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Improvement of the wettability and dissolution of fenofibrate compacts by plasma treatment

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ABSTRACT

The goal of this study was to investigate the effect of plasma treatment on the wettability and dissolution of fenofibrate compacts. Contact angle measurements and intrinsic dissolution rate studies of untreated and plasma-treated fenofibrate compacts were conducted. The contact angle data clearly show that the wettability of the tablet surface increased with the duration of plasma treatment.

Analyses of stability revealed that the surfaces which were plasma-treated for more than 1 min regained some degree of hydrophobicity after storage in air. Since their hydrophobic recovery finally reached the level observed with 1 min plasma-treated fenofibrate compacts it was deduced that permanent incorporation of hydrophilic groups had already attained saturation upon plasma irradiation for 1 min.

Dissolution studies revealed the advantages of the hydrophilized surface of plasma-treated fenofibrate compacts. Due to the improved wettability of plasma-treated fenofibrate its intrinsic dissolution rate was vastly increased compared to untreated fenofibrate. This study thus demonstrates the potential of plasma treatment to enhance the wettability and dissolution behavior of poorly water-soluble drugs.

1. Introduction

Prior to absorption into the systemic circulation orally administered drugs need to dissolve in the gastrointestinal fluids. This dissolution process may act as absorption rate-controlling step for hydrophobic drugs.

Much effort has been spent on methods for improving solubility and/or dissolution rate of hydrophobic drugs to overcome the issue of their erratic and incomplete absorption. Common approaches to improve drug dissolution include, e.g., an increase of the particle surface area by micronization and the judicious addition of surfactants to improve the apparent solubility of the drug. A method to improve the intrinsic solubility of the drug is its chemical modification, e.g., through introduction of hydrophilic groups.

In the present study fenofibrate was used as a model poorly water-soluble compound undergoing a dissolution-dependent absorption. Fenofibrate has been marketed since the mid-1970s showing a steady increase in bioavailability due to formulation improvements. Besides improvements in wettability most effort has been spent on methods to increase the surface area of the drug. Munoz et al. (1994) reported that the bioavailability of the original formulation of fenofibrate was improved through micronization leading to a decrease of its daily dose. Moreover, co-grinding and spray-drying have shown their effectiveness in improving the dissolution of fenofibrate (Vogt et al., 2008). It is hypothesized that the faster dissolution of the coground fenofibrate is achieved through the intimate contact of the hydrophilic lactose and the surfactant SDS with the lipophilic drug particles resulting in a more effective wetting.

Solid dispersions of different carriers and fenofibrate were prepared by the melting (Buch et al., 2010) or solvent (Sheu et al., 1994) method. High release rates and high bioavailability were obtained with carrier materials such as PEG, PVP and sugars. A further strategy to expedite the dissolution process was reported by Srinarong et al. (2009). They showed that the incorporation of superdisintegrants in solid dispersion tablets can strongly increase the dissolution rate of fenofibrate.

The importance of contact angles and wettability on dissolution rate has been reported in several studies (Brown et al., 1998; Tian et al., 2007). Lippold and Ohm (1986) developed a correlation between wettability and dissolution rate. For hydrophobic drugs like fenofibrate, the "effective surface" involved in the dissolution process is smaller than the geometric surface of the drug particles due to the poor wettability of the hydrophobic surfaces.

Plasma irradiation is a widely used method in the area of automotive (Carrino et al., 2002) and biomedical (Kuzuya et al., 2008) devices to overcome the issue of poor wettability of polymeric materials. Plasma consists of electrons, ions and neutral atoms or molecules (Wang et al., 2009). By oxygen plasma irradiation polar groups are introduced to hydrophobic surfaces resulting in

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an improvement of their wettability (Chen et al., 2008). Moreover, plasma treatment is applied to clean the surfaces of materials using the ablative effect of kinetic transfer of electrons and ions with the surface.

Compared to other technologies for surface modification plasma irradiation has many benefits, for instance suitability for many materials and low environmental pollution. However, very limited information has been reported concerning plasma treatment of hydrophobic active substances to overcome the issue of poor wettability. Naseem et al. have analyzed the effects of plasma irradiation on griseofulvin (Naseem et al., 2004) and furosemide (Naseem et al., 2003). Plasma treatment was found to increase the wettability but not the dissolution rate of the tabletted form of both compounds. It was suggested that the positive effect of altered wettability of the compacts was counterbalanced by a fusion of the surface caused by plasma treatment.

In the present study the effects of oxygen plasma treatment on fenofibrate compacts were investigated in terms of alterations in wettability and intrinsic dissolution rates. Following plasma treatment the high log *P* compound fenofibrate should exhibit wettability properties of a low log *P* drug. A relationship between log *P* and wettability is presented. Moreover, the durability of plasma treatment was examined. Finally, FT-IR, Raman spectroscopy and ^{1}H NMR analytic methods were applied to assess structural changes in plasma-treated fenofibrate.

2. Materials and methods

2.1. Materials

Fenofibrate was purchased from Labochim (Milan, Italy). Budesonide was obtained from SkyePharma AG (Muttenz, Switzerland). Trospium chloride was donated by Midas Pharma (Ingelheim, Germany). Furosemide was obtained from Synopharm (Barsbüttel, Germany). Quercetin was purchased from Voigt Global Distribution (Kansas City, MO). All other chemicals were of analytical reagent grade.

2.2. Preparation of compacts

Fenofibrate tablets were produced with a PW 20 GS manual tablet press (Paul Weber, Remshalden, Germany). 200–250 mg fenofibrate powder was filled into the 13 mm die and compressed to tablets with a compression force of 20 kN applied for a duration of 30 s.

2.3. Contact angle measurements

Contact angle measurements were conducted under ambient conditions with a DataPhysics Contact Angle System OCA 20 (DataPhysics Instruments, Filderstadt, Germany). The sessile drop method was used to determine the contact angle: a small droplet of distilled water is placed on a compact. The contact angle is measured immediately after the drop reached a quasiequilibrium shape. At least triplicate determinations were carried out for each compact.

2.4. Solubility studies

Solubility studies were conducted in McIlvaine buffer containing 1.5% SDS at a pH value of 6.8. An excess of fenofibrate powder (3 mg) was added to 5 ml dissolution medium. The suspension was agitated at 37 °C in an orbital shaker at 200 rpm until an equilibrium was reached. For UV analysis the samples were centrifuged (14,000 rpm, 15 min, 37 °C). Each experiment was run in triplicate.

2.5. Intrinsic dissolution measurements

Disk intrinsic dissolution rate (DIDR) measurements were conducted using a Wood's apparatus (Pharma Test, Hainburg, Germany) with a 0.5 cm^2 surface area in a USP II dissolution tester (Erweka DT6R, Erweka, Heusenstamm, Germany). Non-disintegrating disks of fenofibrate were compressed using a PW 20 GS manual tablet press (Paul Weber, Remshalden, Germany) at a compression force of 20 kN and a dwell time of 30 s. Dissolution was performed with 250 ml McIlvaine's citric acid-phosphate buffer (pH 6.8) containing 2% SDS in a 500 ml vessel. The Wood's apparatus was rotated at 50 rpm in the dissolution medium which was maintained at 37 °C. Absorbances were determined in triplicate using a UV–Vis spectrophotometer (PerkinElmer, Waltham, MA) at a wavelength of 289 nm. DIDR was calculated by

$$J = \frac{V}{\mathrm{d}t}\frac{\mathrm{d}c}{A}$$

where J is the intrinsic dissolution rate, V is the volume of the dissolution medium, c is the concentration, A is the area of the drug disk, and t is the time.

2.6. Plasma treatment

Plasma treatment was conducted using the Plasma Prep 5 instrumentation (GaLa Gabler Labor Instrumente, Bad Schwalbach, Germany). After placing the samples in the plasma chamber, the chamber was evacuated followed by plasma treatment using oxygen plasma. A frequency of 40 kHz was applied for defined periods of time, with a power setting of 150 W.

2.7. FT-IR spectroscopy

All FT-IR spectra were measured using a Nicolet 5DXC FT-IR spectrometer (Thermo Scientific, Waltham, MA), equipped with an "Ever-Glo" light source and a nitrogen-cooled Hg–Cd–Te narrow-band detector. The samples were measured in the dry state using a grazing incidence (80°) reflection on a FT80 setup. The spectra were taken with 2000 scans at 4 cm^{-1} resolution and a Happ-Genzel apodization.

2.8. Micro-Raman spectroscopy

All Raman spectra were recorded at room temperature using a Horiba Jobin Yvon LabRAM HR spectrometer (Horiba, Kyoto, Japan). Raman spectra were excited with the 632.8 nm line of a helium–neon laser. The Rayleigh radiation was blocked using an edge filter, and the scattered light was dispersed by a grating with 950 grooves/mm. A 50× long-distance objective (numerical aperture 0.55) and a slit width of 100 μm were chosen. All spectra were recorded three times.

2.9. ^{1}H NMR spectroscopy

All ^{1}H NMR spectra were recorded on a Bruker DSX 400 MHz FT-NMR spectrometer (Bruker, Billerica, MA) (rotation: 5000 Hz, T = RT, 4 mm rotor). The samples were dissolved in $CDCl_3$. Chemical shifts (δ) were given in ppm relative to trimethylsiloxane as the internal reference, and the coupling constants were given in Hz.

3. Results

The log *P* literature values of fenofibrate (Guichard et al., 2000), budesonide (Lin et al., 2005), furosemide (Camenisch et al., 1998), quercetin (Casagrande et al., 2007) and trospium chloride (Wiedemann and Schwantes, 2007) were related to their

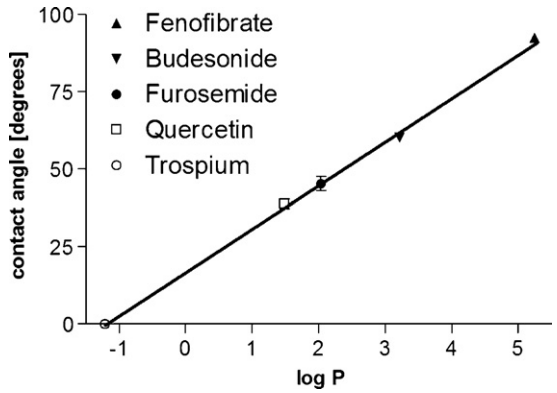

Fig. 1. Plot of log *P* literature values of five compounds versus their experimentally determined contact angle. Each data point is the mean (±SD) of at least three independent experiments.

experimentally determined contact angles (Fig. 1). An excellent correlation between the log *P* values and the wettability of these compounds was shown ($R^2 = 0.999$).

Fig. 2a–c depicts water droplets on compacts of three different compounds. On the highly lipophilic fenofibrate (a) the water droplet maintained its round shape indicating a non-wettable surface. With the less lipophilic furosemide water formed a flatter droplet shape compared to fenofibrate (Fig. 2b). On trospium chloride the water droplet spread out rapidly so that a contact angle cannot be given (Fig. 2c).

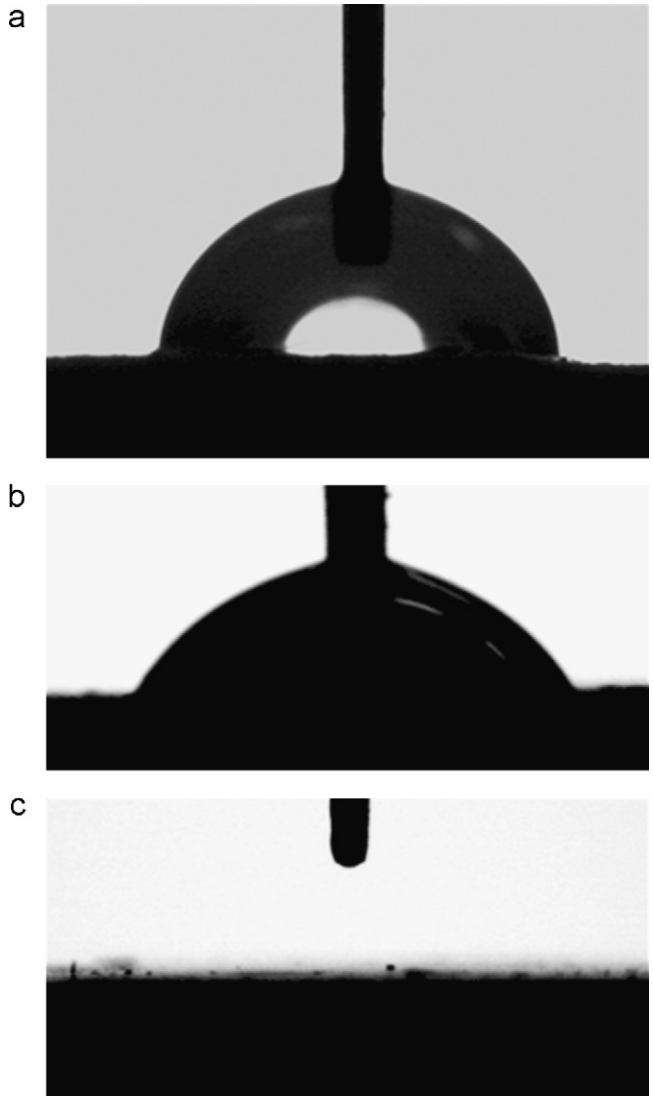

Fig. 2. Water droplets on compacts of fenofibrate (a), furosemide (b) and trospium chloride (c). All pictures were taken for the determination of the contact angle.

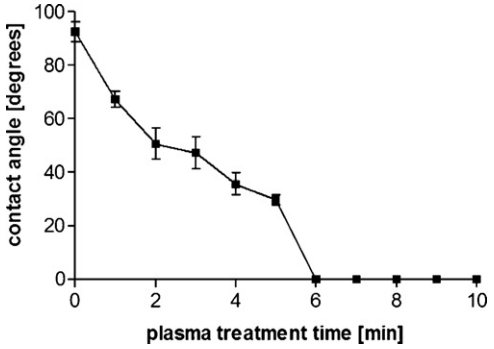

Fig. 3. Effect of plasma treatment time upon the contact angle of fenofibrate compacts (mean, ±SD).

Fig. 3 shows the contact angles of water on fenofibrate compacts modified by oxygen plasma treatment for different durations of time. It becomes obvious that the contact angle decreased with rising duration of plasma treatment. The highest contact angle obtained was approximately 92° belonging to untreated fenofibrate compacts. After 5 min of plasma treatment the contact angle decreased to less than 30°. Longer treatment times resulted in fenofibrate surfaces of very high wettability such that contact angles could not be determined.

Moreover, the water contact angles were monitored as a function of sample storage. In Fig. 4 the effects of storage on the hydrophobicity of plasma-treated fenofibrate compacts are shown. In addition to the already known increase in hydrophilicity of the compact surface with rising plasma treatment times, differences in hydrophobic recovery after storage in air were observed depending on irradiation times. Upon 1 min plasma treatment the values of contact angle varied only slightly with storage time at ambient temperature. However, the wettability of longer plasma-treated fenofibrate compacts decreased with time. But the hydrophobic recovery was only partial with the water contact angle leveling off at values observed with 1 min plasma-treated compacts. The contact angles of the fenofibrate compacts which were oxygen plasma-treated for 4 and 8 min reached a constant level of approximately 67° after 9 days of storage. After 69 days also the fenofibrate tablets which had been treated with plasma gas for 10 min reached this constant wettability indicator.

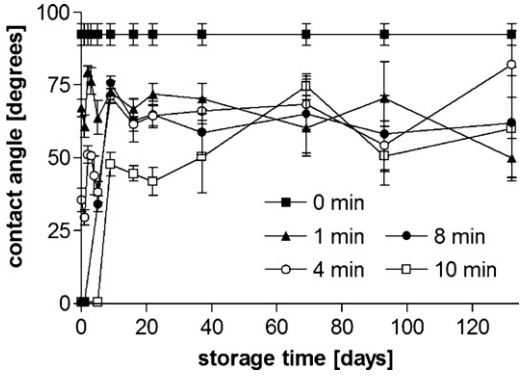

Fig. 4. The development of the contact angle over a sample storage time of 132 days (mean, ±SD). After plasma treatment for 1, 4, 8 or 10 min the fenofibrate compacts were stored under ambient conditions. For comparison the contact angle value of untreated fenofibrate is shown.

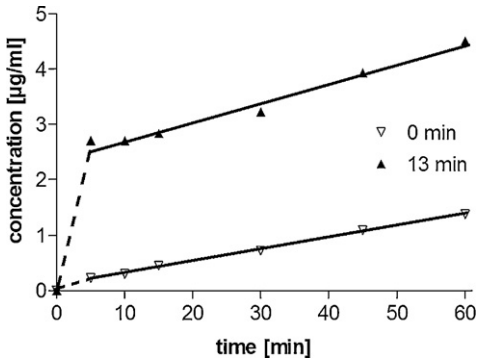

Fig. 5. Concentration–time profiles of untreated and of 13 min plasma-treated fenofibrate in McIlvaine buffer containing 2% SDS. For improvement of clarity, error bars are omitted and SDs are <10%.

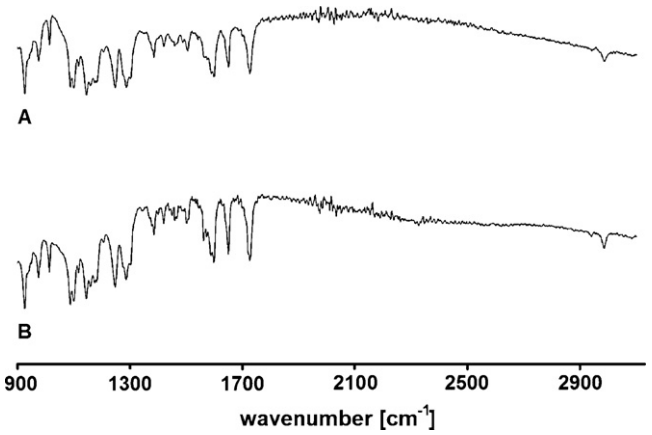

Fig. 6. FT-IR spectra of plasma-treated (a) and untreated (b) fenofibrate compacts.

Solubility studies were conducted with untreated and plasma-treated fenofibrate powder. No significant alteration of the solubility of fenofibrate was observed after 5 min plasma treatment with the mean solubilities being 0.89 for untreated and 0.94 μg/ml for plasma-treated fenofibrate. The fenofibrate solubility increased to a mean value of 1.45 when the plasma treatment time was extended to 13 min.

In accordance with the solubility studies no significant differences were observed in the intrinsic dissolution between untreated and plasma-treated fenofibrate (5 min treatment). When plasma treatment was extended to 13 min, intrinsic dissolution increased as shown in Fig. 5. The course of the dissolution profiles differed, resulting in final concentrations of 1.4 and 4.5 μg/ml for untreated and plasma-treated fenofibrate, respectively. The release of untreated fenofibrate proceeded slowly but steadily. Plasma treatment vastly enhanced the dissolution process at the beginning resulting in a biphasic profile. After 5 min already more than half of the final fenofibrate concentration was reached. Till the end of the dissolution measurement the fenofibrate concentration constantly increased.

Disk intrinsic dissolution rates (DIDR) were calculated for different periods of time (Table 1) because the concentration profile of plasma-treated fenofibrate did not show linearity over the whole examined period. Comparing the first 5 min the DIDR of the plasma-treated fenofibrate is almost 12 times that of the untreated compound. In the time segment between 5 and 60 min the dissolution profiles of untreated and plasma-treated fenofibrate showed linearity. Linear regression analysis for this time segment revealed two almost parallel slopes. Accordingly, the corresponding DIDR values for both kinds of fenofibrate were similar, with values of 0.011 and 0.016 mg/min/cm^2 for the untreated and the plasma-treated fenofibrate, respectively.

Spectroscopic methods were used to examine the effect of oxygen plasma treatment on the chemical structure of fenofibrate. Therefore untreated and plasma-treated fenofibrate were analyzed. The inspection of the FT-IR spectra (Fig. 6) of both kinds of fenofibrate revealed no obvious differences between them. The Raman spectra of untreated and plasma-treated fenofibrate together with the difference of both spectra are depicted in Fig. 7. Both spectra show the same Raman bands, but it is obvious that the band intensities of the plasma-treated fenofibrate are higher compared with the untreated sample. However, comparing the spectra of both kinds of fenofibrate revealed no variation in the Raman bands' full width at the half-maximum (FWHM).

The ^{1}H NMR chemical shifts of the untreated and plasma-treated fenofibrate are listed separately below.

^{1}H NMR (400 MHz, $CDCl_3$) of the untreated fenofibrate: δ 1.171 (d, 6H, J = 8 Hz, CH_3), 1.639 (d, 6H, CH_3), 5.066 (m, 1H, –CH), 6.827 (d, 2H, J = 11.2 Hz, Ar–H), 7.411 (d, 2H, J = 11.6 Hz, Ar–H), 7.664 (t, 4H, J = 12 Hz, Ar–H).

^{1}H NMR (400 MHz, $CDCl_3$) of the plasma-treated fenofibrate: δ 1.173 (d, 6H, J = 8 Hz, CH_3), 1.642 (d, 6H, CH_3), 5.068 (m, 1H, –CH), 6.858 (d, 2H, J = 11.6 Hz, Ar–H), 7.414 (d, 2H, J = 11.2 Hz, Ar–H), 7.667 (t, 4H, J = 11.6 Hz, Ar–H).

Both ^{1}H NMR assays yield identical results concerning the number of hydrogen atoms and their chemical bonds.

Table 1
Disk intrinsic dissolution rates of untreated and 13 min plasma-treated fenofibrate.

Time period [min]	DIDR [mg/min/cm^2]	
	Untreated fenofibrate	Plasma-treated fenofibrate
5–60	0.011	0.016
0–5	0.023	0.271

4. Discussion

In this study the effects of oxygen plasma irradiation on wettability, solubility and intrinsic dissolution rate of the poorly soluble drug fenofibrate were studied. First of all it was confirmed that contact angle measurements can be used to determine the effects of oxygen plasma treatment on highly lipophilic compounds. A corre-

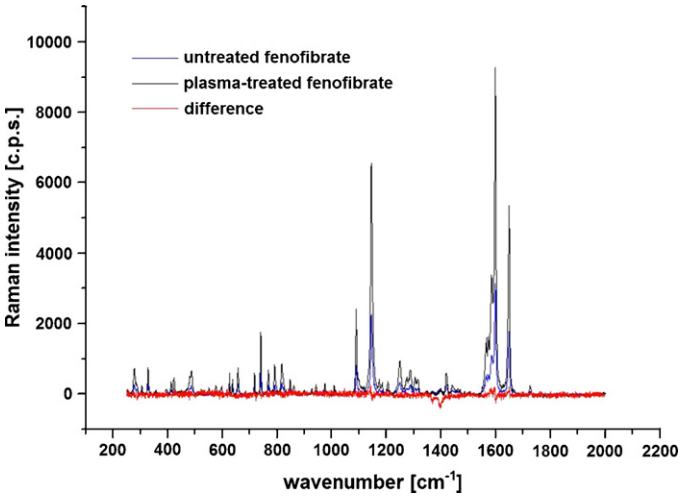

Fig. 7. Raman spectra of untreated and of 4 min plasma-treated fenofibrate together with the difference of both spectra.

lation of log *P* of five different compounds with their experimentally determined contact angles was demonstrated.

It was observed that the wettability of the fenofibrate compacts increased with the duration of plasma treatment leading to ideal wetting after more than 5 min plasma treatment. Furthermore, the wetting effects by plasma treatment were investigated regarding their endurance over time. It was observed that the partial hydrophobic recovery of the fenofibrate compacts was increasingly delayed with prolongation of plasma treatment. The contact angle leveled off at values observed with 1 min plasma-treated compacts which exhibited constant wettability over the entire storage time.

In order to explain these observations it is suggested that hydrophilic groups were to some extent permanently incorporated into the surface of the fenofibrate compacts, resulting in a surface hydrophilization (Clouet and Shi, 1992). Upon saturation with a limited number of hydrophilic groups (Wang, 2007) further oxygen-rich molecules might accumulate at the surface of the fenofibrate compacts leading to a temporary ideal wettability. Since these hydrophilic entities were not bound firmly they might dissipate to the atmosphere over storage time as it is suggested by Everaert et al. (1995). Concerning 1 min plasma-treated compacts no obvious alteration in wettability was observed during the whole storage time. Hence it might be deduced that the described surface of the fenofibrate compacts was already saturated after 1 min plasma treatment. This theory is further supported by the observation that the hydrophobic recovery of longer plasma-treated fenofibrate tablets is only partial, finally matching the wettability of the compacts which were plasma-treated for 1 min.

Regarding the solubility studies an obvious difference between untreated and plasma-treated fenofibrate was solely observed when the duration of plasma treatment was extended from 5 to 13 min. For the solubility studies fenofibrate had been plasma-treated in powder form with an intermediate mixing of the mass. Therefore more fenofibrate molecules were able to react with the plasma gas since a larger surface was presented compared to the treatment of the fenofibrate tablets resulting in a higher solubility.

Additionally, the intrinsic dissolution studies were able to exhibit the advantages of plasma treatment concerning its use with hydrophobic drugs. The course of the drug dissolution profile extremely differed at the beginning of the release process comparing untreated and plasma-treated fenofibrate. The hydrophilized surface of the plasma-treated fenofibrate compact enhanced the drug release so much that more than half of the final fenofibrate concentration was reached after 5 min. After that the dissolution profiles of untreated and plasma-treated fenofibrate were almost identical in terms of the increase in the concentrations. The fact that only the surface of the compacts came in contact with the plasma gas might serve as an explanation for the previously described observations. The hydrophilized surface worked as an accelerator for the initial fenofibrate release whereas the drug below the surface remained more or less unchanged. This is reflected in the late slope of the dissolution profile being similar to the one of untreated fenofibrate.

The calculated DIDRs strengthen the aforementioned results. A vastly difference of the DIDRs between both kinds of fenofibrate was observed regarding the early time period whereas the DIDR values for the time period between 5 and 60 min turned out to be similar. This is in accordance with the findings of Lippold and Ohm (1986) who observed a correlation between the wettability of a drug and its dissolution rate.

To exclude a change in the chemical structure of fenofibrate by oxygen plasma treatment three spectroscopic methods were applied. The analysis of FT-IR measurements revealed no differences in the chemical structure between the untreated and the plasma-treated fenofibrate. Similarly to the FT-IR measurements the development of new chemical bonds could be excluded by Raman spectroscopy. No differences were observed in Raman band positions and FWHM after the plasma treatment of fenofibrate. Therefore, the formation of new chemical bonds was excluded. The higher band intensities of the plasma-treated fenofibrate were attributed to oxygen molecules incorporated at the surface. These were hold responsible for the stronger scattering of the incident light compared to the untreated sample.

No differences in the number of hydrogen atoms and their chemical bonds could be detected by ^{1}H NMR measurements of the untreated and the plasma-treated fenofibrate. Therefore, none of the three spectroscopic methods indicated a sustainable change of the molecular structure of fenofibrate.

5. Conclusions

In conclusion, it appears that plasma treatment can be used to hydrophilize the surface of poorly water-soluble drugs in order to increase their dissolution rate. In this particular case fenofibrate compacts were plasma-treated prior to intrinsic dissolution measurements. Therefore the hydrophilization was limited to the surface of the fenofibrate tablets resulting in an initial high dissolution rate. Upon rapid detachment of the plasma-treated surface the further drug release proceeded similarly to the dissolution process of untreated fenofibrate.

Further work will be necessary in order to investigate the influence of plasma treatment of the fenofibrate powder prior to compression to the compact. This would allow more fenofibrate molecules to react with the plasma gas and might steadily increase the intrinsic dissolution rate of compacts resulting in improved bioavailability.

Moreover, a method to prevent the presented hydrophobic recovery of plasma-treated fenofibrate during storage has to be developed. A way to preserve the positive effects of oxygen plasma treatment on poorly water-soluble drugs might be the coating of powders with hydrophilic polymers.

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