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Effects of plasma irradiation on the wettability and dissolution of compacts of griseofulvin

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Abstract

In this study, the use of plasma irradiation was investigated as a possible technique for increasing the dissolution rate of the poorly soluble drug griseofulvin. Plasma is a partially ionised gas consisting of ions, electrons and neutral species. Oxygen plasma was used to treat griseofulvin compacts as this would lead to the formation of oxygen containing functional groups on the surface of the compact thus increasing the wettability. Compacts containing 300 mg of the drug were prepared using a stainless steel punch and die assembly and plasma treated. The effect of the length and power of the plasma treatment upon the dissolution rate of griseofulvin was investigated. Dissolution experiments of griseofulvin were carried out using the paddle method using 0.1 M HCl and 0.1 M HCl with 2% sodium dodecyl sulphate (SDS) as the dissolution media. The wettability was assessed by contact angle measurements using the sessile drop technique with the contact angle being measured every second for a period of ten seconds using pure water (to European Pharmacopoeia standards). Plasma treated and untreated samples were also analysed by scanning electron microscopy. Although plasma treatment was found to increase the wettability of griseofulvin it was not found to increase the dissolution rate as the treatment caused surface fusion of the material.

Keywords: Poorly soluble drugs; Dissolution; Wettability; Plasma irradiation

1. Introduction

Increasing the dissolution and bioavailability of poorly soluble drugs is a major challenge facing the pharmaceutical industry today as about 40% of potential drugs produced are almost insoluble (Wotton et al., 2001). There are many methods for increasing the dissolution of drugs such as reducing particle size, conversion of the drug to the salt form or polymorph, the use of complexing agents such as cyclodextrins, the use of surfactants or co-solvents and the synthesis of pro-drugs.

A plasma is a partially ionised gas, which contains an equal number of positive and negative charges and unionised neutral species such as molecules, atoms and radicals (Morosoff, 1990; Moisan et al., 2000). The plasma is created by subjecting a gas, for example oxygen, to a radio frequency potential in a vacuum chamber. This leads to the production of electrons, which are accelerated by an electric

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field and collide with neutral molecules (Bell, 1974). During this process bound electrons are removed from neutral molecules leading to the production of free radicals, atoms and ions. In the case of oxygen plasma, oxygen can be excited from the ground state to higher electronic levels leading to the formation of oxygen radicals and ions such as O_2^+ and O_2^-, which can result from the collision of an electron and two oxygen molecules. Dissociation reactions can lead to the production of oxygen atoms and ions such as O^- and O^+. These ions and radicals react further to produce more ions and free radicals. Oxygen radicals formed react with chemical groups on the surface of an exposed sample during plasma treatment leading to the formation of oxygen containing functional groups such as hydroxyl, carbonyl and possibly carboxyl groups (Sugiura et al., 1985; Esumi et al., 1986; Esumi et al., 1987). The production of these oxygen containing functional groups lead to large increases in wettability. Plasma irradiation only modifies the surface of a material so the bulk properties remain unaffected.

Previous studies have suggested a correlation between wettability and dissolution rates of pharmaceutical powders such as Lippold and Ohm (1986) who investigated the dissolution rates of powders in aqueous propan-2-ol mixtures and correlated the calculated quotients of effective surface area (A_{ef}) and the liquid boundary layer thickness (d) with the contact angles of the drug. They found that increasing the wettability increased the effective surface area available for dissolution thus leading to an increased dissolution rate. Studies by Chow et al. (1995) who investigated the doping of phenytoin crystals with various doping agents also seemed to show that increasing the wettability could lead to an increased intrinsic dissolution rate but they concluded that these increases could also in part be due to structural defects caused by the doping agents. In this current study the use of plasma irradiation was investigated as a possible technique for increasing the drug dissolution rate of compacts of griseofulvin, an anti-fungal with aqueous solubility of $0.015\,g\,l^{-1}$. By increasing the wettability of the drug surface it was postulated that it might be possible to increase its dissolution rate given the role of surface wetting in drug dissolution.

2. Materials and methods

Griseofulvin (lot number: 48F0787) was purchased from Sigma Chemical Company, Poole, Dorset, UK. Sodium dodecyl sulphate (SDS) and hydrochloric acid 1 M (general purpose grade) were purchased from BDH Laboratories, Poole, Dorset, UK.

2.1. Particle size analysis

Particle size analysis was carried out using a Malvern Mastersizer (He–Ne laser, output power 5 mW at 632.8 nm), Malvern Instruments Ltd., Spring Lane South, Malvern, Worcestershire, UK.

A 1% Tween 20 (BDH laboratories, Poole, Dorset, UK) solution in distilled water was prepared as a carrier fluid and filtered through a 0.45 μm filter unit to remove unwanted particulate matter. Griseofulvin (20 mg) was added to 20 ml of carrier fluid and sonicated for 2.5 min. The sample unit was washed out with 70 ml of clean carrier fluid (distilled water) and then 80 ml of carrier fluid. A lens with a focal length of 100 mm was used with a measuring size range of 0.5–180 μm. Background measurements were obtained using 80 ml of carrier fluid, which was circulated at half speed so that no bubbles would be produced in the carrier fluid for 10 s beforehand. The laser beam was then aligned automatically; the sample was then added to the sample unit (total volume 100 ml) and circulated at full speed for 10 s so that the particles would quickly disperse into the carrier fluid. It was then allowed to equilibrate at half speed for 20 s so that the sample would remain dispersed in the carrier fluid and to stabilise the obscuration reading in the range 0.1–0.3 before the analysis was carried out. This procedure was then repeated for a second sample. The results of the two samples were averaged using the instrumental software.

2.2. Preparation of compacts

Griseofulvin (300 ± 0.1 mg) was weighed accurately to three decimal places using a four decimal place gram weighing balance. This was then placed in a stainless steel flat punch (diameter: 15.83 mm) and die assembly. The punch and die assembly was placed into a Beckman KBr press (Beckman Ltd., Glenrothes, Fife, Scotland, UK) which was compressed at

a pressure of 7.72×10^7 or 3.86×10^7 Pa for one second under vacuum with a pressure of 1.94×10^4 Pa. The die was cleaned using distilled water and dried. The same procedure was repeated for all compacts.

2.3. Dissolution experiments

The dissolution experiments were carried out using a Caleva model 7ST dissolution apparatus (G.B. Caleva Ltd., Butts Pond Industrial Estate, Sturminister Newton, Dorset, UK) and the absorbance of the samples were measured using a Perkin-Elmer Lambda 2 UV-Vis spectrophotometer (Perkin-Elmer, Beaconsfield, Buckinghamshire, UK).

Dissolution media (0.1 M HCl, 1 l) was poured into each one of the seven beakers and warmed up to 37 °C before starting the experiment. The paddles were set at 25 ± 2 mm from the bottom of the beaker to ensure they met BP specifications and rotated at 100 rpm. The pH of the dissolution media was measured at the start and end of the experiment to ensure that it remained constant. Each of the beakers was fitted with a 10 ml syringe to withdraw samples from the middle of the beaker. Samples were taken at 10 min intervals from each of the beakers and filtered through 0.45 μm disposable filter units (Nalgene surfactant free cellulose acetate (SFCA) Fisher Scientific Ltd., Bishop Meadow Road, Loughborough, Leicestershire, UK). The volume was kept constant by replacing the sample taken with 10 ml of the dissolution media. The absorbance of the samples was measured at 292 nm for griseofulvin with 0.1 M HCl and at 296 nm for 0.1 M HCl with 2% SDS. SDS was used later on for griseofulvin in order to more clearly differentiate between untreated and plasma treated samples due to the increased solubility of griseofulvin in this media. Results are an average of six determinations.

2.4. Plasma treatment

Samples were irradiated using a Fisons polaron, PT7150 RF plasma barrel etcher (Belbrook Business Park, Bell Lane, Uckfield, Sussex, UK). The compact was placed on a glass microscopic slide in the plasma chamber and then plasma treated using oxygen plasma. Griseofulvin compacts were plasma treated for one minute at 6–7, 10, 20 and 30 W on both sides and 80 W on one side only (initial experiment, Fig. 1)

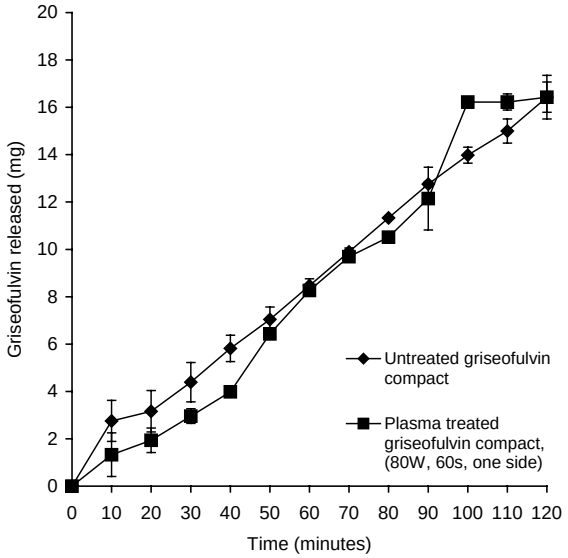

Fig. 1. Dissolution profiles of 300 mg griseofulvin compacts made at a pressure of 7.72×10^7 Pa showing the effect of plasma treatment on one side upon the dissolution rate using 0.1 M HCl as the dissolution media (mean ± S.D., $n = 6$).

to investigate the effect of the power of the plasma treatment upon the dissolution rate and the wettability of the compacts. Griseofulvin compacts were also plasma treated for 10, 20 and 30 s at a power of 10 W. A lower power of 10 W was chosen to investigate the effect of treatment times upon the wettability and dissolution rates of the compacts as earlier experiments had shown that a plasma generated at this power was sufficient to modify the surface of the compact in order to increase its wettability (Figs. 5 and 6).

2.5. Measurement of contact angles

Contact angle measurements were carried out using a FTA200 dynamic contact angle analyser (First Ten Ångstroms, Portsmouth, Virginia, USA). Compacts of griseofulvin were made as described before in Section 2.2 and plasma treated as described in Section 2.4. A syringe fitted with a needle was used to place 10 μl of pure water (to European Pharmacopoeia standards) automatically onto the compact. The contact angle was measured every second for a period of 10 s. At least duplicate determinations were carried out for each compact. Measurements were carried out at room temperature.

2.6. Scanning electron microscopy

This was carried out using a Jeol 6310 Scanning electron microscope (Jeol Ltd., Jeol House, Silvercourt, Watchmead, Welwyn Garden City, Hertfordshire). Compacts of griseofulvin were produced as described in Section 2.2. A compact of the drug was broken into two by hand, one half was plasma treated at 10 W for 60 s whilst the other was left untreated. The samples were mounted onto stainless steel stubs using conductive double-sided carbon mount and the surface of the samples was coated with palladium. All samples were viewed at 5000× magnification.

2.7. Statistical methods

The effect of plasma treatment on one side of the compact upon the dissolution rate of griseofulvin was analysed using a one sample *t*-test for each time point ($n = 6$). One-way ANOVA was used to analyse the effect of plasma treatment upon the contact angle of griseofulvin, the effect of the power of plasma treatment upon the dissolution rate (Figs. 3 and 4) and contact angle of griseofulvin and the effect of treatment time at 10 W upon the dissolution rate and contact angle of griseofulvin compacts. The significance level was set at 0.05.

3. Results and discussion

3.1. Particle size analysis

The particle size analysis found the mean volume particle size for griseofulvin to be 13.53 μm with a modal particle size of 9.2 μm and a median particle size of 8.81 μm. The plot showed no presence of any aggregates.

3.2. The effect of plasma treatment on one side only

The compacts were plasma treated on one side only at 80 W for 60 s in order to obtain an idea of the effect of the plasma treatment. The dissolution profile is shown in Fig. 1. The dissolution rate of the plasma treated compacts (made at 7.72×10^7 Pa) is significantly lower than that of the untreated compacts for the first twenty minutes ($P < 0.05$) but after this the dissolution rates of the plasma treated and untreated compacts are not statistically significant ($P > 0.05$). The dissolution rate of griseofulvin could be delayed due to the fusion effect caused by plasma treatment. The surface can become fused due to cross-linking reactions caused by the oxygen radicals possibly leading to the formation of oxygen bridges or cross-linking of the methoxy groups present.

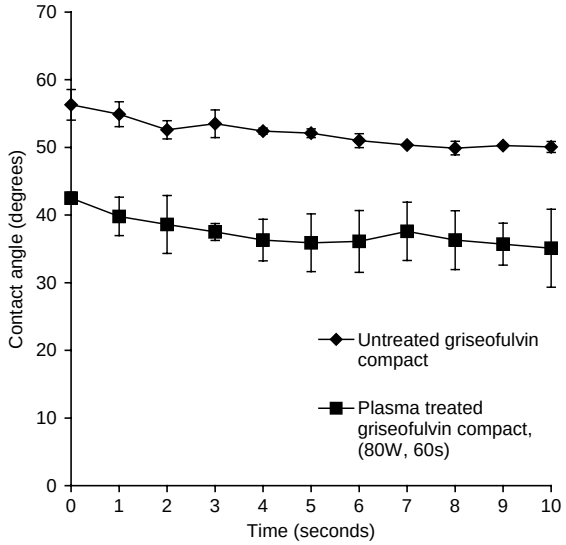

Fig. 2. Effect of plasma treatment upon the contact angle of 300 mg griseofulvin compacts made at a pressure of 7.72×10^7 Pa (median ± range, $n = 2$).

The contact angle data (Fig. 2) demonstrated that the plasma treated compacts are more wettable than the untreated compacts. The contact angle was found to be lowered by approximately a third upon plasma treatment. This could be due to the oxygen functional groups such as hydroxyl or carbonyl groups created on the surface of the compact during plasma irradiation. The presence of such groups after plasma treatment has been shown by Lin and Tiong (2000) who detected hydroxyl, carbonyl and peroxy groups on the surface of plasma treated pdyethylenes using X-ray photon spectroscopy.

3.3. Effect of radio frequency power of plasma treatment

The power of the plasma treatment did not affect ($P > 0.05$) the dissolution rate of 300 mg griseofulvin

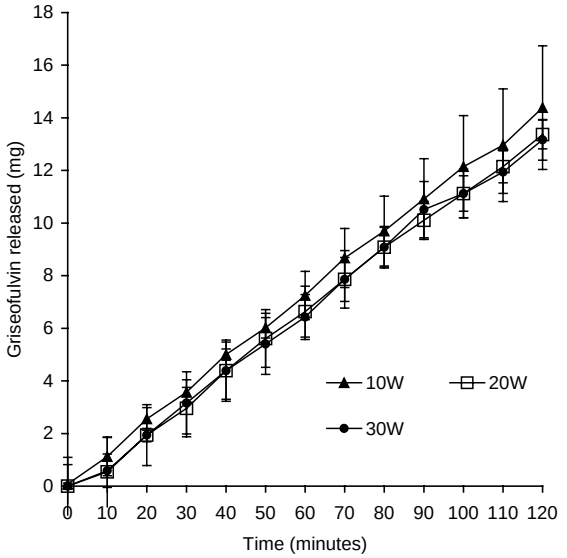

Fig. 3. Effect of the power of the plasma treatment upon the dissolution rate of 300 mg griseofulvin compacts made at a pressure of 3.86×10^7 Pa (mean ± S.D., $n = 6$).

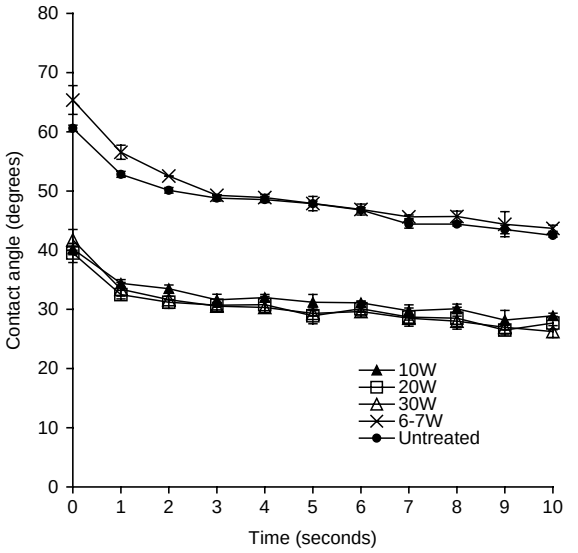

Fig. 5. Effect of the power of the plasma treatment carried out for 60 s on the contact angle of 300 mg griseofulvin compacts made at 3.86×10^7 Pa (median ± range, $n = 2$).

compacts (Figs. 3 and 4). However, the contact angle of the compacts treated at 6–7 W was found to be significantly higher ($P < 0.05$) than those treated at 10, 20 and 30 W (Fig. 5). The contact angle of the compacts treated at 6–7 W are not significantly different from the untreated compacts ($P > 0.05$) showing that the surface of the compacts remains unaffected after plasma treatment at 6–7 W. The SEM images of the tablets treated at 6 and 30 W show that the tablet at 6 W is similar to that of the untreated tablet (Fig. 10) the surface of the tablet at 30 W has possibly fused together giving it what seems like a much improved compacted surface (Fig. 6). This fusion effect could be due to cross-linking reactions between different functional groups caused by the free radicals produced during plasma treatment. Therefore, a power of 6 W is not sufficient to generate a strong enough plasma to modify the surface, which would account for the increased contact angle.

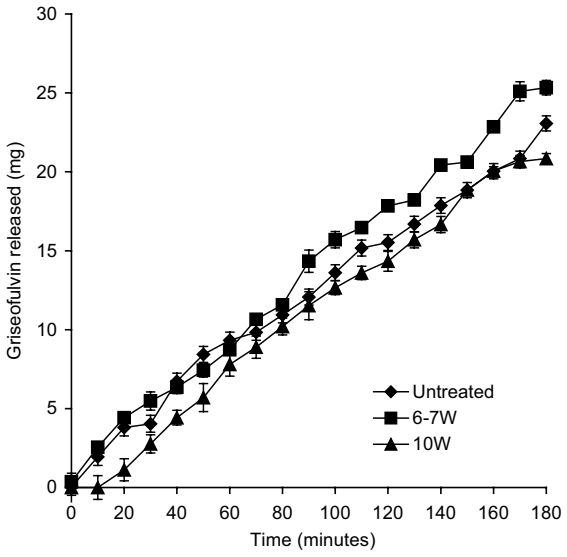

Fig. 4. Dissolution profiles showing the effect of different low powered plasma treatments carried out for 60 s on the dissolution rate of 300 mg griseofulvin compacts made at 3.86×10^7 Pa (mean ± S.D., $n = 6$).

3.4. Effect of different treatment times

The effect of length of the plasma treatment on the dissolution of the griseofulvin compacts was investigated using a 10 W plasma (Fig. 7). The plasma was generated at 10 W as this was the lowest power, which was sufficient to modify the wettability of the surface. No differences were observed in the dissolution rates of the treated drug compacts ($P > 0.05$,) but the different treatment times were found to significantly affect

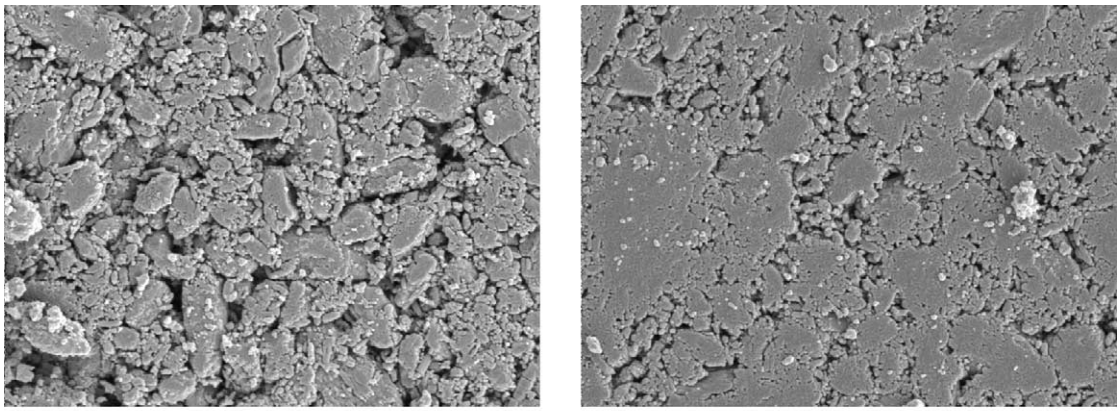

Fig. 6. A typical surface obtained on plasma treatment of a 300 mg griseofulvin compact treated at (a) 6 W and (b) 30 W.

the contact angle of the drug compacts ($P < 0.05$). The contact angle for a treatment time of 30 s is slightly higher than that for 10 and 20 s this could be because the cross-linking reactions could start to occur with a treatment time of 30 s but not with treatment times of 10 and 20 s (Fig. 8) as more free radicals would be produced with longer treatment times increasing the occurrence of possible cross-linking reactions.

3.5. Different dissolution media

In order to more clearly differentiate between the dissolution of the untreated and plasma treated compacts the dissolution media was replaced with hydrochloric acid with 2% SDS as griseofulvin would be more soluble in this media. The dissolution rate of griseofulvin was found to increase with the use

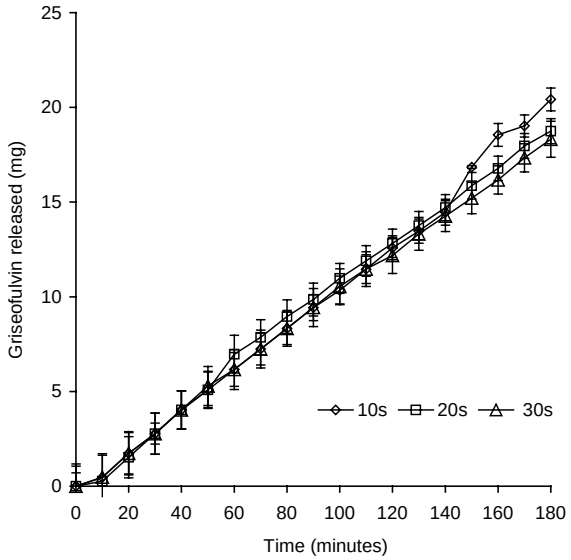

Fig. 7. Effect of the length of plasma treatment at 10 W on the dissolution rate of 300 mg griseofulvin compacts made at 3.86×10^7 Pa using 0.1 M HCl as the dissolution media (mean ± S.D., $n = 6$).

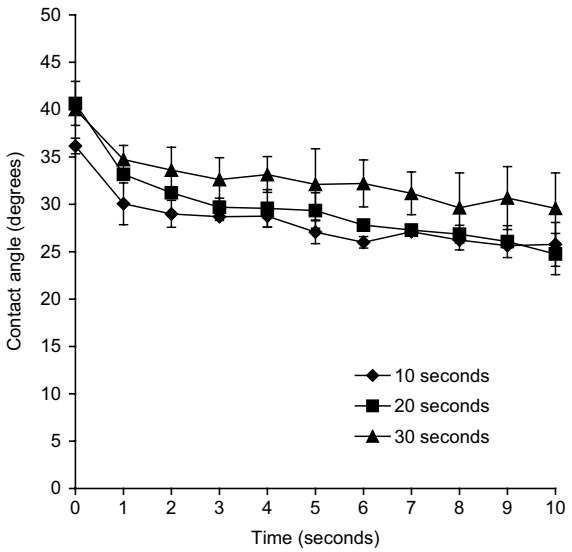

Fig. 8. Effect of the length of plasma treatment at 10 W on the water contact angle of 300 mg griseofulvin compacts made at 3.86×10^7 Pa (median ± range, $n = 2$).

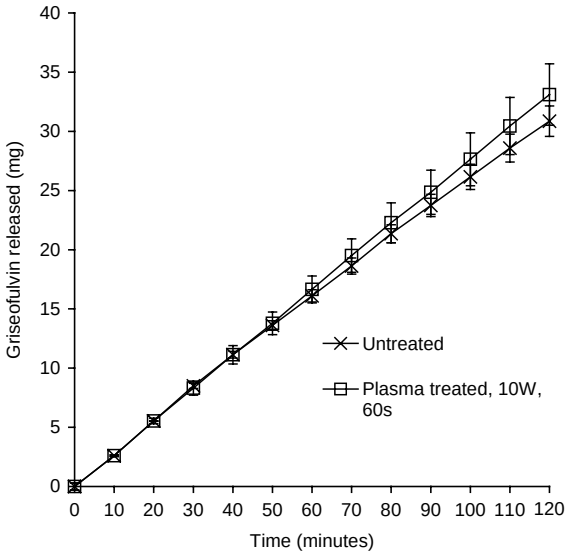

Fig. 9. Dissolution profiles of untreated and plasma treated 300 mg griseofulvin compacts made at a pressure of 7.72×10^7 Pa using 0.1 M HCl with 2% SDS as the dissolution media (mean ± S.D., $n = 6$ for untreated and 5 for plasma treated compacts).

of SDS as about twice as much griseofulvin is dissolved after 120 min in this medium (Fig. 9) compared to that observed on using HCl alone (Fig. 1). With a critical micelle concentration of approximately $0.3\,g\,l^{-1}$ SDS forms micelles at a 2% concentration. As griseofulvin is hydrophobic it is able to dissolve in the hydrophobic layers of the micelles formed by the hydrocarbon chains of the dodecyl groups. Plasma irradiation was found to have no effect ($P > 0.05$) upon the dissolution rate of griseofulvin in this system (Fig. 9).

3.6. SEM analysis

The SEM results indicate that the surface of griseofulvin has probably fused together due to cross-linking reactions after plasma treatment (Fig. 10). This surface fusion may be responsible for the decreased dissolution rate in some cases, particularly with using HCl as the dissolution media, as the fused surface would reduce the overall surface area of the compact available for the dissolution process.

In summary the contact angle data clearly indicates that the wettability of the griseofulvin compacts increases on plasma treatment indicating that the plasma treatment does make the surface of the drug more wettable. During plasma treatment high energy oxygen ions and radicals would be produced. These would collide with the exposed surface groups of the griseofulvin compacts leading to the formation of carbonyl and hydroxyl groups on the surface of the compact which would cause large increases in wettability, the presence of these oxygen containing functional groups has been detected by X-ray photon spectroscopy by Lin et al. as discussed in Section 3.2. The length of plasma treatment or the power at which the treatment was carried out did not seem to affect the dissolution

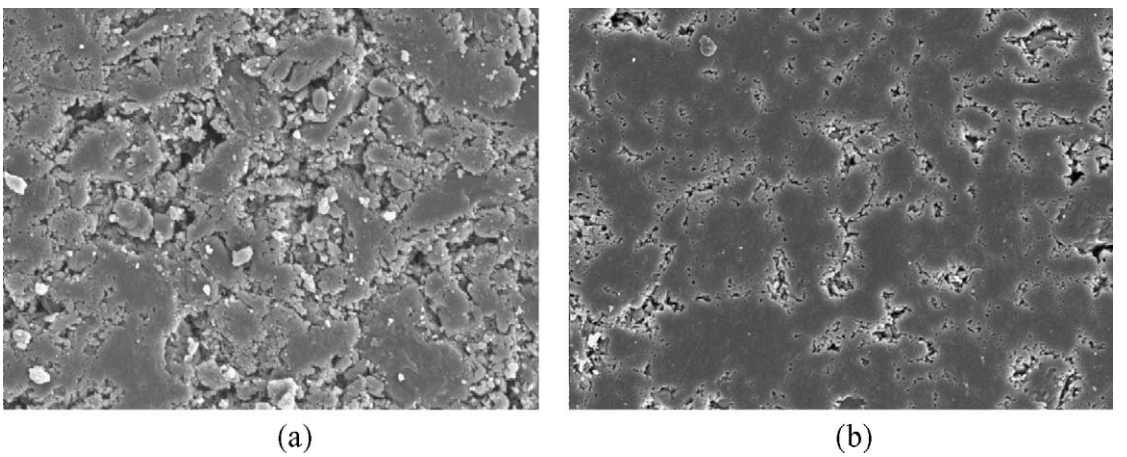

Fig. 10. The surface of the untreated griseofulvin compact (a) and that after plasma treatment at 10 W for 60 s (b) viewed at 5000× magnification.

rate of the compacts ($P > 0.05$). The dissolution rate may be largely unaffected by surface plasma modification of the drug as the bulk of the drug in the tablet is not modified by the plasma treatment. However, the power at which the plasma treatment was carried out did affect the contact angle as with a power of 6 W the contact angle was found to be significantly higher ($P > 0.05$) than the contact angle with 10, 20 and 30 W. This could be because 6 W may be too low to generate a strong enough plasma to modify the surface. The contact angle was also significantly higher ($P < 0.05$) for a treatment time of 30 s at 10 W when compared to treatment times of 10 and 20 s. This could be because cross-linking reactions could start to occur with a treatment time of 30 s which could reduce the effect of surface oxidation leading to a slight decrease in wettability, with longer treatment times the effect of the cross-linking reactions could be overcome with further oxidative reactions. The occurrence of cross-linking reactions would explain the lower dissolution rate of griseofulvin compacts for the first twenty minutes when plasma treated on one side (Fig. 1) as this would delay the release of griseofulvin when compared to the untreated compacts.

4. Conclusion

Although plasma treatment was found to increase the wettability of griseofulvin it was not found to increase the dissolution rate. It would appear that any advantages offered by the increased wettability of the compact are reduced by the fusion of the surface on plasma treatment.

Acknowledgements

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