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Enhancement of the dissolution rate and oral absorption of a poorly water soluble drug by formation of surfactant-containing microparticles

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Abstract

The slow dissolution rate exhibited by poorly water-soluble drugs is a major challenge in the drug development process. Following oral administration, drugs with slow dissolution rates generally show erratic and incomplete absorption which may lead to therapeutic failure. The aim of this study was to improve the dissolution rate and subsequently the oral absorption and bioavailability of a model poorly water-soluble drug. Microparticles containing the model drug (griseofulvin) were produced by spray drying the drug in the absence/presence of a hydrophilic surfactant. Poloxamer 407 was chosen as the hydrophilic surfactant to improve the particle wetting and hence the dissolution rate. The spray dried particles were characterized and in vitro dissolution studies and in vivo absorption studies were carried out. The results obtained showed that the dissolution rate and absolute oral bioavailability of the spray dried griseofulvin/Poloxamer 407 particles were significantly increased compared to the control. Although spray drying griseofulvin alone increased the drug's in vitro dissolution rate, no significant improvement was seen in the absolute oral bioavailability when compared to the control. Therefore, it is believed that the better wetting characteristics conferred by the hydrophilic surfactant was responsible for the enhanced dissolution rate and absolute oral bioavailability of the model drug.

Keywords: Poor solubility; Dissolution; Oral bioavailability; Microparticles; Spray drying; Griseofulvin

1. Introduction

The oral route remains the preferred route of drug administration due to its convenience, good patient compliance and low medicine production costs. In order for a drug to be absorbed into the systemic circulation following oral administration, the drug must be dissolved in the gastric fluids. For hydrophobic drugs, it is this dissolution process which acts as the rate-controlling step and, therefore, determines the rate and degree of absorption. Consequently, many hydrophobic drugs show erratic and incomplete absorption from the gastrointestinal tract of animals and humans. Thus, one of the major challenges to drug development today is poor solubility, as an estimated 40% of all newly developed drugs are poorly soluble or insoluble in water (Naseem et al., 2004). In addition, up to 50% of orally administered drug compounds suffer from formulation problems related to their high lipophilicity (Gursoy and Benita, 2004). As a result, much research has been conducted into methods of improving drug solubility and dissolution rates to increase the oral bioavailability of hydrophobic drugs. One way of improving dissolution involves the reduction of particle size and/or increasing saturation solubility.

One of the most common approaches used to reduce particle size is milling, a mechanical micronization process. Milling is a well-established technique which is relatively cheap, fast and easy to scale-up. However, milling has several disadvantages, the main one being the limited opportunity to control important characteristics of the final particle such as size, shape, morphology, surface properties and electrostatic charge. In addition, milling is a high energy process which causes disruptions in the drug's crystal lattice, resulting in the presence of disordered or amorphous regions in the final product (Saleki-Gerhardt et al., 1994). These amorphous regions are thermodynamically unstable and are therefore susceptible to recrystallization upon storage, particularly in hot and humid conditions (Ward and Schultz, 1995).

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The alteration of the surface properties also changes the milled product's saturation solubility as well as blending and flow properties, which in turn, have an impact on the formulation process. Furthermore, milled particles often show aggregation and agglomeration which results in poor wettability and thus poor dissolution (Tur et al., 1997).

An alternative to milling involves growing the particle from a solution to the desired size range under controlled conditions, for example by spray drying, solvent-diffusion (Quintanar-Guerrero et al., 1998) and supercritical fluid technology (Hu et al., 2003; Moneghini et al., 2003). One of the advantages of these methods is the possibility of designing in certain beneficial characteristics such as enhancing dissolution rate by inclusion of surfactant or increasing the stability of amorphous material by incorporation of sugars.

In our laboratories, we have used spray drying in an attempt to enhance the dissolution rate and oral bioavailability of a model drug (griseofulvin). As well as being an alternative to milling to reduce particle size, spray drying enabled the designing-in of features, such as improved particle wetting by the incorporation of small amounts of a surfactant. The latter had to be hydrophilic, a solid at room temperature, with a melting point higher than 40 °C (the boiling point of the solvent). After screening a range of surfactants, which included Gelucire 50/13, Brij 76 and a sorbitan monostearate/polysorbate 80 blend, Poloxamer 407 was selected as its inclusion did not inhibit drug particle formation. In this paper, we report on the preparation and characterization of these particles and their in vitro dissolution and in vivo absorption profiles.

2. Materials and methods

2.1. Materials

Griseofulvin (99% purity) was obtained from Sigma (UK). Poloxamer 407 (Pluronic F127) was obtained from BASF (Mount Olive, NJ, USA). Sodium hydroxide and polyoxyethylene sorbitan monooleate (Tween 80) were purchased from Sigma (UK). Potassium dihydrogen orthophosphate (AnalaR grade) and dichloromethane (analytical grade) were obtained from BDH Chemicals (Poole, UK). Acetonitrile (HPLC grade) was purchased from Fisher Chemicals Ltd. (UK). All chemicals were used as received.

2.2. Microparticle preparation and characterization

Two types of spray dried griseofulvin formulations were produced:

(A) *Particles consisting solely of griseofulvin.* These particles were produced by dissolving the drug in dichloromethane to produce a 1.5% (w/v) solution. The solution was spray dried using a Büchi 191 mini spray dryer (Büchi Labortechnik AG, Flawil, Switzerland) at a feed rate of 7.5 ml/min, an air flow rate of 900 l/h, aspirator level at 80%, inlet temperature of 50 °C and outlet temperature of 39 °C. The white powder collected from the collecting vessel was stored in a desiccator at room temperature until ready to be used.

(B) *Griseofulvin particles incorporating small amounts of a hydrophilic surfactant.* Griseofulvin particles containing the surfactant, Poloxamer 407, were produced by spray drying a solution of dichloromethane containing 1.5% (w/v) griseofulvin and 0.05% (w/v) Poloxamer 407. The solution was spray dried using the same conditions as for A described above. It was found that the drug: surfactant ratio was maintained at approximately 30:1 as determined using UV spectroscopy after spray drying. The powder collected was again stored in a desiccator until it was ready to be used.

The two types of spray dried particles were characterized in terms of morphology, size, surface area, wetting ability, crystallinity and melting points as described below. All the experiments were carried out in triplicate. To determine the influence of including Poloxamer 407, the triplicate measurements of the two formulations were statistically analyzed using the non-parametric Kruskal–Wallis test.

Particle morphology. Scanning electron microscopy (SEM) was used to determine particle shape. The spray dried particles were fixed on an aluminium stub with conductive double sided carbon tape, sputter-coated with gold at 30 mA for 3 min and observed using a Philips/FEI XL 30 electron microscope (Eindhoven, Netherlands).

Particle size. The volume mean diameter was measured using low angle laser light scattering (Malvern S, Malvern Instruments, UK). The drug particles were suspended in filtered, deionised water containing 0.05% (w/v) polyoxyethylene sorbitan monooleate and briefly bath sonicated prior to measurements to ensure there was no aggregation.

Surface area. The specific surface area of the particles was determined using a SA3100 Surface Area and Pore Size Analyzer (Beckman Coulter Ltd., Buckinghamshire, England). Surface area calculations were made based on the BET equation using the software provided.

Wetting interaction. Contact angle measurements were made using the Wilhelmy-plate method (CAHN Dynamic Contact Angle Analyser DCQ 312, Thermo Cahn, USA) to determine the wetting interaction between the particle surface and water. A glass cover slip was coated with a thin layer of Photo Mounting Adhesive (3M, UK) and dipped into the particles. Excess particles were removed with a soft brush and the cover slip slowly lowered into a beaker containing deionised water. The advancing contact angle of the particles was calculated using the provided software.

Crystallinity. Powder X-ray diffraction patterns of the particles were collected using an X-ray diffractometer (Philips PW3170 Scanning X-Ray Diffractometer, Philips, Cambridge, UK) equipped with a Cu Kα target. The X-rays were generated at 45 kV and 30 mA. The sample was gently compressed into the sample holder and the powder surface was smoothed with a flat Perspex block. The samples were loaded onto the diffractometer and scanned over a range of 2θ values, from 5° to 50°, at a scan rate of 1.0° 2θ/s.

Melting point. Differential scanning calorimetry experiments were carried out using a DSC7 calorimeter (Perkin-Elmer Instruments, Beaconsfield, Bucks, UK). The equipment was calibrated using high purity indium, after which, the samples were heated at a rate of 10 °C/min in aluminium pans under nitrogen atmosphere. The onset melting points were calculated using the software provided.

2.3. In vitro dissolution studies

The two spray dried griseofulvin formulations and the control (raw material used as received) were encapsulated in size 9 (length 8.6 mm, diameter 2.65 mm and volume 0.025 ml) capsules (Torpac, USA) using a filling funnel, such that each capsule contained 12.5 mg of the active drug. Dissolution studies were carried out using 0.05 M phosphate buffer (adjusted to pH 6.8) in a Type II (paddle) dissolution apparatus (Pharmatest PTWS3C Dissolution Bath, Hainburg, Germany). The stirring speed used was 100 rpm and the temperature of the dissolution medium was maintained at 37 ± 0.5 °C. The drug concentration in the dissolution medium was assayed spectrophotometrically at 295 nm (Cecil CE2020 UV Spectrophotometer) every 15 min for 3 h. The dissolution studies on each formulation were repeated five times for each formulation (two types of spray dried particles and the control) and the percentage drug dissolved was calculated. To test for significant differences between the three formulations, one-way between-groups ANOVA, followed by post hoc Tukey HSD tests were conducted using the SSPS 12.0.1 package.

2.4. In vivo absorption studies

Male Wistar rats (160–180 g) in groups of four were used to determine drug absorption following oral administration from the two particle formulations and the control (raw drug material used as received). The rats were allowed free access to both food and water, both prior to and during the study. Each formulation was encapsulated in size 9 gelatin capsules (Torpac, USA) and each capsule contained 12.5 mg of the active drug. Each rat was given one capsule by oral gavage. After dosing, the rats were returned to their cage and allowed to move freely. At times 0.75, 1.5, 2.5, 3.5, 5.0, 8.0 and 24 h post-administration, the rats were bled. Approximately 0.3 ml of blood was collected from the tail vein into heparinised tubes (Microvette CB300, Sarstedt, UK) at all times except for the 24 h time point when 2 ml of blood was obtained via cardiac puncture. The blood samples were centrifuged at 3000 rpm for 10 min (Eppendorf Centrifuge 5415D, Eppendorf AG, Hamburg, Germany fitted with a fixed angle rotor 45°). Plasma collected was then frozen until ready to be analyzed.

To enable the calculations of absolute oral bioavailability, an additional group of four rats were intravenously injected with 0.5 ml of a propylene glycol/absolute alcohol/water solution (4:1:5 v/v) containing 0.5 mg/ml of griseofulvin via the tail vein. The rats were bled and the plasma collected as described above.

2.5. Determination of griseofulvin in plasma

The frozen plasma samples were thawed at room temperature and griseofulvin was extracted using a protein precipitation method. One millilitre acetonitrile was added to 0.3 ml plasma. The sample mixture was bath sonicated briefly and then centrifuged for 10 min at 10 000 rpm. Then, 0.9 ml of the supernatant was transferred into glass test tubes and aspirated to dryness under a stream of nitrogen at 90 °C. The residue was reconstituted using 0.18 ml of mobile phase (65%, v/v acetonitrile and 35%, v/v water) containing 0.15 μg/ml of diazepam as the internal standard.

The samples were assayed using a HPLC method, modified from Hackett and Dusci (1978). The chromatographic system used consisted of a Hewlett-Packard 1050 Series HPLC System (Agilent Technologies, UK) and the peaks obtained were integrated using PC/Chrom+software (H&A Scientific Inc., USA). Fifty microlitres of the reconstituted sample was injected onto a 250 mm × 4 mm column (5 μm C18 Macherey-Nagel GmBH & Co., KG Düren, Germany) fitted with a guard column at room temperature. An isocratic system was used and the flow rate was set at 1.3 ml/min.

Prior to analysis, the assay was validated and recovery and precision studies had been conducted by spiking drug-free plasma with a standard ethanolic solution of griseofulvin in a concentration range of 0.1–3.0 μg/ml. Each sample was analyzed by HPLC using the conditions described above. The results obtained showed that the HPLC method gave baseline resolved peaks with retention times of 3.7 and 5.1 min for griseofulvin and diazepam, respectively. The method was found to be specific and no interferences were seen at the retention times of both griseofulvin and the internal standard. Standard curves were produced based on the peak height ratios of griseofulvin to diazepam and were found to be linear between a concentration range of 0.1–3.0 μg/ml. The correlation coefficient (r^2) was 0.9997. When the griseofulvin-spiked plasma samples were analyzed, the results indicated that the extraction procedure was capable of recovering 96.1 ± 0.2% at 0.5 μg/ml, 97.3 ± 0.6% at 1.0 μg/ml and 98.2 ± 0.6% at 1.5 μg/ml. The chromatogram was devoid of any interference at the retention times of griseofulvin and diazepam. The limit of detection of griseofulvin (4.5 times the noise level) was 0.06 μg/ml while the limit of quantification was 0.1 μg/ml, which was approximately seven times the noise level. The in vitro dissolution studies and in vivo absorption study results were analyzed using one-way between-groups ANOVA tests followed by Tukey HSD when needed.

3. Results and discussion

3.1. Microparticle production and characterization

Spray drying was found to be a suitable method for producing griseofulvin microparticles. The atomization of the griseofulvin and griseofulvin/Poloxamer 407 solutions, followed by the evaporation of dichloromethane resulted in the formation of particles. The spray dried products collected from both formulations were

white in colour and fairly free-flowing. The yield obtained from both formulations was approximately 30%, which is fairly typical for small scale, bench top spray driers (Maa et al., 1998). It has been suggested that the main reasons for this poor yield are the design of the cyclone separator which cannot trap particles smaller than 2 μm, inadequate process conditions which cause the particles to adhere to the inner walls of the spray dryer and the small amount of materials being processed per batch (Giunchedi et al., 2002; Maury et al., 2005).

Scanning electron microscopy showed that both spray dried formulations (i.e. with and without surfactant) consisted of relatively discrete, spherical particles (Fig. 1A and B) which were morphologically quite different from the starting material (Fig. 1C). Poloxamer 407-containing particles showed pronounced dimpling of the particle surface. During and following the formation of droplets in the spray drying process, the surfactant moves preferentially to the liquid/gas interface due to its amphiphilic nature, forming a surfactant "crust". The dimpling seen in the particle surface suggests that this crust is pliable. As the solution was spray dried above the boiling point of dichloromethane, the dichloromethane within the droplet vaporised quickly causing the droplet to inflate. On cooling, the soft crust collapses resulting in the dimpling seen on the particle surface. This process was described by Oakley (1997).

The contact angle measurements confirmed the presence of the surfactant on the particle surface. The particles containing Poloxamer 407 had a significantly lower ($p < 0.05$) contact angle ($81.6 \pm 2.8^\circ$) and therefore better wetting ability than the particles consisting solely of griseofulvin ($92.1 \pm 0.7^\circ$). Surfactants are known to improve the wetting of hydrophobic drugs following their adsorption onto the particle surface by reducing the solid/liquid interfacial tension, which is reflected in the lower contact angle (Sinswat et al., 2005).

The presence of the Poloxamer 407 in the particles resulted in a statistically significant ($p < 0.05$) increase in particle size with the mean volume diameter being 11.24 ± 0.11 μm compared to 8.51 ± 0.16 μm for the griseofulvin-only spray dried particles. A correspondingly significant reduction ($p < 0.05$) in specific surface area (1.25 ± 0.04 m^2/g versus 1.88 ± 0.05 m^2/g) was seen. A possible reason for the increased size could be the slight increase in the concentration of solids in the feed solution when Poloxamer 407 was included (1.55%, w/v versus 1.5%, w/v). It has been shown that higher solid feed concentrations result in larger particles being produced (Oakley, 1997). The

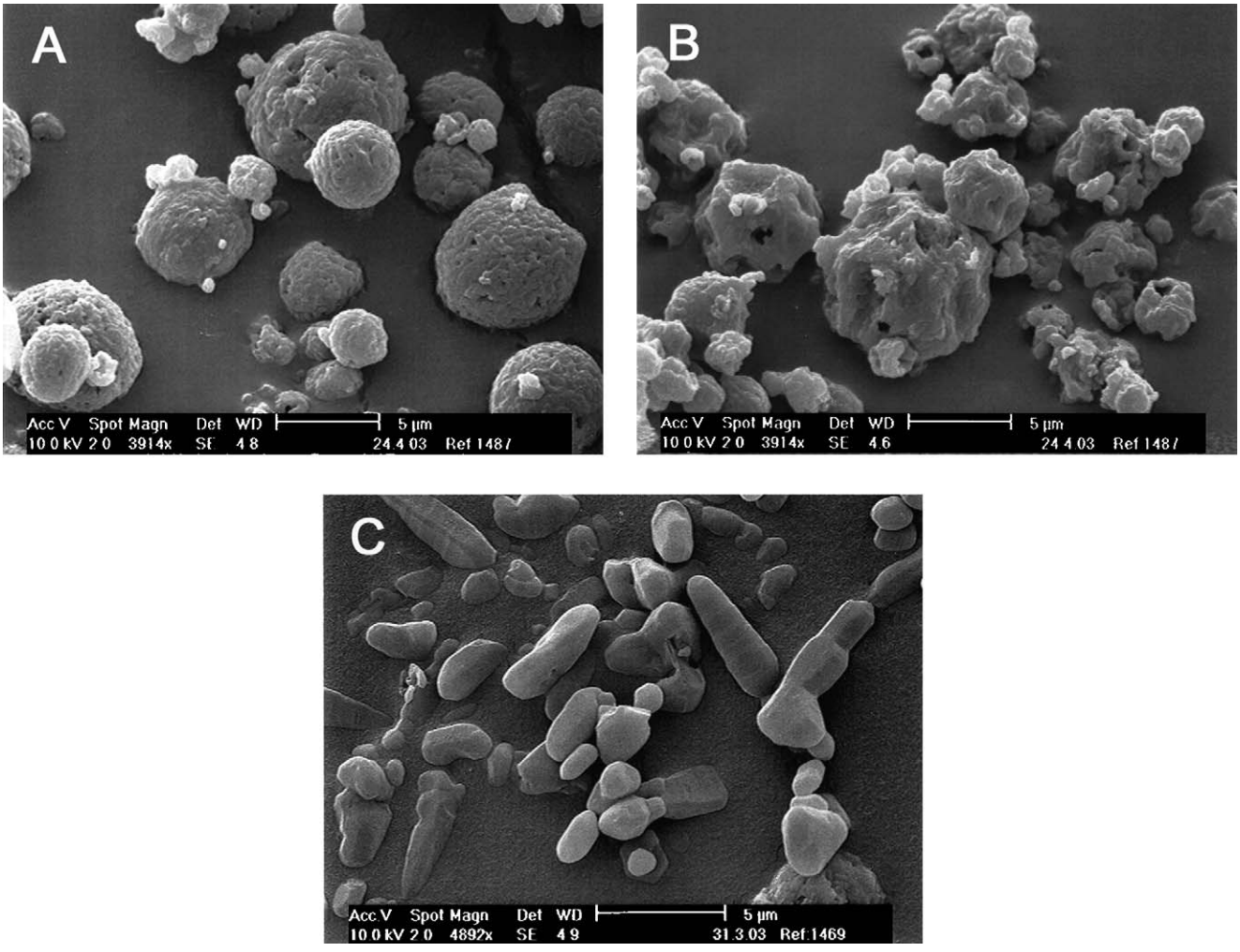

Fig. 1. SEM of spray dried griseofulvin (A), spray dried griseofulvin/Poloxamer 407 (B) and control (C).

increase in solid concentrations of the feed solution was however small (3.3%), and it is likely that other factors contributed to the increased size. For example, the spray drying conditions found to be optimal for producing griseofulvin-only particles might not have been optimal for the production of griseofulvin/Poloxamer 407 particles.

Both spray dried products were found to contain crystalline material, as shown by their X-ray diffraction patterns (Fig. 2A and B) which contained peaks indicative of crystalline material and were similar to that of the starting raw material (Fig. 2C). The three X-ray diffraction patterns in Fig. 2A–C had peaks at similar 2θ values which suggest that the three had the same crystal packing and therefore were of the same polymorphic form. This was surprising, given that spray drying normally produces amorphous material (Yu, 2001; Corrigan et al., 2003). Our own work using the same technique produced amorphous indomethacin particles from an organic solution (unpublished). The absence of amorphous nature in the griseofulvin particles can be attributed to the fact that griseofulvin crystallises easily, even at room temperature and in the absence of moisture (Ahmed et al., 1998). The amorphous solid state has the advantage of increased solubility and therefore faster dissolution rate compared to crystalline material. However, its higher energy status means that it lacks the stability of its corresponding crystalline state, to which it tends to revert during processing or storage (Fromming et al., 1980; Hancock and Zografi, 1997). Therefore, from stability considerations, it is not altogether disadvantageous that the spray dried griseofulvin particles were crystalline. Based on current knowledge of the relative stabilities of crystalline and amorphous materials, we speculate that the crystalline griseofulvin particles have a higher stability, than if they were amorphous.

The crystallinity of the spray dried griseofulvin particles was further confirmed using DSC. Upon heating the spray dried particles, no exothermic peak, which would be indicative of the recrystallization of an amorphous solid was seen before the melting endotherm. The onset melting point of the spray dried griseofulvin particles, 217.7 ± 0.2 and $217.6 \pm 0.1\,^{\circ}C$, in the presence and absence of surfactant, respectively, were slightly lower than that of the control ($219.1 \pm 0.2\,^{\circ}C$). However, all three melting point onset values fell well within the onset melting point range (217–224 °C) reported in the literature (Townley, 1979).

3.2. In vitro dissolution

The dissolution profiles of the spray dried griseofulvin particles and the control (raw drug material) are illustrated in Fig. 3.

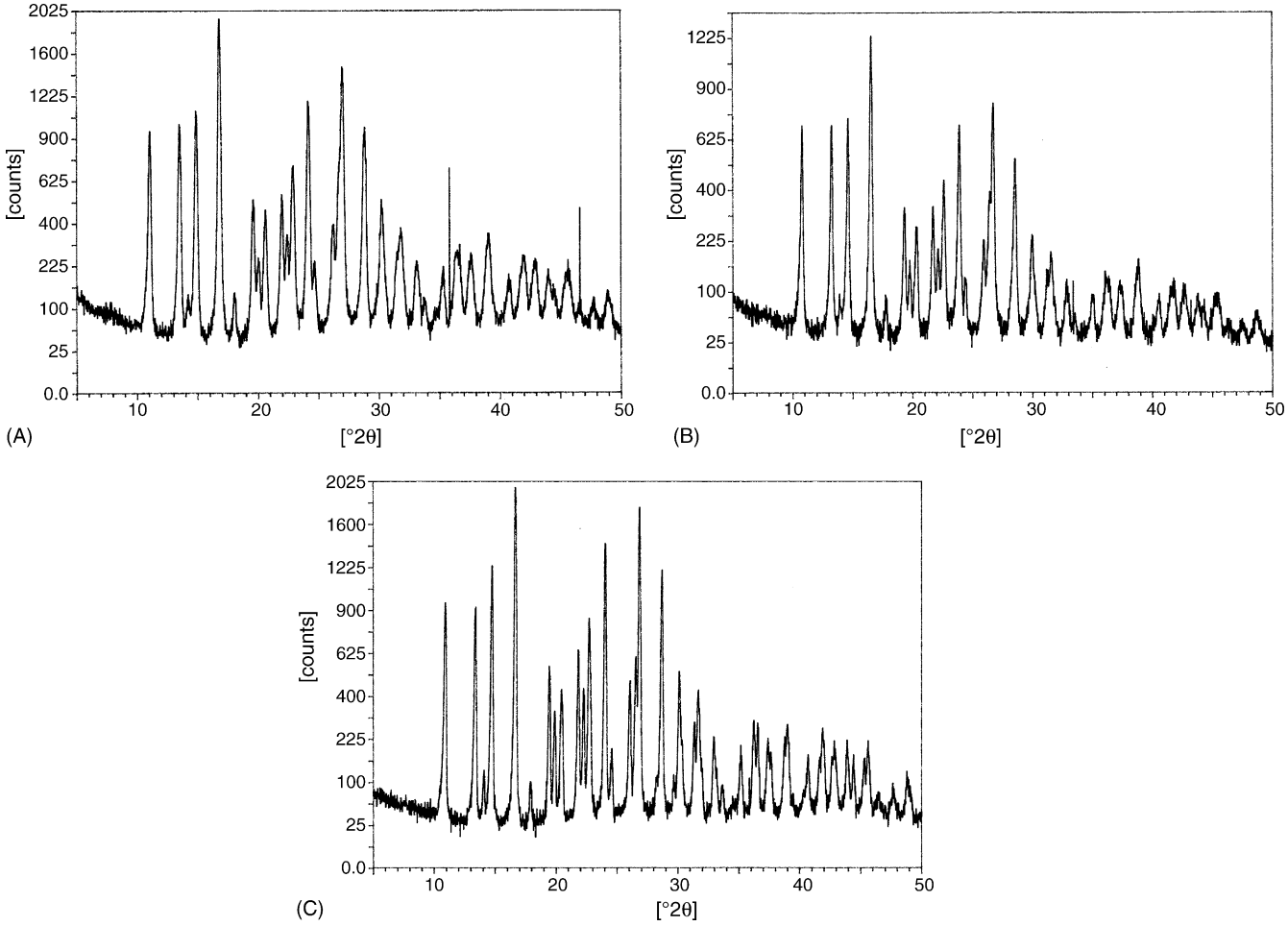

Fig. 2. PXRD pattern for spray dried griseofulvin (A), spray dried griseofulvin/Poloxamer 407 (B) and control (C).

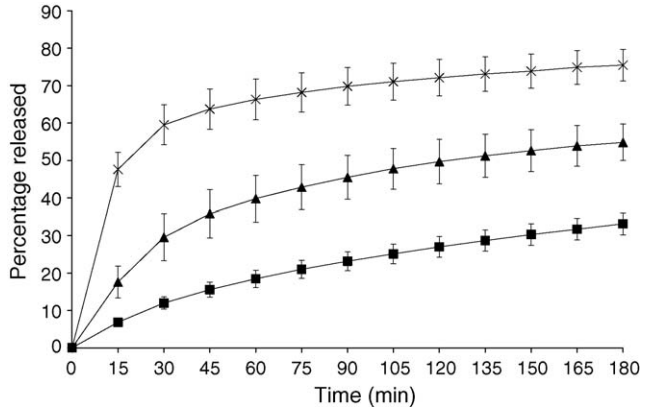

Fig. 3. Mean dissolution profile of griseofulvin formulations at 37 °C (±S.D., $n = 5$). (■) Control; (▲) Spray-dried particles; (×) Spray-dried + Pluronic F127.

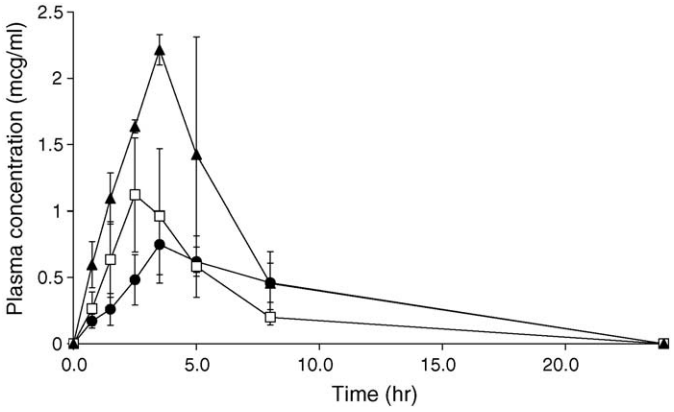

Fig. 4. Mean griseofulvin plasma concentration-time profile following oral administration to rats (±S.D., $n = 4$). (●) Control; (□) Spray-dried; (▲) Spray-dried + Pluronic F127.

Griseofulvin/Poloxamer 407 particles showed the fastest dissolution rate, with approximately 50% of the drug being released within 15 min compared to 18% for the spray dried griseofulvin only particles and just 7% for the control. The percentage of drug dissolved at 180 min for the three preparations tested were significantly different ($p < 0.05$) from one another, as shown by one-way between-group ANOVA and post hoc Tukey HSD tests.

The fact that the spray dried griseofulvin-only particles exhibited a faster dissolution rate than the control shows that spray drying process itself was responsible for increased dissolution. Spray drying has been shown to reduce the aggregation tendencies of particles compared to milling (Kornblum and Hirschorn, 1970; Hirschorn and Kornblum, 1971); reduced aggregation leads to improved wetting and thereby increased dissolution rate.

The fact that the spray dried griseofulvin particles with surfactant exhibited a faster dissolution rate than spray dried particles without surfactant showed that the surfactant inclusion contributed to further increase in the dissolution rate. The mechanism of such additional improvement is believed to be the improved wetting of the formulation containing the hydrophilic surfactant, as indicated by the contact angle values discussed earlier. The significant effect of the improved wetting is evident in the fact that dissolution rate of particles containing the hydrophilic surfactant was increased despite the smaller specific surface area of these particles compared to the griseofulvin only particles ($1.25 \pm 0.04\ m^2/g$ versus $1.88 \pm 0.05\ m^2/g$). Improved wetting ability of the Poloxamer 407-containing particles could be observed during the dissolution studies. Once the gelatin capsule had dissolved, the spray dried griseofulvin/Poloxamer 407 particles dispersed rapidly within the dissolution medium, in contrast to the spray dried griseofulvin only particles and the control which showed some aggregation and floating of a portion of the particles on the surface of the dissolution medium throughout the experiment.

Saturation solubility was not a factor influencing dissolution in this study as the spray dried griseofulvin/Poloxamer 407, spray dried griseofulvin and the control had similar saturation solubilities (14.1 ± 0.17, 13.1 ± 0.18 and 13.5 ± 0.17 μg/ml, respectively).

3.3. In vivo oral absorption

Following the oral administration of a capsule containing 12.5 mg griseofulvin to rats, the latter were bled and the plasma assayed for griseofulvin concentration to investigate the drug absorption profiles. Plasma drug concentrations as a function of time were plotted and are shown in Fig. 4. The three profiles showed that griseofulvin had been completely eliminated from the plasma within 24 h, which indicated that the experimental time period selected was sufficient to assess the absorption characteristics of the different preparations. It is obvious from Fig. 4 that the drug absorption was highest from the griseofulvin/Poloxamer 407 particles. C_{max} for this preparation was significantly higher ($p < 0.05$) than the other two preparations (2.18 ± 0.18 μg/ml versus 1.22 ± 0.44 μg/ml for the griseofulvin-only particles and 0.82 ± 0.11 μg/ml for the starting material). The area under the curve (AUC) which reflects the total amount of drug absorbed over the 24 h time period was also found to be significantly higher ($p < 0.05$) for the griseofulvin/Poloxamer 407 preparation than the other two preparations (13.23 ± 3.78 μg h/ml compared to 6.74 ± 2.17 μg h/ml for the griseofulvin-only particles and 7.54 ± 2.00 μg h/ml for the starting material). Thus, the absolute oral bioavailability, the fraction of the administered dose that reaches the systemic circulation calculated according to the equation below (Eq. (1)) was significantly higher ($6.92 \pm 1.98\%$) than that of the spray dried griseofulvin-only particles ($3.53 \pm 1.13\%$) and that of the control ($3.94 \pm 1.04\%$):

$$\text{absolute oral bioavailability } (F) = \frac{\text{Dose}_{\text{intravenous}}}{\text{Dose}_{\text{oral}}} \times \frac{\text{AUC}_{\text{oral}}}{\text{AUC}_{\text{intravenous}}} \times 100\% \quad (1)$$

The highest absolute oral bioavailability of the griseofulvin/Poloxamer 407 particles reflects the greatest in vitro drug dissolution from this formulation (Fig. 3). This indicates that the improvement in the absolute oral bioavailability of the spray dried griseofulvin/Poloxamer 407 particles may be due to higher drug dissolution rate in the gastrointestinal tract following oral

Table 1
Pharmacokinetic parameters of griseofulvin formulations—control and spray dried particles (with and without Poloxamer 407)

Parameters	Control	Spray dried griseofulvin particles	Spray dried griseofulvin/ Poloxamer 407 particles
AUC (μg h/ml)	7.54 ± 2.00	6.74 ± 2.17	13.23 ± 3.78*
C_{max} (μg/ml)	0.82 ± 0.11	1.22 ± 0.44	2.18 ± 0.18*
T_{max} (h)	3.88 ± 0.75	2.75 ± 0.05	3.88 ± 0.75
K_{el} (h^{-1})	0.56 ± 0.01	0.59 ± 0.19	0.62 ± 0.05
$T_{1/2}$ (h)	1.23 ± 0.03	1.17 ± 0.04	1.11 ± 0.01
Absolute bioavailability (%)	3.94 ± 1.04	3.52 ± 0.02	6.92 ± 1.98*

* Statistical difference at $p < 0.05$, compared to the other two samples.

administration, which in turn is due to the improved wetting of these particles. Improved wetting would result in these particles being dispersed more readily when exposed to aqueous conditions and subsequently, a larger effective surface area for drug dissolution (Table 1).

The C_{max} and AUC values obtained for the spray dried griseofulvin/Poloxamer 407 particles compare favourably with results obtained from a study by Bates and Carrigan (1975). In their experiments, C_{max} of 1.88 μg/ml and AUC of 13.4 μg h/ml were obtained following the oral administration of micronized griseofulvin (at 50 mg/kg) in a corn oil-in-water emulsion to non-fasted male rats. To date, the corn oil-in-water emulsion is considered to be the best delivery system for griseofulvin, in terms of bioavailability (Tur et al., 1997). Bates and Carrigan also showed that griseofulvin was better absorbed when the rats were fasted (C_{max} 1.92 μg/ml and AUC 17.7 μg h/ml).

Interestingly, when griseofulvin-only spray dried particles were compared with the control, no significant difference ($p > 0.05$) was seen in both the C_{max}, AUC and absolute oral bioavailability despite the griseofulvin-only spray dried particles showing a significantly faster in vitro dissolution rate (Fig. 3). This could be due to the smaller volume of fluid available in the gastrointestinal tract of the rats, which limited the in vivo dissolution of the drug. In addition, the griseofulvin-only spray dried particles and the control exhibited statistically similar ($p > 0.05$) wetting ability as indicated by the similar contact angle values ($92.1 \pm 0.7^\circ$ for the griseofulvin-only particles and $92.5 \pm 0.9^\circ$ for the control). Therefore, it is possible that the poor agitation present in the gastrointestinal tract relative to the dissolution bath along with the poor wetting ability of both preparations led to aggregation of the particles within the gastrointestinal tract. Consequently, the specific surface area available for dissolution was low resulting in similar absorption profiles.

The results obtained from this in vivo study whereby the larger griseofulvin/Poloxamer 407 spray dried particles had a higher absolute oral bioavailability than the smaller griseofulvin-only spray dried particles suggests that the wetting ability of a particle was of greater importance than specific surface area and saturation solubility. This is due to the fact that wetting ability prevents aggregation of particles when exposed to the aqueous medium of the gastrointestinal fluid. Subsequently, this allows the particles to present a larger specific surface area available for dissolution.

4. Conclusions

Spray drying was used to produce particles of the model drug griseofulvin in an attempt to improve the drug's dissolution rate and oral bioavailability. Small amounts of hydrophilic surfactant, Poloxamer 407, were also incorporated into the particles in an attempt to enhance particle wetting. Dissolution studies showed the spray dried particles with Poloxamer 407 had the highest dissolution rate, followed by spray dried particles without surfactant, followed by the control. This indicated that both the spray drying process and the inclusion of the hydrophilic surfactant contributed to enhanced dissolution rates. Interestingly, the order of the in vitro dissolution profiles were not totally replicated in the in vivo oral bioavailability studies. The griseofulvin/Poloxamer 407 particles had the highest oral bioavailability. However, spray dried particles without surfactant had the same bioavailability as the control. The improved particle wetting conferred by the presence of the hydrophilic surfactant (as evidenced by contact angle measurements) seems to be the most important determinant for in vivo oral bioavailability.

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