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Effect of the melt granulation technique on the dissolution characteristics of griseofulvin

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Abstract

This work describes a melt granulation technique to improve the dissolution characteristics of a poorly water-soluble drug, griseofulvin. Melt granulation technique is a process by which pharmaceutical powders are efficiently agglomerated by a meltable binder. The advantage of this technique compared to a conventional granulation is that no water or organic solvents is needed. Because there is no drying step, the process is less time consuming and uses less energy than wet granulation. Granules were prepared in a lab scale high shear mixer, using a jacket temperature of 60 °C and an impeller speed of approximately 20,000 rpm. The effect of drug loading (2.5/5%), binder (PEG 3350/Gelucire 44/14), filler (starch/lactose), and HPMC on the dissolution of griseofulvin was investigated using a half two level-four factor factorial design. The granules were characterized using powder XRD, DSC and SEM techniques. A significant enhancement in the in vitro dissolution profiles of the granules was observed compared to the pure drug and drug excipient physical mixtures. The factorial design results indicated that higher drug loading and the presence of HPMC reduced the extent of dissolution of the drug, whereas, the presence of starch enhanced the dissolution rate. XRD data confirmed crystalline drug in formulation matrices. DSC results indicated monotectic mixtures of griseofulvin with PEG in the granulated formulations. In conclusion, the results of this work suggest that melt granulation is a useful technique to enhance the dissolution rate of poorly water-soluble drugs, such as, griseofulvin.
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Keywords: Griseofulvin; Melt granulation; PEG 3350; Gelucire 44/14; HPMC; Dissolution enhancement

1. Introduction

A melt granulation technique is a process by which pharmaceutical powders can be efficiently agglomerated by the use of a molten binder at relatively low temperature (50–80 °C) (Perissutti et al., 2003). This process can be used for the preparation of sustained released dosage forms by using lipophilic binders, such as glycerol monostearate (Thies and Kleinebudde, 1999), a combination of a hydrophobic material such as a starch derivative (Zhou et al., 1996) and stearic acid (Voinovich et al., 2000) or a combination of hydroxypropyl methyl cellulose and hydrophobic polymers (Ochoa et al., 2005; Tiwari et al., 2003; Zhang and Schwartz, 2003). It also can be used to prepare fast release formulations by utilizing water-soluble binders, such as PEG (Voinovich et al., 1999; Hengh et al., 2000; Rodriguez et al., 2002). PEG has been widely used in melt granulation because of its favorable solution properties, low-melting point, rapid solidification rate, low toxicity, and low cost. Another commonly used binder is Gelucire®, which is a mixture of glycerides and fatty acid esters of PEGs. Gelucire® has been shown to further increase the dissolution rate of poorly water-soluble drugs, attributed to the surface active and self-emulsifying properties of this excipient (Dordunoo et al., 1991; Damian et al., 2000). In recent years, the interest in melt granulation has increased due to the advantage of this technique over traditional wet granulation, that is, elimination of water or organic solvents from the melt granulation process. This negates any risk originating from residual solvents; moreover, in melt granulation the drying step is not necessary, thus the process is less consuming in terms of time and energy as compared to wet granulation (Passerini et al., 2002). The apparatus of choice for melt granulation are the high shear mixers, where the product temperature is raised above the

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melting point of the binder either by using a heating jacket or via the heat of friction generated by the impeller blades, when the impeller speed is high enough (Schaefer, 1997).

In recent years, melt granulation technique has been successfully employed to improve the dissolution rate of poorly soluble compounds. Passerini et al. (2002) has proved that melt granulation can be used to enhance the in vitro dissolution rate of ibuprofen, employing poloxamer 188 as a melting binder.

The objective of this work was to evaluate the feasibility of the melt granulation technique to improve the dissolution characteristics of a poorly water-soluble drug, griseofulvin. Griseofulvin is an antifungal agent and is practically insoluble in water. Several literature reports reveal that solid dispersions have increased the dissolution rate and gastrointestinal absorption of griseofulvin (Saito et al., 2002; Lo and Law, 1996; Chiou and Riegelman, 1969; Flego et al., 1988). This work is focused primarily on evaluating the melt granulation technique on a lab scale (10–15 g) for improving the dissolution characteristics of griseofulvin. In addition, it also evaluates the use of a half two level-four factor factorial design to study the effect of drug loading (2.5/5%), filler (starch/lactose) and HPMC (as a crystallization inhibitor) on the dissolution rate. The use of factorial design along with the small batch size would serve as a powerful screening tool to improve the dissolution characteristics of poorly soluble molecules in early drug development. The effect of various excipients on the dissolution profile of the compound can thus be rapidly evaluated using limited material quantities. The in vitro release of the drug from the granules was investigated and compared to that of the pure drug and drug excipient physical mixtures. 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.

2. Materials and methods

2.1. Materials

Griseofulvin reagent grade was obtained from Acros Organics (Fairlawn, NJ); polyethylene glycol (PEG) 3350 reagent grade was purchased from Dow Chemical Company (Nitro, WV); starch 1500 was obtained from Colorcon Inc. (Westpoint, PA); lactose monohydrate was obtained from Foremost Farma (Rothschild, WI); Gelucire 44/14 was received from Gattefosse Corporation (Westwood, NJ) and HPMC 5 was obtained from Dow Chemical Company (Midland, MI). All organic solvents were high-performance liquid chromatography (HPLC) grade. All other chemicals were reagent grade.

2.2. Methods

2.2.1. Half-fractional two level-four factor factorial design

A 2^4 factorial design was used to study the effect of drug loading and other excipients on the release characteristics of griseofulvin. A fraction of the full factorial design (FFD) was used to determine the main effects and their interactions. The half fractional 2^4 factorial design allowed the additions of experiments after preliminary data evaluation to further interpret the interrelationship of the factors. The higher order interactions were ignored and the values determined from them attributed to the random variation of the experimental system. Thus, the fractional FFDs reduced the number of experiments in a systematic manner.

Table 1
The lower and upper levels of independent variables

Independent variables	Lowest level (−1)	Highest level (+1)
Drug content (X_1)	2.50%	5.00%
Filler (X_2)	Starch	Lactose
Binder (X_3)	PEG 3350	Gelucire 44/14
HPMC (X_4)	Without	With

The concentration of drug (X_1), filler (X_2), binder (X_3) and HPMC (X_4) were used as independent variables and the drug released at 15 min was used as the dependent variable. In this two level four-factor half-fractional factorial experimental design, the confounding rule was: 0 = 1234, 1 = 234, 2 = 134, 3 = 124, 4 = 123, 12 = 34, 13 = 24 and 14 = 23. The resolution was 4. The lower and upper levels of independent variables used are as listed in Table 1. These four independent variables are major factors that were expected to have pronounced effects on the release of the drug from the granules.

2.2.2. Preparation of the granules, physical mixtures and placebos

Eight formulations were prepared according to the half-fractional two level four factor factorial design. The formulation compositions are as shown in Table 2. The granules were prepared in a laboratory scale jacketed high shear mixer connected to a recirculating water bath to maintain constant temperature. Griseofulvin was mixed with either lactose or starch for 5 min at approximately 20,000 rpm. For granulations containing HPMC, the HPMC was added along with lactose or starch. The temperature was then increased to 60 °C and maintained at that temperature for the entire granulation. The binder, PEG 3350 or Gelucire 44/14, was then added to the dry blend and mixed until a suitable granulation was obtained. At the end of the granulation process, the granules were allowed to cool at room temperature and then passed through a 30-mesh sieve.

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 vortexed (Vortex Genie®, Scientific Industries) for 2 min to give a uniform blend. In case of physical mixtures containing Gelucire 44/14, mixing had to be done in small quantities due to the physical characteristics of the excipient. 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 griseofulvin.

Preparation of capsules. An accurate amount of sample consisting of the granules, physical mixture or drug was weighed and transferred into a size two empty gelatin capsule.

Table 2
Formulations based on 2^4 factorial design

Granulations	Drug (X_1)	Filler (X_2)	Binder[a] (X_3)	HPMC[b] (X_4)
1	2.5% (−1)	Starch 77.5% (−1)	PEG 3350 (−1)	Without (−1)
2	5.0% (1)	Starch 70.0% (−1)	PEG 3350 (−1)	With (1)
3	2.5% (−1)	Lactose 72.5% (1)	PEG 3350 (−1)	With (1)
4	5.0% (1)	Lactose 75.0% (1)	PEG 3350 (−1)	Without (−1)
5	2.5% (−1)	Starch 72.5% (−1)	Gelucire 44/14 (1)	With (1)
6	5.0% (1)	Starch 75.0% (−1)	Gelucire 44/14 (1)	Without (−1)
7	2.5% (−1)	Lactose 77.5% (1)	Gelucire 44/14 (1)	Without (−1)
8	5.0% (1)	Lactose 70.0% (1)	Gelucire 44/14 (1)	With (1)

[a] Binders, PEG 3350 and Gelucire 44/14 were used at a concentration of 20%.
[b] HPMC concentration used was 5%. All concentrations are expressed on a w/w basis.

2.2.3. *In vitro dissolution studies of the granules*

The dissolution test was performed in a USP dissolution apparatus two (Vankel® VK 700) using paddles operating at 50 rpm. The dissolution medium consisted of 900 ml of 0.05% SLS maintained at 37 ± 0.1 °C. Five millilitres aliquot samples were withdrawn at different time points (5, 15, 30 and 60 min), filtered (Acrodisc®, 0.45 μm) and analyzed by reversed-phase HPLC using the conditions described in Section 2.2.5. The dissolution data analysis was performed by SAS® 8.2 software (SAS Institute Inc.).

2.2.4. *Drug content determination*

Weighed accurately about 300 mg of the granules or physical mixtures into a 25 ml volumetric flask and added 20 ml of methanol. The flasks were sonicated in a bath sonicator (Branson sonicator) for 30 min. The samples were allowed to cool to

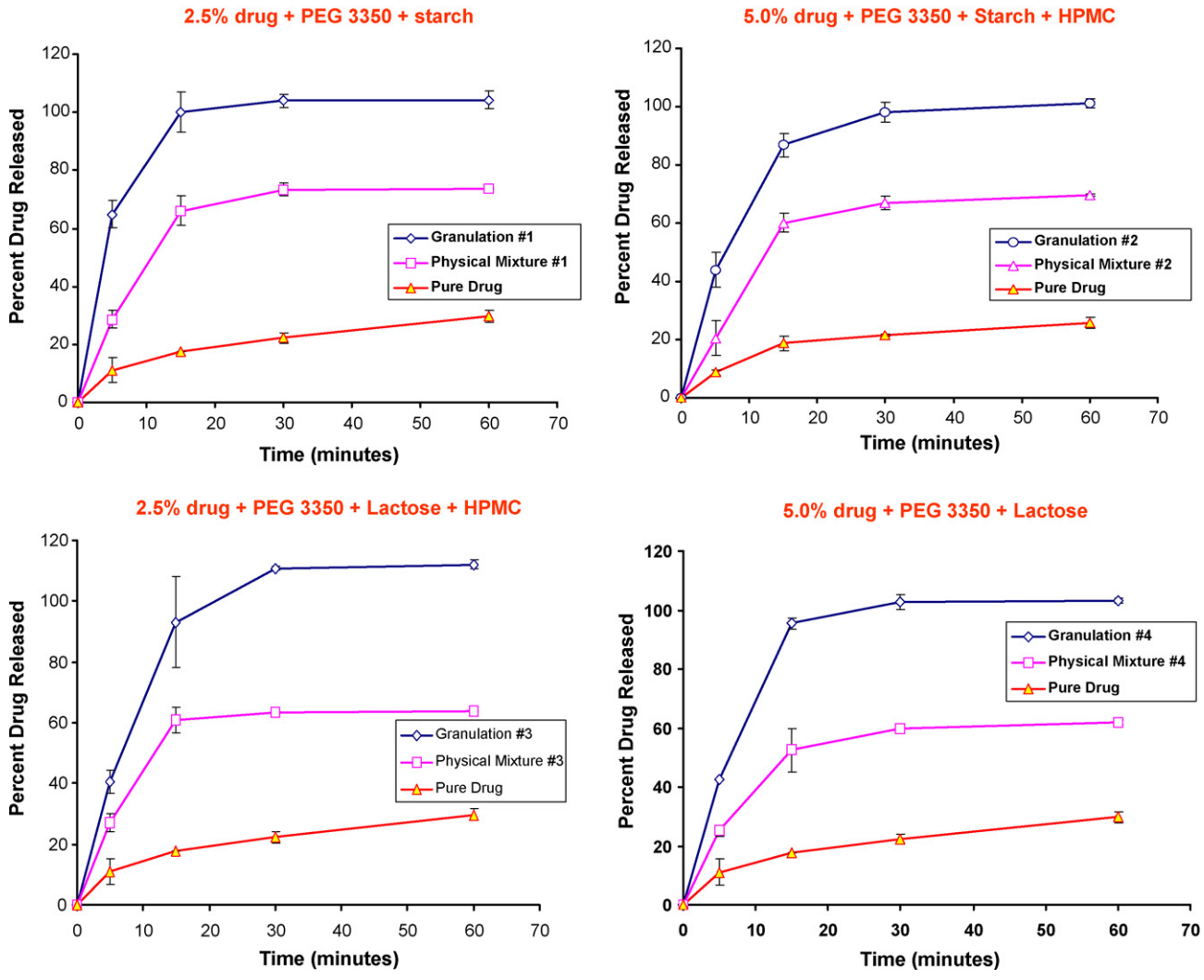

Fig. 1. In vitro dissolution profiles of PEG 3350 granulates in comparison with physical mixtures and pure griseofulvin.

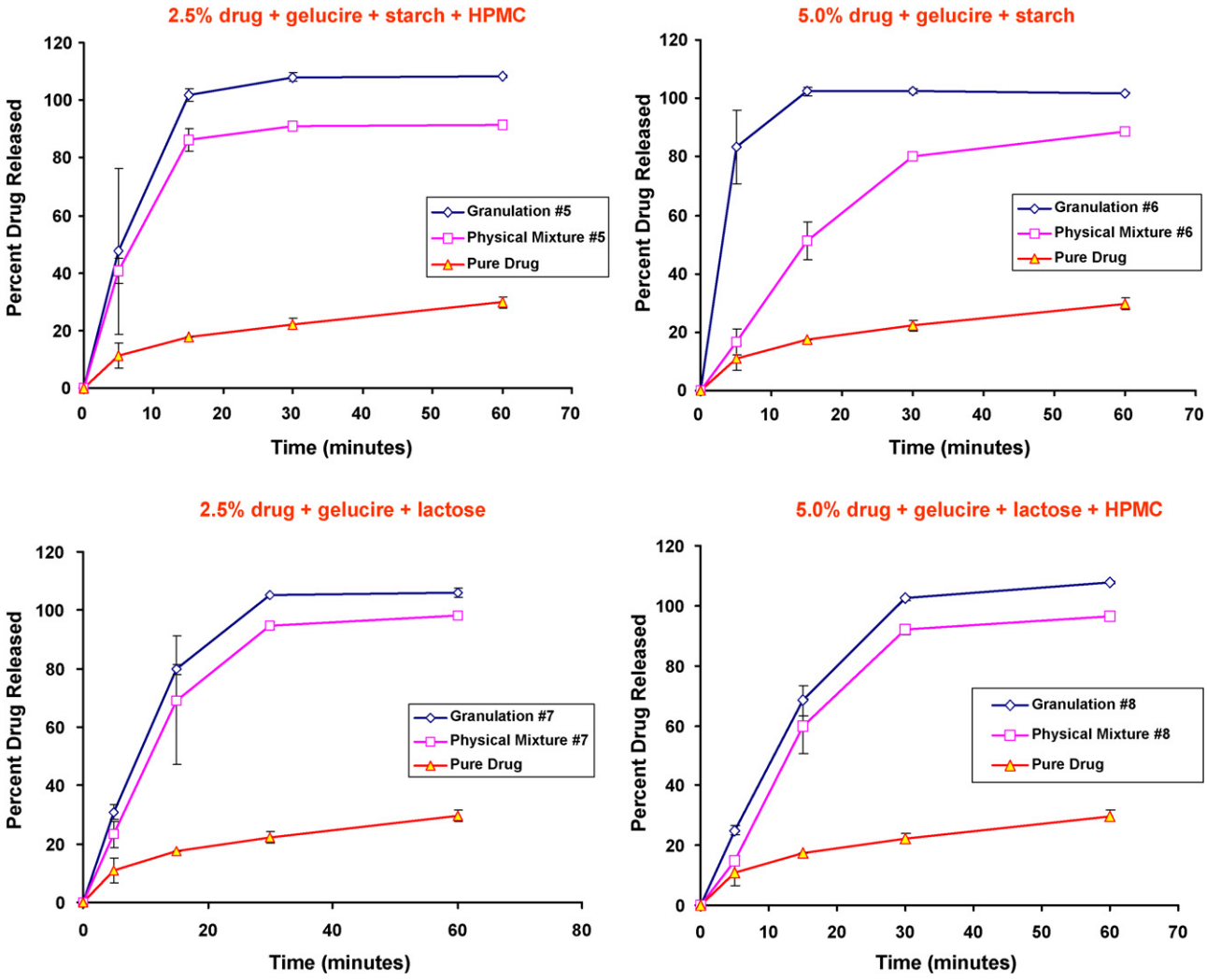

Fig. 2. In vitro dissolution profiles of Gelucire 44/14 granulates in comparison with physical mixtures and pure griseofulvin.

room temperature, diluted to volume and then filtered through a 0.45 μm nylon syringe filter. Samples were appropriately diluted and analyzed for drug content by HPLC.

2.2.5. Drug analysis

Chromatographic analyses were performed on a Hewlett Packard Series 1050 equipped with an Applied Biosystems 1000s Diode Array Detector and software. Griseofulvin was analyzed at 292 nm by using an Alltima phenyl column (Alltech, 5 μm, 250 mm × 4.6 mm) at ambient temperature. The mobile phase, a mixture of acetonitrile (60%) and 0.1% TFA (40%) was pumped at 1 ml/min. The injection volume used was 5 μl. Standard curves for griseofulvin was measured over a range of 0–500 μg/ml and was found to be linear.

2.2.6. Solid state analysis

Thermal analyses of the drug, physical mixtures and granules were performed on a DSC with autosampler Model 2920 (TA, Instruments). Samples were accurately weighed into aluminum pans and thermograms obtained at a heating rate of 5 °C/min over a temperature range of 25–300 °C. Universal Analysis software (TA, Instruments) was used for the analysis. Furthermore, samples were studied by means of XRD technique using a Siemens D5000 X-ray diffractometer with Cu Kα radiation (λ = 1.5418 Å). The scanning angle ranged from 4° to 40° of 2θ, steps were 0.02° of 2θ and the counting time was 3 s/step. The current used was 40 mA and the voltage of 50 kV.

2.2.7. Scanning electron microscopy (SEM)

Electron micrographs of selected granulations were taken by a SEM using a FEI XL30 FEG ESEM. Samples were sputter coated with Au/Pd for 60 s at 45 mA and 50 m Torr using a Denton Desk II sputter coater. The samples were subsequently imaged in high vacuum mode.

3. Results and discussion

3.1. In vitro dissolution of the granules

The in vitro dissolution profiles of the granules prepared by melt granulation were compared with that of pure drug and a physical mixture. The dissolution rate of pure griseofulvin was

very low, with the amount of drug dissolved in 15 min being less than 20%. The in vitro dissolution rate of all prepared granules was higher as compared to the pure drug and its physical mixtures. In the case of granules containing PEG 3350 as the binder, a large enhancement was observed in the dissolution rate relative to both, the physical mixture and the drug alone. In comparison, the Gelucire 44/14 granules showed a significant increase in the dissolution rate as compared to the drug, but only a slight enhancement was observed compared to physical mixtures. The increase in dissolution rate could be attributed to the higher hydrophilic character of the system due to the presence of water-soluble carriers and that part of the drug dissolves in the binder. These results show that melt granulation can be a useful technique to improve the dissolution rate of griseofulvin.

The effects of each component (drug concentration X_1; filler X_2; binder X_3; HPMC X_4) on the dissolution profiles of griseofulvin were studied by a half fractional 2^4 factorial design (Table 2). The release profiles of granules are shown in Figs. 1 and 2. The values of drug released from granules at 15 min (Y) are listed in Table 3. These data were analyzed using SAS software and the main factor effects of the independent variables on drug release are shown in Fig. 3. The estimated coefficients of Y model were tested by t-test and are listed in Table 4.

Fractional factorial design is based on the *sparsity of effects* principle. This principle states, "The responses are driven largely by a limited number of main effects and lower-order interactions in most of the systems, and that higher-order interactions usually are relatively unimportant" (Neter et al., 1996). In the half-fractional factorial design, the main effects confound with the third order interactions. Based on the *sparsity of effects* principle, main effects (drug concentration, X_1; filler, X_2; binder, X_3, and HPMC, X_4) are more important than the third order interactions ($X_1X_2X_3$, $X_1X_2X_4$, $X_1X_3X_4$ and $X_2X_3X_4$). In this experiment, only main effects were considered and the third and fourth order interactions were ignored. As can been seen, except for the p-value of binder (X_3), those of X_1 (drug concentration), X_2 (filler), and X_4 (HPMC) are 0.0160, 0.0005 and 0.0530 (less than 0.05), respectively, suggesting that drug concentration, filler, and HPMC have significant effects on the release rate of the drug. The dissolution rate of griseofulvin (Y) was reduced by increasing drug content (X_1) from 2.5% to 5.0% (w/w). The

Table 3
Percent drug released from granulation formulations at 15 min

Granulations	Experiments	X_1	X_2	X_3	X_4	Y
1	1	−1	−1	−1	−1	99.97
	2	−1	−1	−1	−1	95.36
	3	−1	−1	−1	−1	104.92
2	4	1	−1	−1	1	102.90
	5	1	−1	−1	1	100.76
	6	1	−1	−1	1	101.63
3	7	−1	1	−1	1	102.93
	8	−1	1	−1	1	95.43
	9	−1	1	−1	1	81.11
4	10	1	1	−1	−1	79.30
	11	1	1	−1	−1	83.98
	12	1	1	−1	−1	75.95
5	13	−1	−1	1	1	85.26
	14	−1	−1	1	1	67.38
	15	−1	−1	1	1	86.30
6	16	1	−1	1	−1	101.75
	17	1	−1	1	−1	101.36
	18	1	−1	1	−1	104.08
7	19	−1	1	1	−1	95.91
	20	−1	1	1	−1	98.17
	21	−1	1	1	−1	92.09
8	22	1	1	1	1	61.56
	23	1	1	1	1	66.98
	24	1	1	1	1	76.63

Table 4
Estimated coefficients of Y model by t-test

Effect	Estimate	S.E.	t-Ratio	p-Value
X_1	−7.2317	2.6856	−2.6928	0.0160
X_2	−11.802	2.6856	−4.3944	0.0005
X_3	−3.9967	2.6856	−1.4882	0.1561
X_4	−8.6633	2.6856	−3.2258	0.0053
$X_1X_2 + \cdots$	2.6717	2.6856	0.99481	0.3346
$X_1X_3 + \cdots$	1.87	2.6856	0.69631	0.4962
$X_1X_4 + \cdots$	−16.21	2.6856	−6.0359	<0.0001

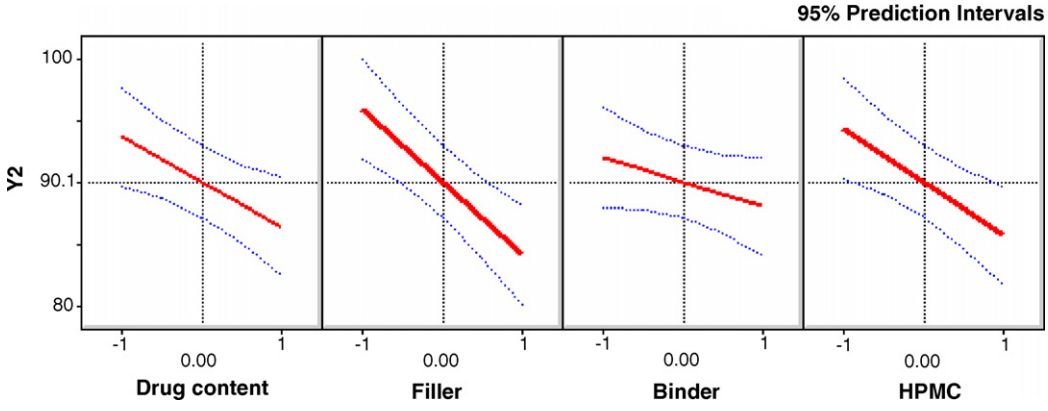

Fig. 3. Main effects of independent variables on the dissolution rate of griseofulvin.

dissolution rate (Y) was also reduced by changing the filler (X_2) from starch to lactose and in the presence of HPMC (X_4). If second order interactions were considered, then X_1X_2 confounds with X_3X_4, X_1X_3 confounds with X_2X_4, and X_1X_4 confounds with X_2X_3. To distinguish between these second order interactions, further experiments will be required and were not considered for this investigation.

Based on the results from the dissolution analysis, all further characterization was performed only on the PEG based formulations. Two formulations were considered for XRD, DSC and SEM, one with 2.5% drug loading (granulation 1) and the other with 5% drug loading (granulation 4).

3.2. Drug content analysis

Drug content analysis was done on all physical mixtures as well as granulation formulations in duplicate. All formulations had drug content values within the range of 95–105%.

3.3. Solid-state analysis of the granules

In order to understand the type of system griseofulvin forms with PEG 3350, binary mixtures of griseofulvin: PEG 3350 at different ratios were prepared. The following ratios were included – griseofulvin: PEG 3350 from 100:0, 80:20, 60:40, 50:50, 40:60, 20:80, 10:90 and 0:100. Physical mixtures were prepared by geometric mixing of drug with each excipient followed by vigorous vortex mixing. Fig. 4 shows DSC curves for each of these samples and also a thermal curve for griseoflvin only. The onset melting point of griseofulvin is 217.4 °C and its heat of fusion is 119.9 J/g for drug substance assumed to be 100% crystalline, within 3% of the heat of fusion (116.5 J/g) reported previously (Law et al., 2002). Samples mixed with PEG exhibited endothermic DSC transitions attributed to crystalline drug, however, the melting temperature ranges decreased as the drug concentration in these binary mixtures decreased. The literature reports griseofulvin forms monotectic systems with PEGs (Law et al., 2002). The first endothermic transition in sample thermal curves that include PEG is the melting event for excess PEG in these mixtures. Following PEG melting, the results show low energy thermal events at about 90 °C consistent with reports for glass transition events for amorphous griseofulvin (Nair et al., 2001; Kerc and Srcic, 1995). The data also indicate the glass transition events increase in size as the drug concentrations decrease. The thermal events above the glass transition events

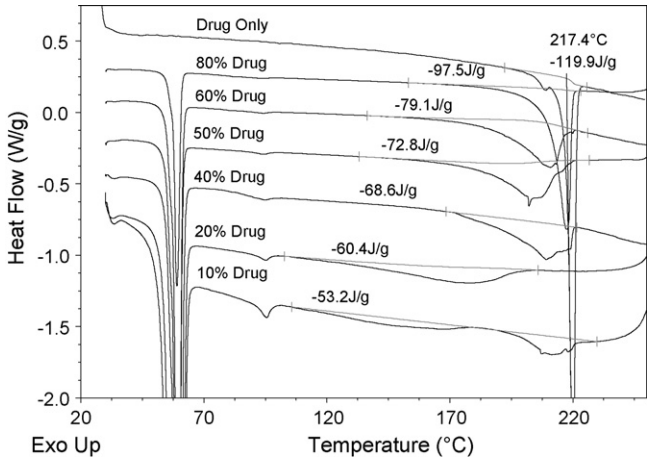

Fig. 4. Differential scanning calorimetry curves of: (a) 100:0, (b) 9:1, (c) 8:2, (d) 6:4, (e) 5:5, (f) 4:6, (g) 2:8 and (h) 0:100 PEG 3350/griseofulvin binary mixtures.

is monotectic melting of the griseofulvin-PEG where the melting transition is dramatically reduced as the drug concentration decreases (Kaur and Grant, 1980; Law et al., 2002).

Estimated enthalpies for the crystalline phases are based on the theoretical weight of the drug only in each mixture and would be equal to the heat of fusion of pure crystalline drug if the drug in each binary mixture was 100% crystalline. As can be seen, enthalpies for crystalline phases decrease as the drug concentration decreases, suggesting a decrease in crystallinity. The decrease in crystallinity for the different griseofulvin: PEG 3350 ratios are as listed in Table 5 and by difference the amorphous material present. The crystalline portions would be expected to produce PXRD patterns for its presence while the amorphous fraction produces a low energy DSC glass transition event that increases in size as the drug concentration decreases.

Vigorous physical mixing of the binary systems apparently produced some amorphous drug (T_g during DSC). It is hypothesized that vigorous mechanical mixing also amorphosized some of the low-melting PEG material which combined with drug to produce lower melting monotectic drug/PEG mixtures. Some thermal curves suggest there may also be some higher melting crystalline drug not incorporated into monotectic drug/PEG mixtures.

Fig. 5 reports the DSC curves for pure griseofulvin, granulation 1 prepared by melt granulation, corresponding physical mixture and placebo. A 2.0410 mg of griseofulvin shows a melt-

Table 5
Percent decrease in crystallinity for different griseofulvin:PEG 3350 ratios

Drug:PEG ratios	Drug load (%)	Drug weight (mg)	PEG weight (mg)	Actual (J/g)	Crystalline (%)	Decrease in crystallinity (%)
100:0	100.0			119.9	100	
80:20	80.0	3.712	0.950	97.5	81	19
60:40	60.0	2.701	1.800	79.1	66	34
50:50	50.0	1.878	1.878	72.8	61	39
40:60	40.0	1.872	2.810	68.6	57	43
20:80	20.0	0.951	3.800	60.4	50	50
10:90	10.0	0.410	3.690	53.2	44	56
0:100	0.0					

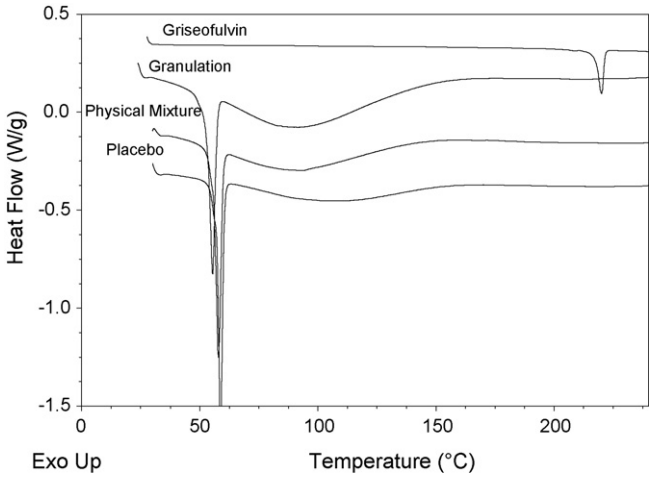

Fig. 5. Differential scanning calorimetry curves of griseofulvin, granulation 1, physical mixture 1 and placebo 1.

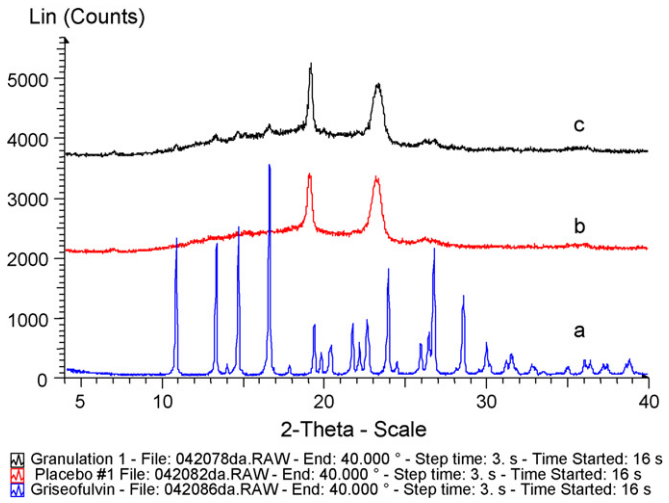

Fig. 7. X-ray diffraction patterns of: (a) griseofulvin, (b) placebo 1 and (c) granulation 1.

ing endotherm peak onset at 217.49 °C and produces 243.6 mJ of heat (figure not shown). The sample weight of granulation #1 was 7.882 mg. It was theoretically 2.5% drug, that is, this 7.882 mg of granulation should have contained 0.197 mg of drug. Based on the pure drug substance, 0.197 mg of crystalline material would produce a melting transition corresponding to 18 mJ or a melting peak that is roughly 13× smaller in peak area. The pure drug thermal curve in Fig. 6 shows a crystalline drug melting transition that would be the size of the melting endotherm if this granulation contained 100% crystalline drug. As can be seen, neither the granulation nor the physical mixture exhibited a melting event similar to crystalline drug only suggesting that higher temperature processing for the granulation and even high shear mixing only for the physical mixture converted griseofulvin into monotectic mixtures with PEG. The large broad endothermic event after melting of PEG for the placebo is attributed to loss of water from the starch, which overlaps with melting of monotectic drug: PEG at 2.5% drug load for both the granulation and physical mixture.

Fig. 6 shows the DSC curves for granulation 4 in comparison with that of drug, corresponding physical mixture and placebo. Granulation 4 contains lactose monohydrate in addition to drug and PEG 3350. After melting of PEG, the placebo shows a large endothermic event at 114 °C attributed to loss of water of crystallization from lactose monohydrate concurrent with crystallization of anhydrous lactose which subsequently melts at 215 °C. The final endothermic event is consistent with thermal decomposition after anhydrous lactose melts. The size of the melting endotherm for drug only is roughly the size that the drug peak would be if the granulation contained 100% crystalline drug. If drug were present in excess of a monotectic phase with PEG, its melting event would likely occur simultaneously with lactose melt and decomposition transitions and possibly not be detected. Consequently, thermal analysis does not provide insight into the phase composition of drug in granulation 4, however, it is assumed that processing conditions for granulation 4 would also produce monotectic drug: PEG mixtures.

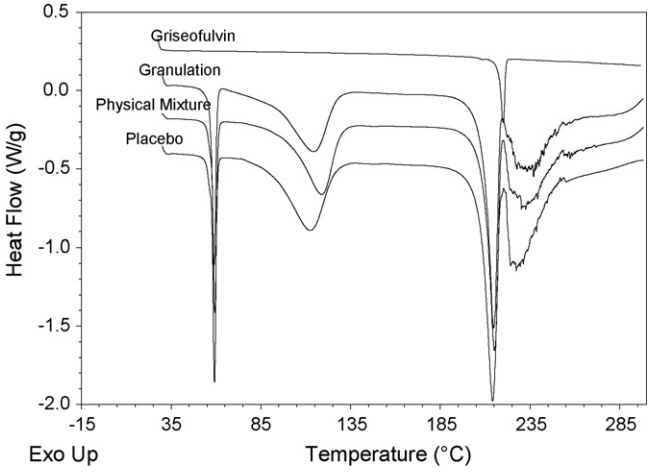

Fig. 6. Differential scanning calorimetry curves of griseofulvin, granulation 4, physical mixture 4 and placebo 4.

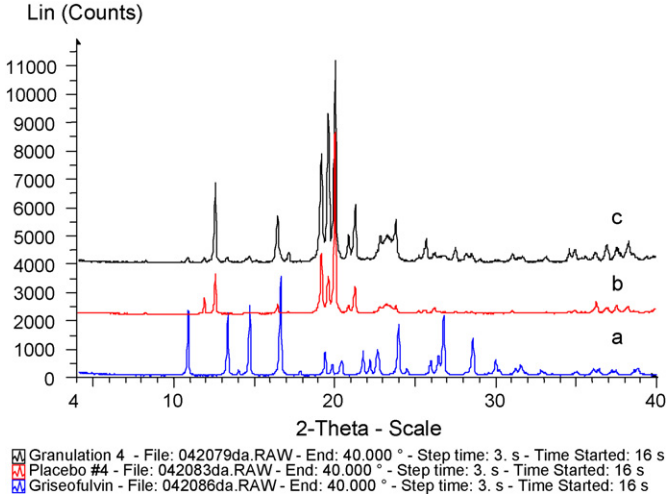

Fig. 8. X-ray diffraction patterns of: (a) griseofulvin, (b) placebo 4 and (c) granulation 4.

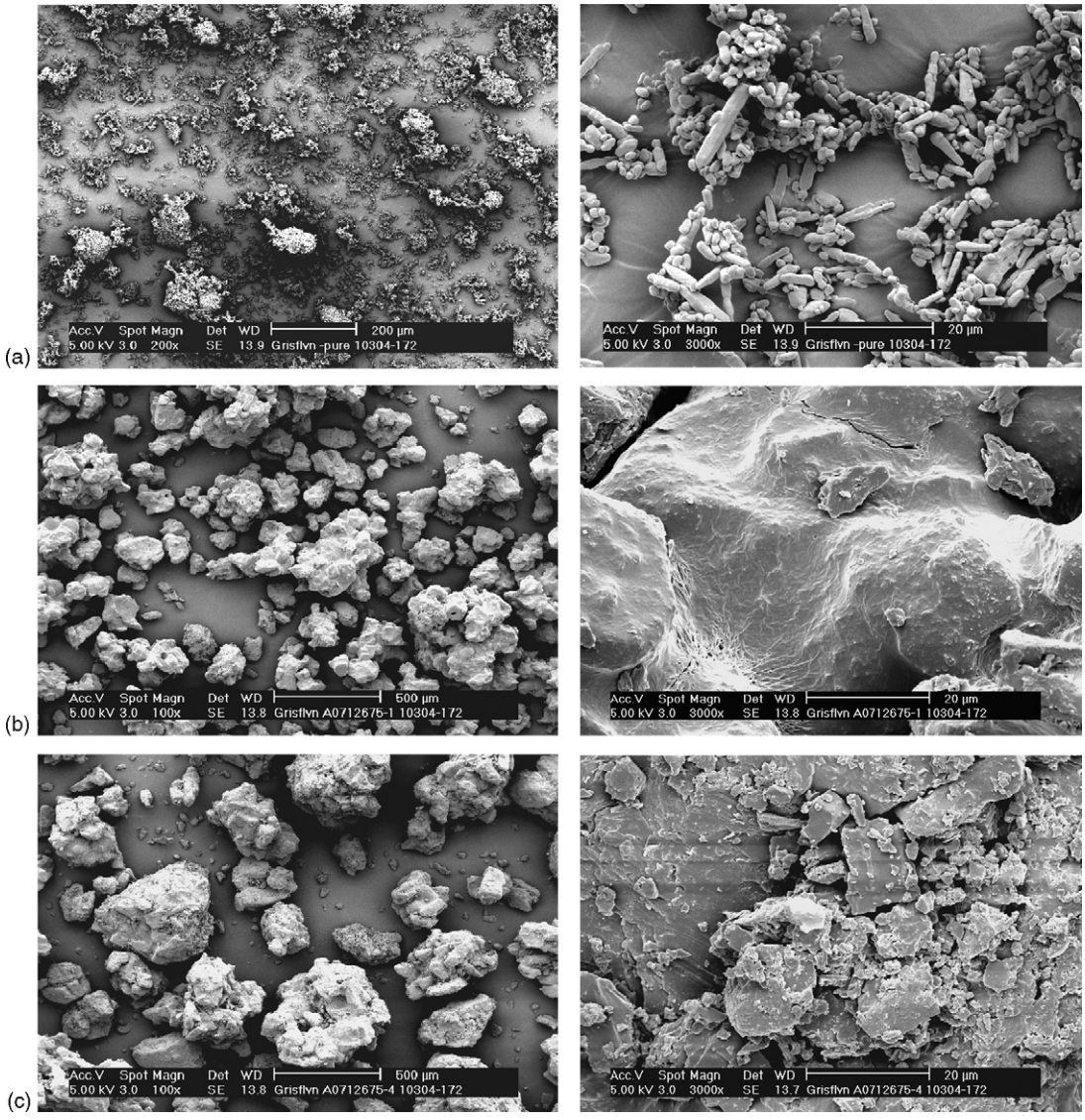

Fig. 9. Scanning electron microscopy images of: (a) griseofulvin, (b) granulation 1 (2.5% drug loading) and (c) granulation 4 (5% drug loading).

Granulations 1 and 4 were also subjected to X-ray diffraction analysis. The diffraction patterns of pure drug, placebos (1 and 4) and granulations (1 and 4) are depicted in Figs. 7 and 8, respectively. Diffractograms of pure griseofulvin clearly show the drug is crystalline, as demonstrated by numerous sharp and intense peaks. The diffractogram of the 2.5% loaded granules indicate characteristic drug peaks, even if the intensities are attenuated due to the lower drug content. In case of the 5% loaded granules, peaks corresponding to drug were also apparent compared to the pure drug and the placebo formulation. While X-ray analyses suggest the presence of crystalline drug in these test samples, it cannot be deduced if it is or is not in a monotectic phase with PEG.

3.4. Scanning electron microscopy

SEM micrographs for the pure drug showed griseofulvin as rod-shaped particles of different sizes. The granules appeared as irregular particles and the 2.5% drug loaded granules had different surface morphology as compared to the 5% drug loaded granules. The 2.5% drug loaded granules had a smoother surface as compared to the 5% granulates. No drug crystals were observed on the surface of the granules, suggesting that the drug was likely dispersed within the PEG matrix. The SEM photomicrographs are shown in Fig. 9.

4. Conclusions

In conclusion, melt granulation has been proved to be a viable technique to enhance the dissolution rate of griseofulvin. Meltable binders like PEG 3350 and Gelucire 44/14 were found to have a positive effect on the dissolution rate of griseofulvin. X-ray analyses of the granules prepared by melt granulation, revealed the crystalline nature of the system at 2.5% and 5% drug loading. The increase in the dissolution rate can thus be attributed to the hydrophilic character of the system due to the presence of water-soluble carriers (PEG 3350, Gelucire 44/14) and the fact that the drug forms monotectic mixtures with PEG. Further

studies are in progress to test the use of this technique with other binders to improve the dissolution rate of poorly water-soluble compounds.

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