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Effects of oxygen plasma treatment on the surface wettability and dissolution of furosemide compacts

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Abstract

The plasma irradiation of furosemide (frusemide) was investigated as a possible technique for increasing the dissolution rate of this drug. Oxygen plasma was used to generate oxygen-containing functional groups on the surface of the compact to increase the wettability of the surface and the dissolution rate of the drug. Compacts of furosemide (300 mg) were produced using a stainless steel die and punch assembly, which was placed into a KBr press. The time of the plasma treatment was varied to assess the effect if any upon the dissolution rate and the wettability of the drug. Dissolution experiments of the plasma-treated and untreated compacts were carried out using the paddle apparatus method. Dissolution was carried out at 37 °C using 1 L of 0.1 M HCl and phosphate buffer (pH 6). The wettability was assessed by contact angle measurements using the sessile drop technique. Untreated and plasma-treated samples were analysed by scanning electron microscopy at × 5000 magnification. Plasma treatment was found to lower the equilibrium contact angle from approximately 50 to 35 ° but the dissolution rate was not significantly affected. This was attributed to fusion of the surface by the plasma treatment.

Introduction

Improving the dissolution of poorly soluble drugs is a major challenge facing the pharmaceutical industry today as 40% of potential drugs produced have limited aqueous solubility (Wotton 2001). There are a number of commonly used methods for improving the dissolution of drugs, including the use of surfactants, cyclodextrins, complexing agents and co-solvents, conversion of the drug to the amorphous form, the synthesis of pro-drugs and the use of alternative salt forms. Previous studies have demonstrated a correlation between wettability and dissolution rates of pharmaceutical powders (Lippold & Ohm 1986). Within the automotive and biomedical devices industries the technique of plasma irradiation is widely used to increase the wettability of surfaces of polymeric materials. A plasma is a partially ionised gas that is created by subjecting a gas to a radio frequency potential in a vacuum chamber (Moisan 2000). This leads to the production of charged species, which are accelerated by an electric field leading to partial ionization of the oxygen gas. Other species such as radicals and oxygen atoms can also be produced due to the occurrence of electronic and dissociation reactions. The free radicals produced react with surface chemical groups to lead to the formation of oxygen-containing functional groups such as carbonyl, hydroxyl or carboxyl groups, which enhance surface wettability (Sugiura et al 1985). This study sought to investigate whether this technique had any application in the pharmaceutical field for enhancing the dissolution of drug compacts through the enhancement of surface wettability using furosemide (frusemide), a diuretic with an aqueous solubility of 0.029 g L^{-1}, as a model drug.

Materials and Methods

Materials

Furosemide (Lot number: 69H1237) was purchased from Sigma Chemical Company (Poole, Dorset, UK). Hydrochloric acid 1 M (general purpose grade) was purchased

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from BDH laboratories (Poole, Dorset, UK). Potassium dihydrogen orthophosphate (purity 99–100%) was purchased from Surechem products Ltd (Needham Market, Suffolk, UK). Disodium hydrogen orthophosphate dihydrate (Sörensons salt) (purity > 98%) was purchased from Fisher scientific Ltd (Bishop Meadow Road, Loughborough, Leicestershire, UK).

Particle size analysis

Particle size analysis was carried out using the 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 solution in distilled water was prepared as a carrier fluid and filtered through a 0.45-μm filter unit to remove any particulate matter. Tween 20 was added to help disperse furosemide in the distilled water. Furosemide (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 focal length of 100 mm was used to allow sizing in the range 0.5–180 μm. Background measurements were obtained using 80 mL of carrier fluid, which was circulated at half speed for 10 s beforehand. The laser beam was then aligned automatically, the sample was added to the sample unit (total volume 100 mL) and circulated at full speed for 10 s. It was then allowed to equilibrate at half speed for 20 s before the analysis was carried out. This procedure was repeated for a second sample. The results of the two samples were averaged using instrumental software.

Preparation of tablets

Furosemide (300 mg) was weighed accurately to 3 decimal places using a 4 decimal place balance. The drug substance was then placed in a stainless-steel punch and die assembly. The punch and die assembly was placed into a Beckman KBr press (Beckman Ltd, Glenrothes, Fife, Scotland, UK) and compressed at a pressure of 77 MN m^{-2} for one second under vacuum. The die was cleaned using distilled water and dried.

Dissolution experiments

The dissolution experiments were carried out using the Caleva model 7ST dissolution apparatus (G.B. Caleva Ltd, Butts Pond Industrial Estate, Sturminister Newton, Dorset, UK) and the absorbance of the samples measured using the Perkin Elmer Lambda 2 uv/vis spectrophotometer (Perkin Elmer Ltd, Beaconsfield, Buckinghamshire, UK). One litre of dissolution media (0.1 M HCl, pH 2 or phosphate buffer, pH 6) 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 and rotated at 100 rev min^{-1}. Phosphate buffer was made up using 91.9% potassium dihydrogen orthophosphate (KH_2PO_4) and 8.1% Sorensons salt ($Na_2HPO_4.2H_2O$). The pH was measured at the start and end of the experiment to ensure that it remained constant and that it had not changed with any dissolved furosemide. Each of the beakers was fitted with a 10-mL syringe to withdraw samples. Samples were taken at 10-min intervals from each of the beakers and filtered through a 0.45-μm disposable filter unit (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 270 nm for furosemide with 0.1 M HCl and at 275 nm for phosphate buffer (pH 6).

Plasma treatment

Samples were irradiated using Fisons polaron, PT7150 RF plasma barrel etcher (Belbrook Business Park, Bell Lane, Uckfield, Sussex, UK). The compact was placed on a microscopic glass slide in the plasma chamber. The compact was then plasma treated using oxygen plasma. Furosemide compacts were plasma treated for 15, 30 and 60 s at 80 W on both sides (excluding initial experiment) for the HCl experiments and at 10 W for 60 s with the phosphate buffer experiment. A lower power was used as other experiments carried out with another drug showed that a plasma generated at a power of 10 W was sufficient to improve the wettability of the surface while a plasma generated at 80 W could be too harsh and cause some surface degradation.

Measurement of contact angles

Contact angle measurements were carried out using the FTA200 Dynamic Contact Angle Analyser (First Ten Ångstroms, Portsmouth, VA). Compacts of the drug furosemide were made as described above. A syringe was used to place a drop of pure water 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.

Scanning electron microscopy

This was carried out using the Jeol 6310 Scanning electron microscope (Jeol Ltd, Jeol House, Silvercourt, Watchmead, Welwyn Garden City, Hertfordshire, UK). Compacts of furosemide were produced as described above. Each compact was broken into two, one half was plasma treated at 10 W for 60 s while the other was left untreated. The samples were mounted onto stainless-steel stubs using conductive double-sided carbon mount (Leit-C, Neubauer Chemicals, Germany) and the surface of the samples was coated with palladium. All samples were viewed at ×5000 magnification.

Stability studies

Compacts of furosemide were plasma treated at 10 W for 60 s and stored at room temperature. The contact angle of the compacts was measured every day for a period of five days (n = 12).

Infra-red spectroscopy

This was carried out using Perkin Elmer 1600 series FTIR (Perkin Elmer Ltd, Beaconsfield, Buckinghamshire, UK). Each sample was scanned sixteen times.

Solubility studies

An excess of furosemide was added to 100 mL of phosphate buffer (pH 6) and 0.1 M HCl. The beakers were then placed into an orbital shaker which was covered with a lid (Grant 025 200 watershaker; Grant Instruments Ltd, Shepreth, Cambridgeshire, UK) and set at 37 °C and 100 rev min^{-1}. Samples were taken after 24 h and filtered through a 0.45-μm disposable filter unit as for dissolution studies. The samples were scanned in the region of 220–350 nm. Further samples taken after 36 h showed no increase in the amount of furosemide dissolved, therefore it was assumed that saturation was reached after 24 h. Each result is an average of three determinations.

Statistical methods

The effect of plasma treatment on one side of the compact upon the dissolution rate of furosemide was analysed using a one sample *t*-test for each time point (n = 6). The effect of plasma treatment upon the contact angle of furosemide was evaluated using a one way analysis of variance (n = 4), individual post-hoc comparisons of the treatments were performed using Dunnett's test. Two way analysis of variance was used to analyse the effect of the treatment time upon the contact angle (n = 4) and dissolution rate of furosemide (n = 6). The significance level was set at 0.05.

Results and Discussion

Particle size analysis

The particle size analysis showed the mean, median and mode particle sizes for the furosemide powder to be 11.27 μm, 5.08 μm and 3.70 μm, respectively. The particle size analysis for furosemide also showed the presence of some aggregates. This could lead to agglomeration of any drug in the dissolution media, which could also lead to a decreased dissolution rate as it would decrease the effective surface area of the drug available (Lippold & Ohm 1986).

The effect of plasma treatment on one side only

The compacts were plasma treated on one side only at 80 W for 60 s to obtain an idea of the effect. The dissolution profiles of the compacts before and after plasma treatment were not markedly different up to 90 min (Figure 1). Plasma treatment significantly lowered the dissolution rate of furosemide after 90 min ($P < 0.05$, n = 6) when compared with the untreated drug. Very little furosemide was dissolved at the end of 2 h, as furosemide is a weakly acidic drug that would be expected to be poorly soluble in hydrochloric acid. The contact angle data (Figure 2) demonstrated that the plasma-treated tablets were significantly more wettable than the untreated tablets ($P < 0.05$, n = 4), with the contact angle of pure water upon the plasma-treated tablets being half that of the untreated tablets. This could be due to the formation of carbonyl and hydroxyl groups on furosemide, although the presence of these oxygen-containing functional groups was not detected by infra-red spectroscopy of plasma

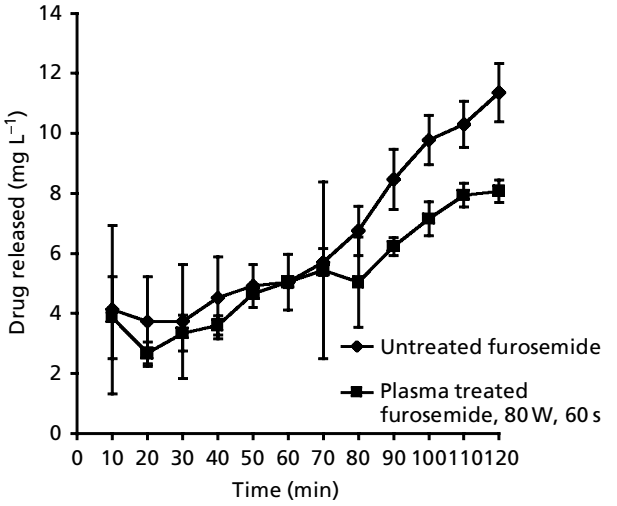

Figure 1 The dissolution profiles of 300 mg furosemide compacts before and after plasma treatment on one side using 0.1 M HCl as the dissolution medium (mean ± s.d., n = 6).

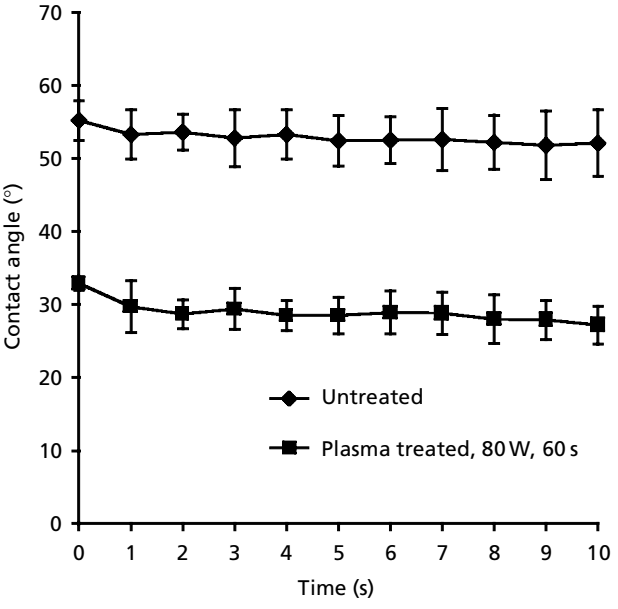

Figure 2 The effect of plasma treatment upon the contact angle of 300 mg furosemide compacts (mean ± s.d., n = 4).

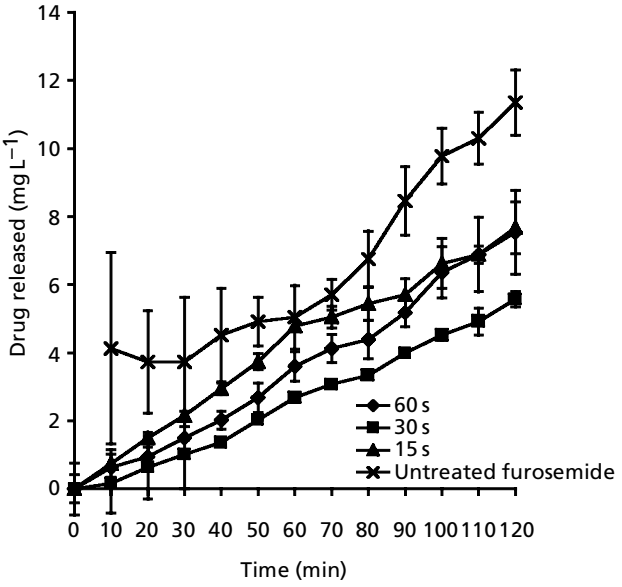

Figure 3 The effect of the length of plasma treatment at 80 W on both sides upon the dissolution profiles of 300 mg furosemide compacts using 0.1 M HCl as the dissolution medium (mean ± s.d., n = 6).

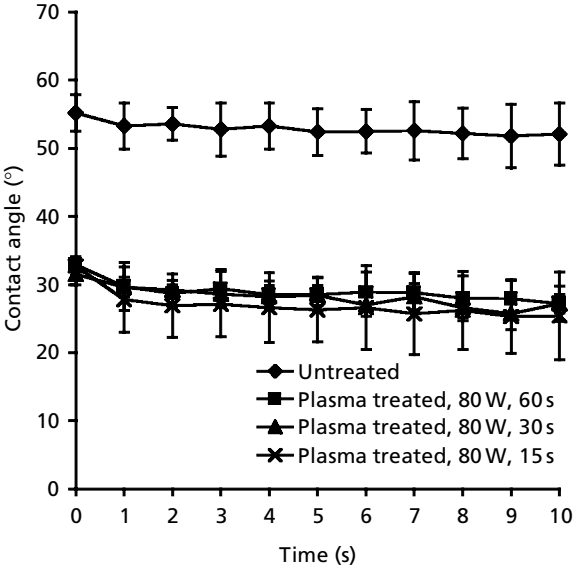

Figure 4 The effect of the length of the plasma treatment at 80 W upon the contact angle of furosemide compacts (mean ± s.d., n = 4).

treated furosemide. Kuzuya et al (1995) have used electron spin resonance to study chemical changes on plasma irradiated ethylene-tetrafluoroethylene copolymer powders using an Argon plasma. They were able to detect the radicals formed even after a few seconds of plasma irradiation. Similarly Lin & Tiong (2000) detected oxygen-containing functional groups such as hydroxyl, carbonyl and peroxy groups on the surface of plasma-treated polyethylenes using an oxygen plasma. These techniques were unavailable to us but one can conclude that similar functional groups would be generated on the surfaces of the tablets. As the modification is surface specific it is unlikely that the depth of penetration of the infra-red into the sample would allow detection of the surface changes by infra-red spectroscopy. Stability studies using contact angle analysis demonstrated that the surface remained wettable for a period of at least five days.

Effect of different treatment times

The length of the plasma treatment was varied at 80 W to investigate the effect of the plasma treatment time upon the dissolution rate and wettability. The plasma treatment reduced the initial surface dissolution from the tablet in all cases. Although the dissolution of the samples treated for 30 s was lower than that of those treated for 15 s over the first hour, the dissolution of the samples treated for 60 s over this period was higher than that observed after treatment for 30 s (Figure 3). Statistical analysis shows that the effect of the treatment time upon the dissolution rate of furosemide was significant ($P < 0.05$, n = 6). In all cases the dissolution was significantly lower ($P < 0.05$, n = 6) than that of untreated furosemide compacts. Figure 4 shows that increasing the length of the plasma treatment had no effect on the contact angle of the furosemide compacts ($P > 0.05$, n = 4) suggesting that short plasma treatment times are sufficient to modify the surface wettability of the material.

Effects of different dissolution media

To more clearly differentiate between the dissolution of the untreated and plasma-treated compacts, the dissolution media was replaced with phosphate buffer. Using phosphate buffer (pH 6), the amount of furosemide released from the compact after 120 min was increased five fold (Figure 5) compared with 0.1 M HCl (Figure 1). The solubility studies show that furosemide was approximately twelve times more soluble in phosphate buffer compared with 0.1 M HCl (Table 1). Again no difference in dissolution rate was seen on plasma treatment of the furosemide compacts, further confirming that plasma treatment had no effect upon the dissolution rate of furosemide ($P > 0.05$, n = 6).

SEM analysis

The SEM results indicated that the surface of furosemide had probably fused together after plasma treatment (Figure 6). 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.

Conclusion

The contact angle data clearly show that the wettability of the tablets increases upon plasma treatment, indicating

that the plasma treatment does make the surface of the drug compacts more wettable. However, there are no significant differences in the dissolution rate of furosemide after plasma treatment in any of the experiments. This is in contrast to the findings of other authors who generally state that increasing the wettability of the drug leads to an increased dissolution rate as this would increase the surface area wetted by the solvent (Lippold & Ohm 1986). Brown et al (1998) found that increasing the wettability of danazol by the adsorption of the surfactant docusate sodium led to an increase in the dissolution rate. However, in this case the effect of the increased wettability appears to be overcome by the fusing of the surface caused by plasma irradiation of the drug and hence the dissolution rate is not seen to increase. The length of treatment did not seem to affect the dissolution rate or the contact angle to a great extent. In certain media, such as HCl, the dissolution rate is delayed for the first ten minutes but this is not the case with phosphate buffer. This could be because furosemide is poorly soluble in HCl resulting in the fused surface delaying the initial dissolution in this media, whereas in phosphate buffer the plasma treatment has no effect as the furosemide is more soluble in this media, and any delay due to surface fusion is masked by the more rapid dissolution.

In summary, although plasma treatment was found to increase the wettability of furosemide it was not found to increase the dissolution rate of this drug. 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.

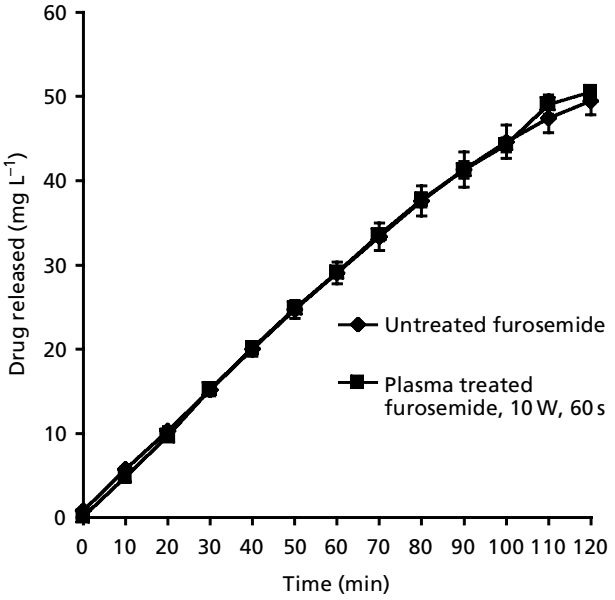

Figure 5 The dissolution profiles of untreated and plasma-treated furosemide tablets in phosphate buffer, pH 6 (mean ± s.d., n = 6 for untreated and 5 for plasma-treated compacts).

Table 1 Solubility of furosemide in the various dissolution media.

Dissolution medium	Solubility (mg mL^{-1})
Phosphate buffer	11.6
0.1 M HCl	0.96

References

Brown, S., Rowley, G., Pearson, J. T. (1998) Surface treatment of the hydrophobic drug danazol to improve drug dissolution, *Int. J. Pharm.* **165**: 227–237

Kuzya, M., Niwa, J., Noguchi, T. (1995) Electron spin resonance study on plasma-induced surface radicals of ethylene-tetrafluoroethylene copolymer. *Polymer J.* **27**: 251–255

Lin, J.-C., Tiong, S.-L. (2000) Surface characterization and platelet adhesion studies on fluorocarbons prepared by plasma-induced graft polymerization. *J. Biomater. Sci. Polymer Edn.* **11**: 701–714

Lippold, B. C., Ohm, A. (1986) Correlation between wettability and dissolution rate of a pharmaceutical powder. *Int. J. Pharm.* **28**: 67–74

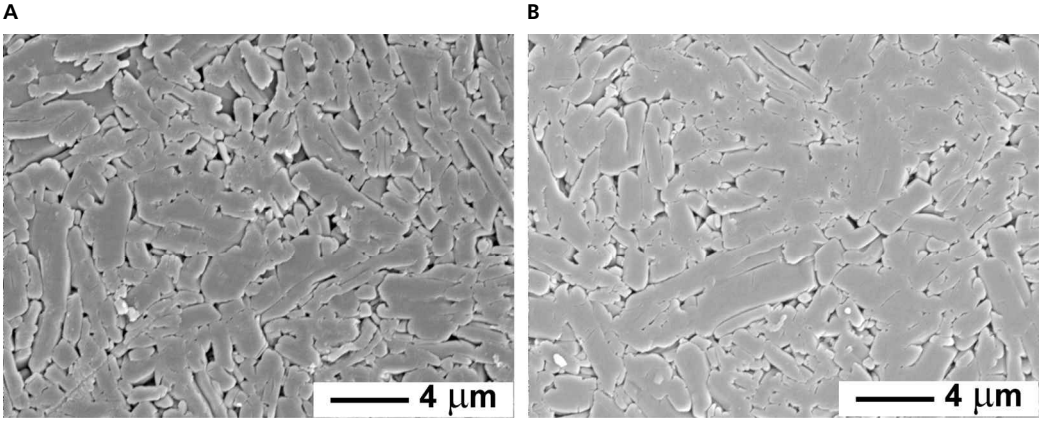

Figure 6 Scanning electron micrographs showing the surface of the untreated furosemide tablet (A) and the plasma-treated surface of the furosemide compact (B) at ×5000 magnification.

Moisan, M., Barbeau, J., Moreau, S., Pettetier, J., Tabrizian, M., Yahia, L. H. (2000) Low temperature sterilisation using gas plasmas: a review of the equipments and an analysis of the inactivation mechanisms. *Int. J. Pharm.* **2276**: 1–21

Sugiura, M. (1985) Surface treatment of meso-carbon microbeads by oxygen plasma. *Bull. Chem. Soc. Jpn.* **58**: 2638–2640

Wotton, P. K. (2001) Making the insoluble soluble. *Scrip Magazine* 12–13