and physicochemical properties have been evaluated and compared. The utilization of DF technique had strong impact on the lumefantrine particle size in solid dispersion, particle size distribution of the granules and on their morphology. The drug particle size was significantly lower in DF granules than IF granules. SEM of agglomerates showed strong impact of granulation technique on morphology and granulation mechanism. The other physical properties of granules, density and flowability, were found to be independent of techniques. The drug melting temperature range has decreased significantly in DF than IF granules. The XRD characteristics of the products were found to be independent of the technique. The dissolution behaviors of LMF granules manufactured using DF technique showed a significant increase of the drug dissolution rate. In conclusion DF technique is a superior and scalable solid dispersion process for industrial manufacturing of pharmaceutical dosage forms.

Keywords: LMF, solid dispersion, poloxamer, dispersed fusion, in-situ fusion.

INTRODUCTION

Solid dispersions can improve the dissolution rate and hence the predicted bioavailability of poorly-water soluble BCS class II drugs. A combination of factors can act to enhance the dissolution of drugs from solid dispersions including particle size reduction, reduced agglomeration, improved wettability and solubility, or dispersion of the drug as either micro-fine crystals, amorphous materials or in a molecular form.¹

Though the traditional ways of preparation of solid dispersions, i.e., fusion, solvent and solvent-fusion method have often proved to be successful but, there is limited application in pharmaceutical products and need research into new ways of generating solid disperse systems.² The reason for this may be problems with the method of preparation, the reproducibility of physicochemical properties, the formulation into dosage forms, the scale up of the manufacturing method and/or the stability.³ Traditionally in fusion method, solid dispersions are prepared by melting the carrier in which the drug is dispersed and then solidifying the mixture on an ice bath.⁴ The solidified dispersion is then pulverized and sieved. This method, which is difficult to apply in a large pharmaceutical scale, usually produces materials that are soft, tacky and have poor flow properties and compressibility.⁵ It is desirable to improve the flow properties and the compressibility of solid dispersion material to improve the processing of the material.

The main aim of research was to evaluate novel solid dispersion technique 'Dispersed Fusion' to improve dissolution rate of water insoluble drug, lumefantrine (LMF), with particular attention to technological characteristics of granules. Novel DF technique involves spraying of molten drug and hydrophilic carrier on diluent in fluidized bed. This study also investigates comparative characteristics of granules prepared by DF and *in-situ* fusion (IF) techniques with respect to in vitro release of drug from the granules, carrier and compression characteristics of granules. SEM was used to study the surface characteristics of the granules. Furthermore, differential scanning calorimetry and X-ray powder diffraction were utilized to investigate the crystallinity of the system. Particle size of LMF was evaluated in granules by Zetasizer. In addition, compression suitability of granules was evaluated.

MATERIALS AND METHODS

Materials

LMF (LMF) was obtained as a gift sample from Ipca Laboratories Ltd. (India). Poloxamer 188 was obtained from BASF (Germany) whereas lactose anhydrous from DFV International (Netherlands). All other chemicals were of analytical grade and were used as received from Merck Ltd. (India).



Methods

Dispersed Fusion (DF)

Granules were prepared by the DF technique using a fluidized-bed system (Model: GPCG 1.1, Fluidized Bed, Glatt GmbH, Germany). LMF (12%) and Poloxamer 188 (48%) were melted together at the temperature $100 \pm 10^\circ\text{C}$. The lactose (40%) was taken into column of fluidized bed processor. The molten material was sprayed on fluidized lactose under specified condition. Atomization air was heated at 100°C to prevent solidification of molten material during atomization. Inlet air temperature was maintained at 40°C , pneumatic spray nozzle diameter was 1.2 mm, and atomization air pressure was maintained at 1.5 bar. The granules were subjected to cooling on completion of spray.

In-situ fusion (IF)

The experiments were performed using a Mini-Glatt fluidized bed (Glatt GmbH, Germany). A granulation process consisted of three steps: mixing, heating-kneading and cooling. The granule components were placed at the centre of the bottom grid and were mixed by fluidizing air at ambient temperature; the mixing phase lasted for 5 min. The temperature was raised to 100°C ; as a consequence, the temperature of the powders gradually increased as well (heating phase). Once the product temperature reached 100°C , the timing of the kneading phase started; after 3min, the granulation end point was reached. Finally the flow rate of the inlet air was kept constant, while its temperature was decreased to 25°C to achieve the consolidation of the granules; this cooling phase lasted until the product temperature reached 40°C . At the end of the granulation process (total processing time was 15 min), the granules were discharged, collected and sieved.

The physical mixture of each formulation was prepared using the same ratio of individual components. Geometric mixing was used to mix individual components. The physical mixture was finally triturated in mortar with pestle for 2 min to give a uniform blend. However, a free flowing mixture was obtained after thorough mixing.

The placebo samples were prepared in the same manner as the physical mixtures, except that they did not contain lumefantrine.

Characterization of Granules

Granule Size Analysis

An Advantech Sonic Sifter (Model L3P, Advantech Manufacturing, New Berlin, Germany) equipped with a series of stainless steel screens and a fines collector was used for the determination of particle size distribution of the granules. The screens used were 106 to $850 \mu\text{m}$ and a fine collector pan. An approximately 10-gram sample was tested in duplicate with a sift setting of 5 and sifting time of 10 min. The percent retained was calculated from the amount retained on each screen divided by the sample size. The average of the two

determinations was reported.

Yield

The yield of the granulation process was calculated by dividing the total weight of the granules in the range $100\text{--}841 \mu\text{m}$ by the weight of the initial powder (in percentage).

Determination of Carr's Index

The granules were weighted and poured into a 100-ml graduated cylinder. The bulk volume V_b and the tapped volume V_t were determined by a tap density apparatus (Erweka SVM 12, Erweka GmbH, Germany) and used to calculate the bulk density d and the tapped density D . Then, the Carr index (or Compressibility Index, CI%) values were calculated as follows:

$$CI = 100 \frac{(D - d)}{D} \%$$

Scanning Electron Microscopy

The morphology of the granules was examined using scanning electron microscopy (SEM); ZEISS EVO Series EVO 50 (Carl Zeiss International, Germany); the samples were previously sputter-coated with gold.

Differential Scanning Calorimetry (DSC)

Thermal properties of powders were investigated using a Perkin-Elmer DSC-7 differential scanning calorimeter/TAC-7 thermal analysis controller with an intracooler-2 cooling system (Perkin-Elmer Instruments, Waltham, MA, USA). About 3–5 mg of the product was placed in perforated aluminium-sealed 50- μL pans and the heat runs for each sample was set from 30°C to 150°C at $10^\circ\text{C}/\text{min}$, under an inert environment using nitrogen.

Powder X-ray Diffraction (PXRD)

PXRD diffractograms of drug granules were recorded using a Panalytical Xpert Pro Diffractometer (PANalytical, JB Eindhoven, Netherlands) with a Copper line as the source of radiation. Standard runs using a 40 kV voltage, a 40 mA current, and a scanning rate of $0.02^\circ \text{min}^{-1}$ over a 2θ range of $3^\circ\text{--}40^\circ$ were used.

Particle Size of Drug in Granules

The average diameter of drug in granules was recorded by Zetasizer (Nano ZS, Malvern Instruments, Malvern UK). Since the granules have water soluble ingredients, except drug, water was selected as dispersant. A small amount of Nonidet P40 was added in water as wetting agent. The granules were dispersed uniformly in dispersant and suitably diluted to measure the particle size.

In-vitro Dissolution Studies

A USP dissolution apparatus (Model: 2100C, Distek Dissolution system, New Zealand) type II (paddle method) with a paddle operating at 50 rpm was used for dissolution studies. Comparative dissolution profiles were ascertained using 0.1N HCl containing 0.25% (w/v) Tween 80. The volume and temperature of the dissolution



medium was 1000 mL and $37\pm 0.5^{\circ}\text{C}$, respectively. Samples were withdrawn at predetermined time intervals, filtered in-line and the amount of drug dissolved at each sampling time point was monitored at a UV wavelength of 342 nm.

RESULTS AND DISCUSSION

Morphological and Technological Properties

The particle size distribution of the granules prepared by either IF and DF techniques have a low amount of fine powder (size $< 106\mu\text{m}$) and big lumps (size $> 850\mu\text{m}$). The particle size distribution of the DF granules was narrow; the prevalent size of DF granules is in the range 180–400 μm , while IF granules have coarser particle size (main fraction is 425–710 μm). The narrow granule size distribution of DF granules indicates uniform distribution of solid dispersion carrier/binder throughout the mass as compared to IF granules.

Granule formation and growth have been described by either a distribution mechanism or an immersion mechanism.^{6,7} In the nucleation phase, the tendency for coalescence between initial particles, or between an initial particle and nuclei will be larger than the tendency for coalescence between two nuclei as the potential for granule growth is inversely proportional to the size of the particle granules.^{8,9} The nucleation phase, therefore, is characterized by the disappearance of fines. In IF, the nucleation phase might be very short. This is because the solid particles become suddenly wetted when the melting point of the binder is reached, contrary to the more gradual wetting obtained by atomized binder liquid upon a solid material (DF). The sudden wetting might lead to a formation of large, loose granules within the first minute after melting. However the mechanical forces acting in the process ensure breakage of loose granules to facilitate coalescence of nuclei by distribution mechanism IF. In IF, the predominant granule mechanism is controlled by distribution mechanism that leads to denser nuclei formation.^{10,11} In DF, the predominant granule mechanism is controlled by the surface deformability of

the granules and consequently by the immersion mechanism.

Table 1 reports the yields and the physical properties of the four batches of granules; the yield was comparable for both the process. The DF samples showed bulk and tapped densities slighter lower than IF granules and lower Carr's index; as the Carr's index is dependent upon size, size distribution and shape of the granules (regularly shaped particles have better flow properties than irregularly shaped ones, while the decreasing of the particle size in general corresponds to lower flowability), the results suggested that in our case the regular spherical shape of DF more affected the flowability than granule size. In any case, all IF and DF granules possessed Carr's index < 10 , indicating excellent flowability.

SEM analysis showed that the granulation technique had a strong influence on the morphology of the granules. No drug crystals were observed on the surface of the DF agglomerates, suggesting that the drug was likely dispersed within matrix. Both IF and DF granules were quite irregular in shape (Fig. 1A and 1B) and appeared quite porous. However the DF granules possessed a more homogenous structure. The difference in morphology can be correlated to different granulation mechanism.

Solid state characterization of granules

Differential Scanning Calorimetry (DSC)

In order to understand the type of system LMF forms with Poloxamer 188, binary mixtures of LMF:carrier at different ratios were prepared. The following % w/w drug in binary mixtures was included – from 100, 70, 50, 30, 20, 15, 10 and 0.

Figure 2 shows DSC curves for LMF:poloxamer binary mixtures. The melting point of LMF is 133°C . Samples mixed with poloxamer exhibited endothermic DSC transitions attributed to crystalline drug, however, the melting temperature ranges decreased as the drug concentration in these binary mixtures decreased.

Table 1: Technological properties of granules

Technique	BD (g/cc)	TD (g/cc)	Carr's index	Yield (%)
DF	0.41	0.49	16.3	96
IF	0.47	0.55	14.5	98

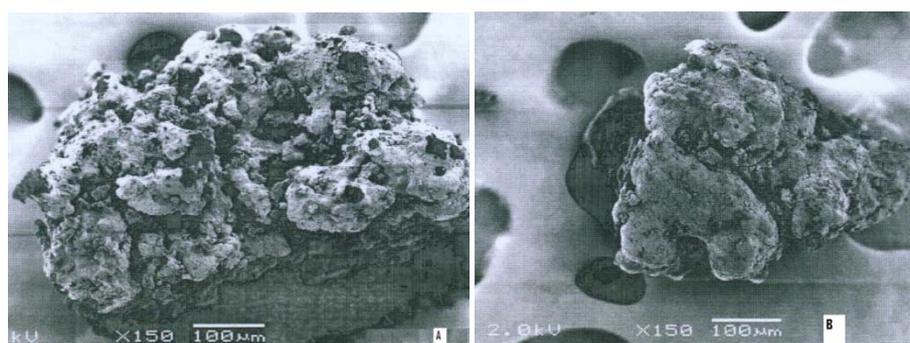


Figure 1: Scanning electron microscopy images of: (A) DF granules (B) IF granules.

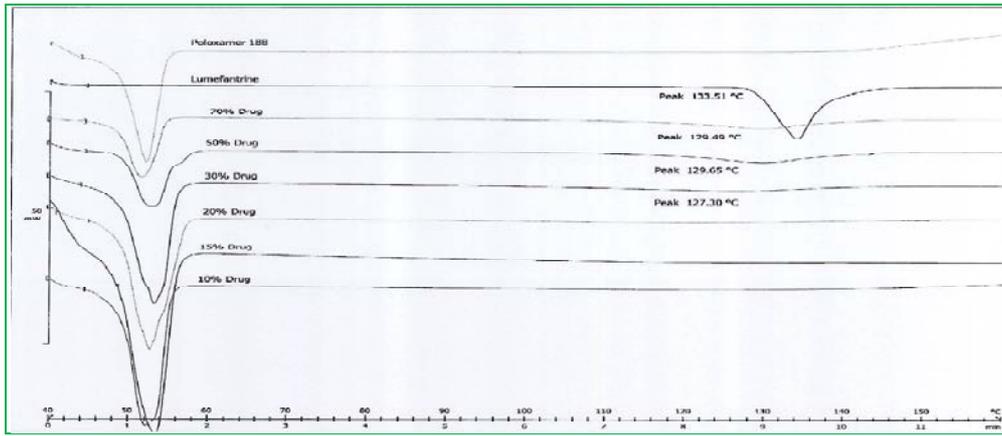


Figure 2: Differential scanning calorimetry curves of lumefantrine, Poloxamer 188 and binary mixtures of lumefantrine/ Poloxamer 188.

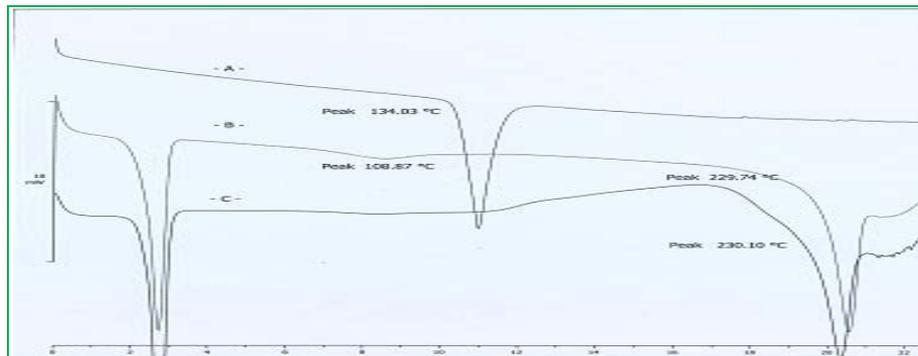


Figure 3: Differential scanning calorimetry curves of lumefantrine (A), DF granules (B) and placebo (C).

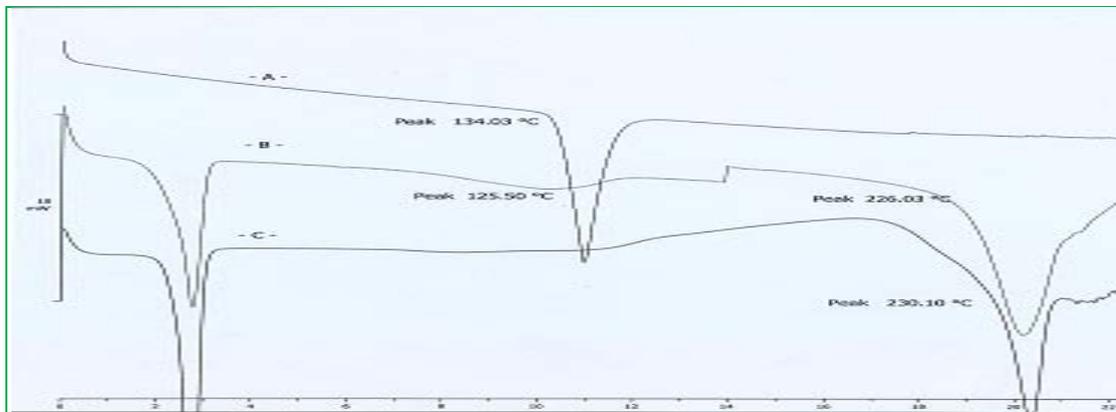


Figure 4: Differential scanning calorimetry curves of lumefantrine (A), IF granules (B) and placebo (C).

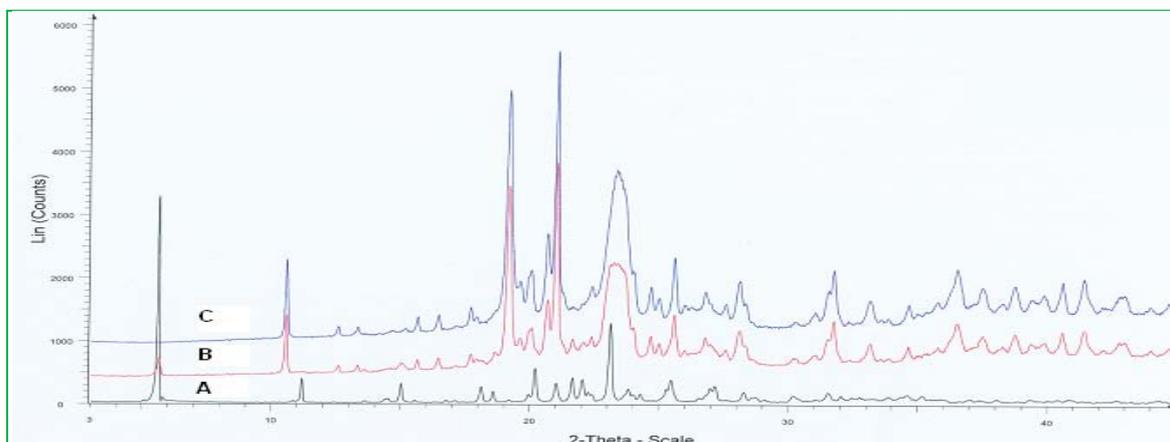


Figure 5: X-ray diffraction patterns of: lumefantrine (A), DF granules (B), and placebo (C).

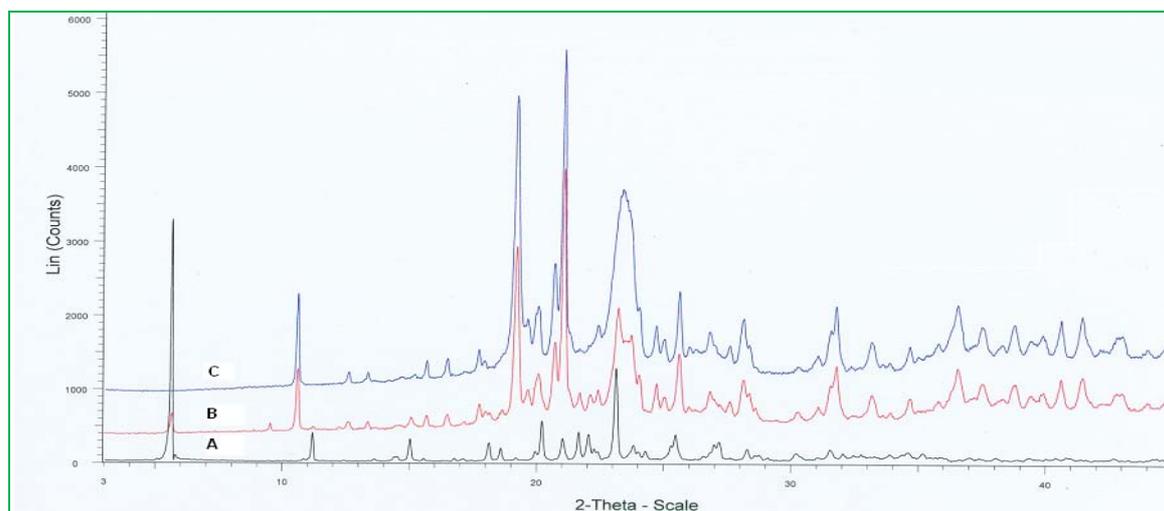


Figure 6: X-ray diffraction patterns of: lumefantrine (A), IF granules (B), and placebo (C).

The DSC curves of the samples containing 30–70% of LMF show two endothermic peaks. The first peak reflects the melting of poloxamer, while the second peak is acknowledged as the fusion of the drug. The absence of LMF fusion peak in poloxamer 188-rich samples (LMF content, 20%) may be a consequence of formation of monotectic mixture or spreading of fine crystal form of the drug into the molten carrier.¹²

Figures 3 and 4 report the DSC curves for pure LMF, DF granules, IF granules and respective placebo. The first endothermic peak represents the melting of carrier. In DF, the granules show a large endothermic event at 109°C attributed to melting of LMF followed by large endothermic event at 227°C consistent with thermal decomposition of lactose. In IF, however, the melting of LMF appears at 125°C. A significant decrease in melting point of LMF was observed in DF granules as compared to IF granules indicating enhanced interaction of drug and carrier in DF technique. The decreased melting temperature range of LMF in granules indicates spreading of fine crystal form of the drug into the molten carrier.

XRD

IF granules and DF granules were also subjected to X-ray diffraction analysis. The diffraction patterns of pure drug, placebos and DF granules and IF granules are depicted in Figures 5 and 6 respectively. Diffractograms of pure LMF clearly show the drug is crystalline, as demonstrated by numerous sharp and intense peaks. The diffractogram of granules indicates characteristic drug peaks, even if the intensities are attenuated due to the lower drug content. From PXRD characterization studies, it appeared that the crystal form of LMF was unchanged.

Particle Size of LMF in Granules

For drugs whose GI absorption is rate limited by dissolution, reduction of the particle size generally increases the rate of absorption and/or oral bioavailability. Figure 7 depicts particle size of LMF in pure LMF, IF granules and DF granules as measured by Zetasizer. The average diameter of LMF particle was

observed to be 40, 37 and 14 micron in pure LMF, IF granules and DF granules respectively. No significant change was observed in the particle size of LMF in IF granules. In DF, however, particle size of drug particle is significantly lower. The significant reduction in particle size of LMF in DF granules may be consequence of rapid cooling of molten mass on atomization resulting in increased surface area.

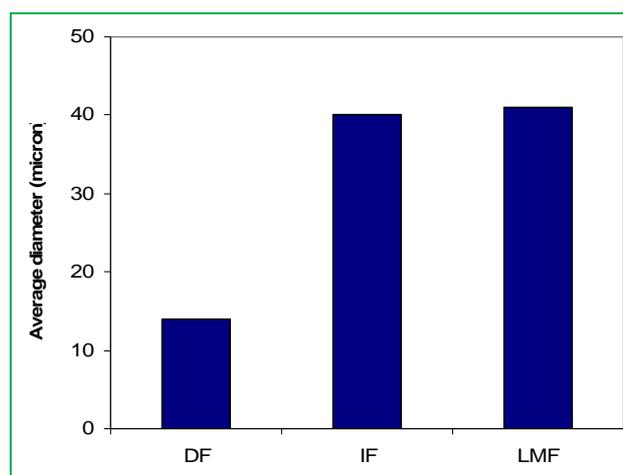


Figure 7: Particle size of LMF in pure lumefantrine (LMF), IF granules and DF granules.

In-vitro Dissolution Study

Dissolution profiles were obtained with pure lumefantrine, physical mixtures of the compounds, and agglomerates. It is seen that pure lumefantrine has a markedly lower dissolution rate compared with the dissolution rates obtained with DF (Fig. 8) and IF (Fig. 9) granules and physical mixtures indicating that the solid dispersion enhances the dissolution rate. The dissolution rates obtained from granules are higher than to the dissolution rates obtained from the corresponding physical mixtures. The higher dissolution of LMF from DF granules may be consequence of increased surface area of LMF in granules, intimate contact of carrier and LMF and uniform distribution of solid dispersion.¹³

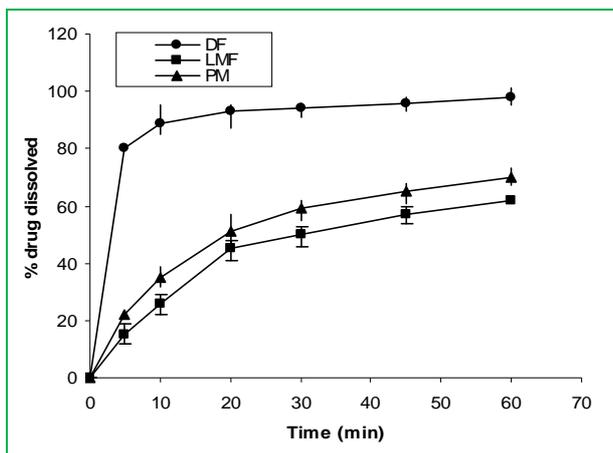


Figure 8: In vitro dissolution profiles of DF granules in comparison with physical mixtures and pure lumefantrine.

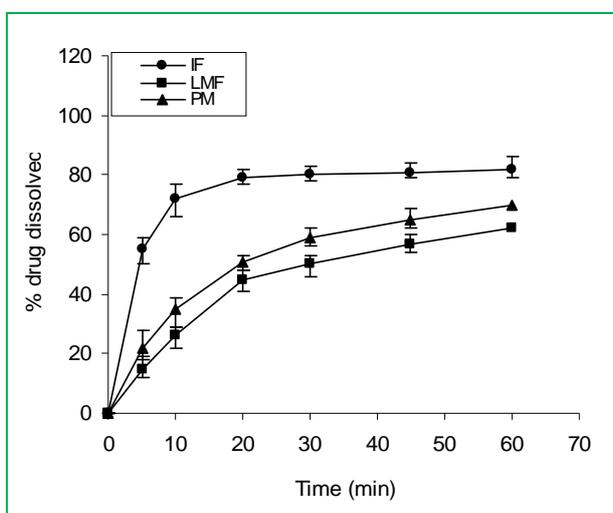


Figure 9: In vitro dissolution profiles of IF granules in comparison with physical mixtures and pure lumefantrine.

CONCLUSION

The results of this research show that solid dispersion manufacturing of pharmaceutical powders can be performed by 'in-situ fusion' and 'dispersed fusion' technique in fluidized bed granulators. The drug particle size in agglomerates was significantly reduced in DF technique indicating strong impact of technique. Due to the different granular growth mechanism, the utilization of a different technique has strong impact on the particle size distribution of the granules and on their morphology. A narrow size distribution of granules indicates fine distribution of carrier in granules. On the contrary, the technique effects on others technological properties are little, as all the granules possess low friability and excellent flowability. DSC thermogram shows significant decrease in drug melting range in DF as compared to IF technique. However the XRD

characteristic was found to be practically independent of the technique. Both IF and DF show increase of the drug dissolution rate however the increase is significantly more in DF. This evaluation becomes important as it indicates a superior solid dispersion 'possible to scale up' process using minor modification in commercial equipments.

REFERENCES

1. Craig DQM. The mechanisms of drug release from solid dispersions in water-soluble polymers. *Int J Pharm.* 231, 2002, 131-144
2. Serajuddin ATM. Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems, and recent breakthroughs. *J Pharm Sci.* 88, 1999, 1058-1066.
3. Breitenbach J. Melt extrusion: from process to drug delivery technology. *Eur J Pharm Biopharm.* 54, 2002, 107-117.
4. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. *Eur J Pharm Biopharm.* 50, 2000, 47-60.
5. Ford JL, Rubinstein MH. Formulation and ageing of tablets prepared from indomethacin-polyethylene glycol 6000 solid dispersions. *Pharm Acta Helv.* 55, 1980, 1-7.
6. Schæfer T, Mathiesen C. Melt pelletization in a high shear mixer. IX. Effects of binder particle size. *Int J Pharm.* 139, 1996, 139-148.
7. Schæfer T, Johnsen D, Johansen A. Effects of powder particle size and binder viscosity on intergranular and intragranular particle size heterogeneity during high shear granulation. *Eur J Pharm Sci.* 21, 2004, 525-531.
8. Ennis BJ, Tardos GI, Pfeffer R. A microlevel-based characterization of transport phenomena. *Powder Technol.* 65, 1991, 257-272.
9. Tardos GI, Khan MI, Mort PR. Critical parameters and limiting conditions in binder granulation of fine powders. *Powder Technology.* 94, 1997, 243-250.
10. Abberger T. Influence of binder properties, method of addition, powder type and operating conditions on fluid-bed melt granulation and resulting tablet properties. *Pharmazie.* 56, 2001, 949-952.
11. Vilhelmsen T, Eliassen H, Schæfer T. Effect of a melt agglomeration process on granules containing solid dispersions. *Int J Pharm* 303, 2005, 132-142.
12. Naima Z, Siro T, Manuel GDJ, Chanta C, Rene C, Jerome D. Interactions between carbamazepine and polyethylene glycol (PEG) 6000: characterisations of the physical, solid dispersed and eutectic mixtures. *Eur J Pharm Sci.* 12, 2001, 395-404.
13. Seo A, Holm P, Kristensen HG, Schæfer T. The preparation of granules containing solid dispersions of diazepam by melt agglomeration in a high shear mixer. *Int J Pharm.* 259, 2003, 161-171.

