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Fast-dissolving microparticles fail to show improved oral bioavailability

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Abstract

Oral dosage forms are the preferred means of delivering drugs for systemic absorption. However, development problems occur for drugs with poor water solubility and/or gastrointestinal permeability. It is generally believed that the in-vivo bioavailability of poorly water-soluble drugs from Class II of the Biopharmaceutics Classification System can be improved by increasing the dissolution rate. We have attempted to increase the in-vivo oral bioavailability of a model Class II drug (griseofulvin) by preparing rapidly-dissolving particles. The solvent-diffusion method was used to prepare particles with hydrophilic surfactants (Brij 76/Tween 80 surfactant blend) and in-vivo studies were conducted in rats. The griseofulvin particles produced were bipyramidal in habit with a particle size of $2.18 \pm 0.12\,\mu$m; they contained crystalline drug and a relatively large proportion (12% w/w) of hydrophilic surfactant. The latter and the small particle size ensured rapid particle dispersion and dissolution in-vitro. Thus, within 30 min of the in-vitro dissolution test, the bipyramidal particles had released ~70% of drug compared with ~10% from the starting material (particle size $12.61 \pm 1.11\,\mu$m). However, the rapid and increased drug dissolution in-vitro was not translated to rapid and enhanced absorption in-vivo, and the oral bioavailability of the model drug was found to be the same from the control and from the bipyramidal particles. The poor in-vivo performance of the bipyramidal particles showed that although the dissolution rate of a Class II drug is thought to be a good indicator of its in-vivo bioavailability, this is not always the case.

Introduction

Therapeutic agents can be administered by a variety of routes, such as the oral, transdermal and intravenous route. However, to achieve systemic effects, the oral route remains the most desirable as it allows easy and convenient self-medication, which encourages patient compliance. In addition, oral dosage forms are more cost-effective to manufacture as they do not require the sterile conditions needed by intravenous and ocular formulations. As a result, oral medication is generally the first avenue investigated by the pharmaceutical industry when discovering and developing new drug entities and/or new pharmaceutical formulations (Kim & Singh 2002). Developing oral dosage forms, however, becomes challenging when the therapeutic agent is poorly absorbed from the gastrointestinal tract. Although a variety of reasons can cause poor absorption and subsequent therapeutic failure, the two main parameters that determine gastrointestinal drug absorption are considered to be the drug's aqueous solubility and its gastrointestinal permeability. For absorption to occur following oral administration, the drug must dissolve in the aqueous gastrointestinal fluids and then permeate across the gastrointestinal membrane into the blood.

These parameters were recognized when the Biopharmaceutics Classification System (BCS) was set up (Amidon et al 1995). Under this system, drugs are divided into four classes (Class I to Class IV) based on their solubility and permeability. Class I drugs have both good solubility and permeability; Class II drugs have good permeability but poor aqueous solubility; Class III drugs have good aqueous solubility but poor permeability; while Class IV drugs have both poor solubility and permeability. Thus, aqueous solubility and permeability are the rate-limiting factors in the absorption of Class II and III drugs, respectively.

Poor permeability (of Class III drugs) is considered to be more of a problem than poor solubility (of Class II drugs) as, unlike poor permeability, insolubility can be addressed

more easily using formulation strategies (Lipinski 2001). For example, saturation solubility can be increased by using surfactants (Florence 1981; Florence & Attwood 1988), co-solvents (Jouyban-Gharamaleki et al 1999) or by formulation, for example, in lipid-based systems (Humberstone & Charman 1997; Pouton 2000). Enhanced solubility of Class II drugs is therefore expected to increase both the rate and extent of the absorption of poorly water-soluble drugs. Other ways of increasing dissolution rate include the reduction of drug particle size, for example, by milling or by the de-novo formulation of small particles, e.g. by solvent diffusion (Quintanar-Guerrero et al 1998), evaporative precipitation into aqueous solution, spray freezing into liquid and precipitation from supercritical fluid (Mosharraf & Nystrom 1995; Sarkari et al 2002; Turk et al 2002; Hu et al 2003; Moneghini et al 2003; Jinno et al 2006). De-novo drug particle formation has the advantage that the particles can be engineered with desirable properties, e.g. with improved wetting which results in enhanced dissolution rate and subsequently enhanced oral bioavailability.

To the formulation scientist, the BCS Classification points towards formulating dosage forms of Class II drugs with increased dissolution. Thus, in our laboratories, we prepared particles of griseofulvin (a model Class II drug) with improved dissolution profile, in an attempt to increase the oral bioavailability of the model poorly water-soluble drug. In this paper, we have reported on the preparation and characterization of these fast-dissolving particles and their in-vivo bioavailability profiles, and discussed the lack of in-vitro–in-vivo correlations.

Materials and Methods

Materials

Griseofulvin (99% purity), diazepam and Tween 80 were purchased from Sigma Aldrich Company (Poole, UK). Brij 76 was obtained from Fluka Chemika (Germany). Potassium dihydrogen orthophosphate and acetone (analytical grade) were obtained from BDH (VWR International Ltd, Poole, UK). Acetonitrile (HPLC grade) was purchased from Fisher Chemicals Ltd (UK).

Animals

Male Wistar rats, obtained from Harlan, UK, were maintained on a normal rat diet and water was freely available. All procedures were approved by the School's Ethical Review Committee and were conducted in accordance with Home Office standards under the Animals (Scientific Procedures) Act, 1986.

Preparation of griseofulvin particles

Griseofulvin was dissolved in acetone to form a 3.0% w/w solution. Aqueous surfactant solutions containing between 0.1–2.5% (w/w) Brij 76/Tween 80 surfactant blend (9:1 w/w ratio) were prepared. The griseofulvin solution (0.6 mL) was slowly added into the surfactant solution (30 mL) while homogenizing (T25 Ultra-Turax, IKA Werke GmBH & Co KG, Germany) at 24 000 rev min^{-1} for 5 min. The suspension formed was then freeze dried (Drywinner 110, Heto-Holden A/S, Gydevang, Denmark) for approximately 24 h. The freeze-dried product was washed a total of three times to remove any surfactant which was unassociated with the particles. To wash the particles, the particles were suspended in water, the suspension was centrifuged (SciQuip 3K30, Sigma Laboratory Centrifuges, Poole, UK) at 15 000 rev min^{-1} for 15 min, after which the supernatant was discarded. After the final washing, the pellet was once again freeze dried for 24 h. The final product obtained was used in further experiments.

Characterization of griseofulvin microcrystals

Morphology and size

The microparticles were mounted onto an aluminium stub using double-sided adhesive carbon tape and sputter-coated with gold for 3 min at 3 mA (Emitech K550, Ashford, Kent, UK). They were then examined using a scanning electron microscope (Philips/FEI XL30, Eindhoven, The Netherlands). The volume mean diameter was measured using low angle laser light scattering (Malvern S, Malvern Instruments, UK). The drug particles were suspended in filtered, deionized water containing 0.05% w/v polyoxyethylene sorbitan monooleate and briefly bath sonicated before measurements were taken to ensure there was no aggregation.

Griseofulvin content of microparticles

To determine the content of griseofulvin in the microparticles, a known mass of particles ($n = 3$) was dissolved in an absolute ethanol/water mixture and the solution was assayed using UV spectroscopy (Cary 3E UV-Visible Spectrophotometer, Varian, Inc. Scientific Instruments, USA).

Crystallinity

The crystallinity of the particles was studied using powder X-ray diffraction (PXRD). PXRD patterns were collected using a Philips PW3710 Scanning X-ray Diffractometer (Philips, Cambridge, UK) with a Cu K_α filter generated at 30 mA and 45 kV. The samples were gently compressed into a round disc sample holder and the surface smoothed before being loaded onto the diffractometer. The samples were scanned over a range of 2θ values from 5–50° at a scan rate of 1.0° 2θ s^{-1}. The starting material was used as the control.

Melting point and polymorphism

Differential scanning calorimetry (DSC) experiments were carried out using a DSC7 instrument (Perkin Elmer Instruments, Beaconsfield, Bucks, UK). Before each experimental session, the calorimeter was calibrated using high purity indium. The samples were loaded into aluminium pans which were sealed, then heated at a rate of 10°C min^{-1} under a nitrogen atmosphere. The onset melting points and enthalpies of fusion (△H) were calculated using Pyris software. Four replicates were performed and the starting griseofulvin material was used as the control.

In-vitro dissolution studies

The griseofulvin particles and the control (raw material) were encapsulated in size 9 (2.65×8.6 mm) gelatin capsules (Torpac, USA); each capsule containing 12.5 mg of the active drug. Dissolution studies were carried out at 37±0.5°C and 100 rev min^{-1} stirring speed using phosphate buffer (adjusted to pH 6.8±0.05) in a Type II (Paddle) dissolution apparatus (Pharmatest PTWS3C Dissolution Bath, Hainburg, Germany). The drug concentration in the dissolution medium was assayed spectrophotometrically at 295 nm (Cecil CE2020 UV Spectrometer) every 15 min for 3 h. Each formulation was analysed five times and the mean percentage of drug release was calculated.

In-vivo absorption studies

Absorption studies were carried out using male Wistar rats (160–180 g), in groups of four. The rats were allowed free access to both food and water before and during the study. Each rat was given one gelatin capsule (size 9) containing 12.5 mg active drug (in the form of griseofulvin microparticles or starting material) by oral gavage. After administration, the rats were placed in a cage where they were allowed to move freely.

Approximately 0.3 mL blood was collected from the tail vein of the rats into heparinized tubes (Microvette CB300, Sarstedt, UK) at 0.75, 1.5, 2.5, 3.5, 5.0 and 8.0 h post-administration. At 24 h, 2 mL blood was obtained via cardiac puncture. The blood samples were centrifuged and the plasma obtained was collected and frozen until required for analysis.

To determine the absolute oral bioavailability of the formulations, 0.5 mL of a 0.5 mg mL^{-1} solution of griseofulvin in a propylene glycol/absolute alcohol/water mixture (in a 4:1:5 v/v ratio) was administered intravenously through the tail vein of a different group of rats. The latter were then bled and the plasma drug levels were determined as for the oral group. The absolute oral bioavailability (fraction of the total drug dose absorbed into the systemic circulation) of the griseofulvin formulations was calculated using equation 1.

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

Determination of griseofulvin in plasma

To assay plasma griseofulvin concentrations, the frozen plasma samples were thawed by standing at room temperature. Acetonitrile (1 mL) was added to 0.1 mL plasma. The mixture was sonicated in a water bath for 1 min and then centrifuged at 10 000 rev min^{-1} for 10 min. A 0.9-mL sample of 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 mobile phase (65% acetonitrile/35% water v/v containing 0.15 $\mu g\,mL^{-1}$ internal standard, diazepam) and analysed using an HPLC method modified by Hackett & Dusci (1978). The chromatographic system used consisted of a Hewlett-Packard 1050 Series HPLC System (Agilent Technologies UK Ltd) and the peaks obtained were integrated using PC/Chrom+software (H&A Scientific Inc., USA). Reconstituted sample (50 μL) was injected into a 250 mm×4 mm column (5 μm C18 Macherey-Nagel GmBH & Co., KG Düren, Germany) fitted with a guard column at room temperature. The flow rate was 1.3 mL min^{-1}.

Before 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 $\mu g\,mL^{-1}$. Each sample was analysed 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 $\mu g\,mL^{-1}$. The correlation coefficient (r^2) was 0.9997. When the griseofulvin-spiked plasma samples were analysed, the results indicated that the extraction procedure was capable of recovering 96.1±0.2% at 0.5 $\mu g\,mL^{-1}$, 97.3±0.6% at 1.0 $\mu g\,mL^{-1}$ and 98.2±0.6% at 1.5 $\mu g\,mL^{-1}$. 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 $\mu g\,mL^{-1}$, while the limit of quantification was 0.1 $\mu g\,L^{-1}$, approximately seven-times the noise level.

Statistical analyses

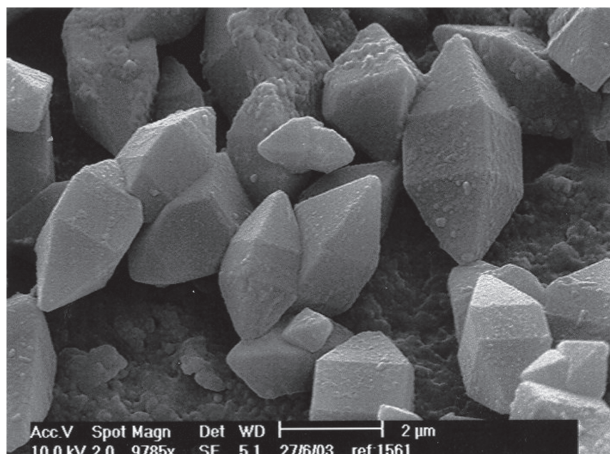
Repeated measures analysis of variance was used to determine statistically significant differences between the in-vitro dissolution profiles of the control and of the prepared particles. The same test was used to determine differences between their in-vivo absorption profiles. The Mann Whitney U-test was used to determine any statistically significant differences between their values for $AUC_{0–24}$, t_{max} and C_{max}.

Results and Discussion

Microparticle production and characterization

Griseofulvin microparticles were prepared by the solvent-diffusion method. Following the addition of the griseofulvin-in-acetone solution to an aqueous surfactant solution, the acetone, which was completely miscible with water, diffused into the aqueous phase causing the griseofulvin to precipitate out of solution. Scanning electron microscopy (Figure 1A) revealed the particles to be bipyramidal structures that were quite different in shape and size to the starting material (Figure 1B). Laser light scattering revealed a particle size of 2.18±0.12 μm, which was much smaller than that of the starting material (12.61±1.11 μm). Such a bipyramidal crystal habit of griseofulvin had been produced by supercritical fluid crystallization, in an attempt to produce particles with good processability

A



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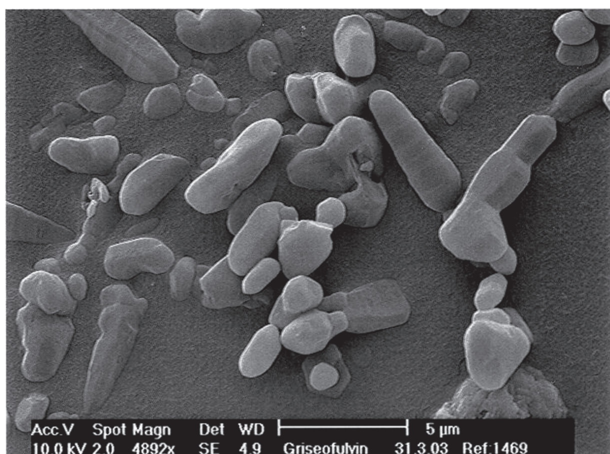

Figure 1 Scanning electron micrographs of the (A) bipyramidal griseofulvin particles produced by solvent-diffusion in a 1% w/w aqueous surfactant solution and (B) control (starting material).

(De Gioannis et al 2004; Jarmer et al 2005). From Figure 1, it can be seen that the surface of the particles was not completely smooth; this is believed to be due to the presence of the surfactant. It was expected that some of the surfactant (Brij 76/ Tween 80) initially dissolved in the aqueous medium adsorbed onto the newly-formed hydrophobic surfaces of the particles and thereby sterically stabilized the particles against further growth. Additives such as surfactants and polymers are known to influence the various stages of precipitation, such as crystal growth and nucleation (Davey 1982; Stefen 1988), and to adsorb onto the crystal/liquid interface as the crystals precipitate out of solution (Mackellar et al 1994).

In our preparation, the initial surfactant concentration in the aqueous medium was found to influence the formation of the bipyramidal structures. A 1% w/v Brij76/Tween 80 blend produced the particles of fairly uniform size shown in Figure 1A. Increasing the surfactant concentration to 1.5% w/w resulted in the dissolution of the drug and absence of particle formation. Decreasing the surfactant concentration to 0.5% w/w led to particles with a wider size distribution (Figure 2).

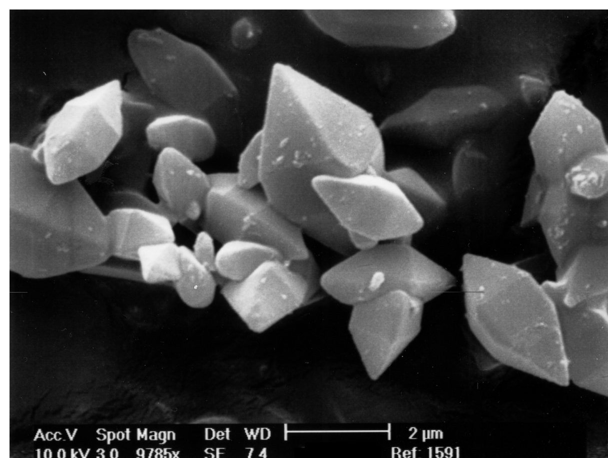

Figure 2 Scanning electron micrograph of griseofulvin particles produced by solvent-diffusion using 0.5% w/w aqueous surfactant solution.

Content analysis of the particles (shown in Figure 1A) revealed a griseofulvin content of 88% w/w (range 87–89% w/w, n = 3). Assuming that the bipyramidal particles were only composed of griseofulvin and surfactant, and that any residual solvent content was minimal, the surfactant (Brij 76 and Tween 80) concentration of the bipyramidal particles was calculated to be 12% w/w.

Differential scanning calorimetry (DSC) showed that the griseofulvin content of the bipyramidal particles was crystalline in nature. Only an endothermic melting peak with an onset temperature of 218.0 ± 0.5°C (n = 4) was seen on the DSC thermogram. Although this onset temperature was slightly lower than that of the starting material, (219.1 ± 0.2°C), it fell within the onset melting point temperatures (217–224°C) reported in the literature (Townley 1979). This suggested that the solvent-diffusion method of particle preparation had not altered the polymorphic form of the drug. The enthalpy of fusion (△H) of the bipyramidal particles was calculated to be approximately 87% of that of the starting material (102.92 ± 1.72 and 118.35 ± 1.84 $J g^{-1}$, respectively, n = 4), which confirmed that all the griseofulvin in the bipyramidal particles was crystalline.

X-ray diffraction of the bipyramidal particles was different to that of the starting material, as shown in Figure 3 (A and B). While the diffraction pattern of the starting material was composed of narrow peaks indicative of crystallinity, the diffraction pattern of the bipyramidal particles suggested the presence of both amorphous and crystalline material. The amorphous part of the diffraction pattern was thought to be due to the relatively large quantity of surfactant remaining in the sample (12% w/w). All the surfactant was thought to be on the surface of the particles, as surfactant incorporation within the crystal lattice would have led to changes in the melting point and enthalpy of fusion (△H), and this was not observed from the DSC experiments.

In-vitro dissolution studies

The in-vitro dissolution studies showed that the bipyramidal particles exhibited a much faster rate of griseofulvin dissolution

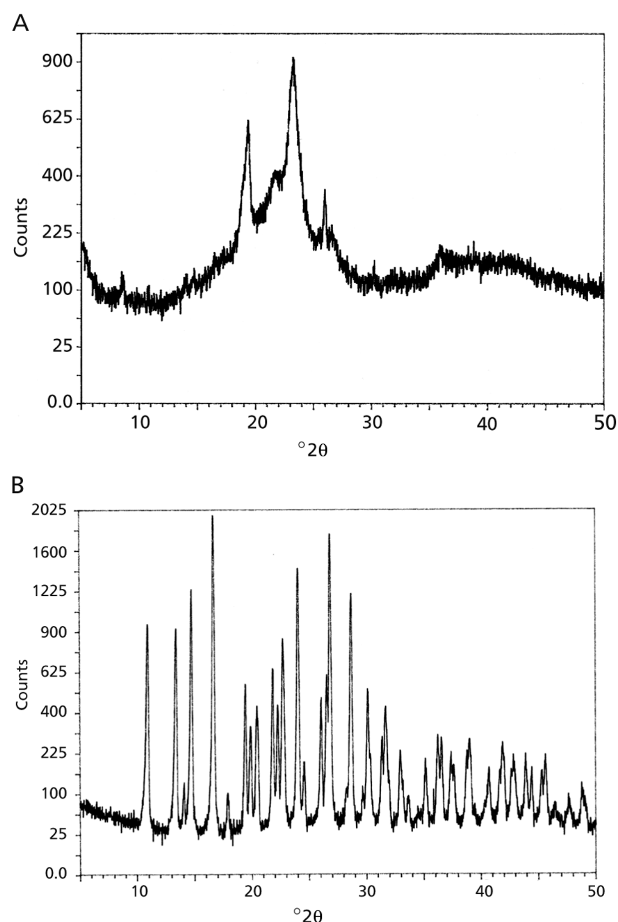

Figure 3 X-ray diffraction pattern for (A) bipyramidal particles and (B) control.

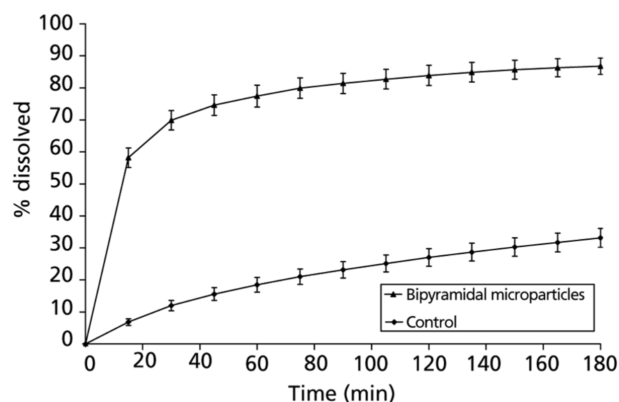

Figure 4 Mean in-vitro dissolution profile of griseofulvin bipyramidal (upper) and control (lower) particles at 37°C (n = 5, ± s.d.).

compared with the control (Figure 4). Repeated measures analysis of variance showed the two profiles to be significantly different ($P < 0.0005$). Within half an hour, approximately 70% of griseofulvin had dissolved compared with only 10% of the control material. The fast dissolution was likely to be due to the presence of the hydrophilic surfactant on the particle surface, which would facilitate particle wetting and dispersion in the aqueous medium and, consequently, lead to a relatively large specific surface area being available for dissolution. Improved wetting of the bipyramidal particles was observed during the dissolution experiments; following dissolution of the gelatin capsule, the bipyramidal particles dispersed rapidly within the dissolution medium, in contrast to the control material which aggregated and a portion of which remained (incompletely wetted) on the surface of the dissolution medium for the duration of the 3-h experiment.

In-vivo absorption studies

Following oral administration of the gelatin capsules (containing 12.5 mg of the active drug in the form of bipyramidal particles or control), the capsule disintegrated, following which the capsule contents had to dissolve in the gastrointestinal tract before drug absorption could take place. The mean absorption profiles of the bipyramidal and the control particles are shown in Figure 5, while the absorption profiles for individual rats in the two groups are shown in Figure 6 (A and B). The pharmacokinetic parameters are shown in Table 1. In the control group, griseofulvin plasma concentration increased to a maximum before decreasing to 0 at 24 h, with a t_{max} of 3.9 h, a profile which was fairly similar to those reported by Bates & Carrigan (1975). In contrast, the absorption profiles of the bipyramidal particles were erratic and absorption was not completed by 24 h, which suggested a slow, discontinuous dissolution of the bipyramidal particles in the rat gastrointestinal tract. Griseofulvin is known to be absorbed primarily in the duodenum, and to a smaller extent from the jejunum and ileum, and not at all from the colon (Bedford et al 1960; Lin et al 1973; Becker 1984). The fact that all four rats dosed with bipyramidal particles showed an elevated griseofulvin plasma level at 24 h post-dose suggested that the griseofulvin particles were still located in the small intestine at 24 h post-dose and that absorption was continuing.

The erratic absorption of the bipyramidal particles led to t_{max} being highly variable, ranging from 0.75 to 24 h. The

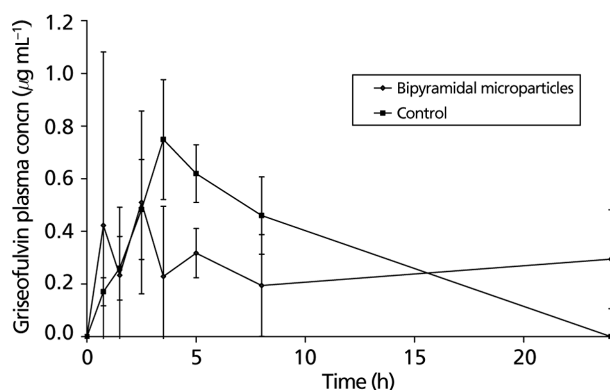

Figure 5 Mean in-vivo griseofulvin plasma concentration–time profile of griseofulvin bipyramidal (lower) and control (upper) particles following oral administration to rats (n = 4, ± s.d.).

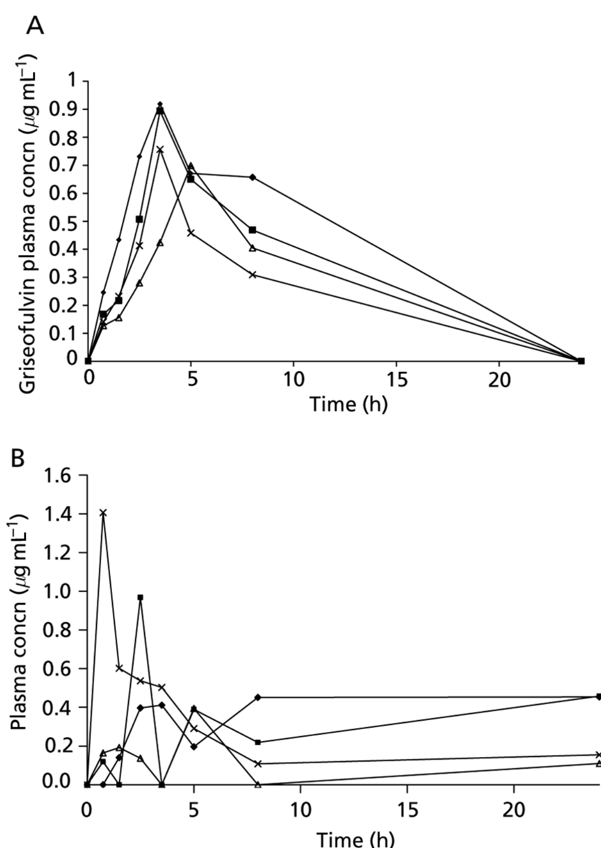

Figure 6 Plasma concentration–time profile of (A) control griseofulvin microparticles obtained from individual rats and of (B) griseofulvin microparticles produced by solvent-diffusion obtained from individual rats.

Table 1 The pharmacokinetic parameters of the bipyramidal and the control particles

Parameters	Control	Bipyramidal particles
AUC (h.μg mL^{-1})	7.53 (± 2.0)	6.23 (± 3.1)
C_{max} (μg mL^{-1})	0.82 (± 0.1)	0.81 (± 0.5)
t_{max} (h)	3.9 (± 0.8)	8.06 (± 10.8)
Absolute bioavailability (%)	3.94 (± 1.0)	3.36 (± 1.97)

latter t_{max} for one rat resulted in a much higher (but not statistically significant, $P > 0.05$, Mann Whitney) mean t_{max} for the bipyramidal particles than for the control group. The C_{max}, 24-h area-under-the-curve ($AUC_{0–24}$), and the absolute oral bioavailability for the bipyramidal particles and for the control were similar ($P > 0.05$, Mann-Whitney). Repeated measures analysis of variance showed the two absorption profiles were not significantly different from one another ($P > 0.05$). The statistically indistinguishable in-vivo absorption profiles of the bipyramidal and control particles was surprising, given the large difference seen in the in-vitro dissolution profiles shown in Figure 4. The excellent in-vitro dissolution of the bipyramidal particles was not reflected in its in-vivo absorption.

Poor drug dissolution in-vivo could be due to several reasons. For example, Brij 76, one of the surfactants used as the stabilizing agent, was a pasty solid at room temperature. The presence of this surfactant on the surface of the griseofulvin bipyramidal particles resulted in the particles showing a degree of cohesiveness. Although the cohesiveness of the particles did not appear to be a problem in-vitro, it is possible that in-vivo, the smaller volume of dissolution medium in the rat stomach and gentler agitation did not enable good dispersion of the griseofulvin microparticles. Such poor bioavailability of griseofulvin due to 'cohesiveness' of drug particles has been reported by Aoyagi et al (1982), who showed low drug bioavailability in man, thought to be due to slow dissolution of ultramicrosize particles following the formation of a paste-like agglomerate upon griseofulvin tablet contact with a small amount of water (such as in the stomach). Aoyagi et al (1985) surmised that the deaggregation force in human stomach might not be sufficiently strong to deaggregate the adhesive agglomerate and allow drug dissolution. It seems that this might have held true in our experimental rats. If the majority of the griseofulvin microparticles remained aggregated into a large pellet, and was treated as indigestible material, they could have been retained in the rat stomach for a long period of time (Kaus et al 1984). In some rats, pulsatile increases in griseofulvin concentration were seen in the plasma. This could have been due to small parts of the particulate pellet breaking off and dissolving intermittently. Such events may have contributed to the large variability in the absorption profiles of the rats dosed with the bipyramidal particles.

In addition, the experimental rats were allowed free access to food. In man, the fed state is known to result in increased capsule disintegration time (Casey et al 1976). A similar increase in capsule disintegration time in the fed experimental rats, compared with the fasted state, can also be expected, although the capsule shell manufacturer quotes a disintegration time of less than 10 min in both fasted and fed states as long as the rats have access to water (http://www.torpac.com/rat.htm & personal communication with Torpac). Gastric emptying is also known to be retarded in the fed state; for example, Haruta et al (2001) reported that in contrast to complete gastric emptying of a liquid within 1 h of dosing a fasted rat, emptying had not completed even 6-h post-dose in two of three fed rats. Such retarded gastric emptying would occur and delay drug absorption in both groups of rats in our study i.e. those receiving the control as well as those receiving the bipyramidal particles. However, the cohesive nature of the bipyramidal particles might further hinder drug absorption, if the particles adsorb onto food matter present in the stomach, adsorption being likely to reduce dissolution rate and to increase variability in drug absorption profiles.

In this study, the in-vitro dissolution test was not predictive of the in-vivo situation. It has been said that good in-vitro–in-vivo correlations can be expected for BCS Class II drugs 'if the in-vitro dissolution rate is similar to the in-vivo dissolution rate, unless the dose is very high' (Löbenberg & Amidon 2000). The difficulty of ensuring similar in-vitro and in-vivo dissolution rates can be readily appreciated. In our experiments, the in-vitro dissolution rate was obviously much faster than the in-vivo dissolution rate. The importance of the

correct in-vitro dissolution rate has been shown previously. For example, Aoyagi et al (1985) reported better in-vitro–in-vivo (in man) correlation when the dissolution studies (of indometacin capsules) were conducted under low, rather than high, agitation intensity. In contrast, Ogata et al (1984) showed improved in-vitro–in-vivo correlation when dissolution rates of nalidixic acid tablets were determined under vigorous agitation. In our experiments, the fact that the animals were allowed access to food further complicated matters. In future, more biorelevant dissolution media, such as Fed State Simulated Intestinal Fluid could be used for the in-vitro dissolution experiments. This might lead to increased in-vitro dissolution rate of the control particles. In addition, the in-vivo experiments should be conducted in fasted animals to remove the food effects. One could also determine the in-vivo drug absorption following the administration of a particle suspension to compare with this study where particles were contained in a capsule shell. While the availability of a rat capsule enables the administration of particulate systems in the solid form, a liquid particle suspension may have a higher gastric emptying rate, or may mix with stomach contents to a greater extent. It is also known that, in man, capsules can lodge between the mucosal folds of the stomach and that following capsule dissolution, the drug released can remain localized, rather than disperse (Hunter et al 1980). Capsule immobilization in some, but not all, of the experimental rats could have contributed to the large variability in drug absorption seen in the experimental animals. In addition, the only commercially available rat capsule used (2.65-mm external diameter, 8.6-mm length when locked, body capacity 25 μL) was much greater in size compared with the largest capsule used in man (size 0, body volume 670 μL) in relation to the stomach capacity of rats and man. This raises concerns about the transferability of the rat results to man and shows the need for smaller rat capsules.

Conclusion

Bipyramidal griseofulvin microparticles were produced by the solvent-diffusion method. Although the particles had a much faster dissolution rate in-vitro compared with the control, the in-vivo absorption and bioavailability of the BCS Class II drug were not improved. The lack of in-vitro–in-vivo correlation could have been due to a number of reasons, such as the much greater in-vitro dissolution medium volume and agitation differences between the in-vitro and in-vivo situation. The results showed that although improving the in-vitro dissolution rate of a poorly water-soluble Class II drug is generally expected to result in enhanced in-vivo bioavailability, it does not always happen.

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