Available online at www.sciencedirect.com
SCIENCE DIRECT®
International Journal of Pharmaceutics 288 (2005) 253–261
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Plasma enhanced chemical vapor depositions to encapsulate crystals in thin polymeric films: a new approach to controlling drug release rates

Ceren Susut, Richard B. Timmons*

Department of Chemistry and Biochemistry, University of Texas at Arlington, Arlington, TX 76019-0065, USA

Received 28 June 2004; received in revised form 5 October 2004; accepted 6 October 2004
Available online 30 November 2004

Abstract

An RF plasma discharge was employed to deposit thin polymeric films on drug particles. This study utilized acetylsalicylic acid (aspirin) crystals and allyl alcohol as polymerizable monomer for this new approach to controlling drug release rates. Release rates of coated and uncoated particles were measured in aqueous solution at a pH of 1.0. The drug release rates could be varied over wide ranges by appropriate control of the polymeric films. These controls included film composition, extent of polymer cross-linking and film thickness. A 360° rotating plasma reactor was employed to provide effective agitation and mixing of the drug particles during the coating operation. The plasma discharge was operated in a pulsed mode to provide improved control of the polymer film compositions and, at the same time, minimize undesirable decomposition of drug molecules. Overall, the results obtained clearly indicate that the pulsed RF plasma coating process developed represents a viable, one-step, solventless route to controlled drug release.
© 2004 Elsevier B.V. All rights reserved.

Keywords: Controlled release; Drug encapsulation; Polymer films; Plasma polymerization; Acetylsalicylic acid; Dissolution profile

1. Introduction

Development of controlled release systems to improve the effectiveness of drug delivery is an extremely active area of research at the present time. The objectives of these studies include not only enhancing the therapeutic activity of a drug relative to the intensity of side effects but also reducing the number of drug administrations and/or eliminating the need for specialized drug administration (Uhrich et al., 1999). In light of the importance of these objectives, there have been many approaches reported in recent years centering on new methods for controlled drug release. As examples, these approaches include layer-by-layer assembly of polyelectrolytes, formation of hydrogel films, systems based on thiolated polymers, various granulation

* Corresponding author. Tel.: +1 817 272 3801; fax: +1 817 272 3808.
E-mail address: timmons@uta.edu (R.B. Timmons).

0378-5173/$ – see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2004.10.004

techniques, emulsion-solvent evaporation processes and sol-gel carrier systems (Rango Rao and Devi, 1988; Bottcher et al., 1998; Sukhorukov et al., 1998; Tamilvanan and Sa, 1999; Bernkop-Schnürch et al., 2000; Luo et al., 2000; Tamilvanan and Sa, 2000; Qiu et al., 2001; Railkar and Schwartz, 2001; Valenti and Fabiani, 2001). Substantial advances have been achieved in terms of improving drug release rates using these techniques.

As an alternate approach to controlled drug release, the present investigation centers on examination of the utility of employing plasma enhanced chemical vapor depositions (PECVD) to encapsulate drug molecules inside thin polymeric films. From the operational standpoint, PECVD offers a simplified approach in that it represents a single-step, solventless process producing pin-hole free and conformable films. This single step approach can be contrasted with the multi-step processes noted above frequently involving rather complex procedures. Additionally, it is relatively easy to control both polymer film thickness and film composition, including the extent of cross-linking, during PECVD coating. These considerations are of obvious importance in terms of controlling drug release rates.

In the present study, pulsed plasmas were utilized in lieu of the conventional continuous-wave (CW) approach. Prior work from this laboratory has shown that the pulsed plasma approach provides excellent film chemistry control during polymer formation, as well as improved film thickness controllability (Rinsch et al., 1996; Beyer et al., 1997; Han et al., 1997, 1998; Han and Timmons, 1998). Additionally, for the present application, the use of the pulsed versus the continuous- wave plasma approach is attractive because it should limit undesirable plasma induced chemical changes to drug molecules. Under continuous-wave conditions, the reactor contains high concentrations of many reactive species including radical ions. The radical species are relatively indiscriminate in their reactivities which, in the present case, could lead to undesirable degradation of drug molecules. Additionally, it is well documented that high photon fluxes, having short wavelengths which extend well into the vacuum UV are present in typical plasma discharges (Fozza et al., 2000). These photons are sufficiently energetic to initiate photochemical dissociation of typical drug molecules. Under pulsed plasma conditions a more selective chemistry is observed in that significant polymer film formation is known to occur during plasma off periods. During plasma off periods, the photon flux is not present and ion-radicals are far less prominent than under CW conditions. Further contrasts of pulsed to CW PECVD are provided in Section 4.

The main objective of the present study was to determine if the pulsed PECVD approach could be successfully applied to control drug release rates. In this initial study, common aspirin was used as a model drug. Aspirin, acetylsalicylic acid, is an antipyretic, anti-inflammatory analgesic with a carboxylic acid backbone group rendering the molecule soluble in various solvents and making its detection by UV–vis spectroscopy possible. Allyl alcohol was the monomer used to encapsulate the drug crystals by plasma polymerization. This monomer is a polar molecule relatively soluble in aqueous solutions at pHs ranging from 1 to 10. Films obtained by the plasma polymerization of allyl alcohol tend to be hydrophilic. Previous work from this laboratory demonstrated excellent control of the density of hydroxyl groups in these films and thus the hydrophilicity of the polyallyl alcohol films (Rinsch et al., 1996). In general, as the plasma duty cycle is decreased, increased retention of the –OH group of the starting monomer is observed generating increasingly hydrophilic films. In the present study, micron-size aspirin crystals were encapsulated in polyallyl alcohol films under pulsed plasma conditions. Subsequently, the release rate of aspirin molecules from the coated particles immersed in aqueous solution were compared with those obtained with the uncoated control particles. It was discovered that the release rates are controllable, over relatively wide ranges, by this pulsed PECVD approach.

2. Materials and methods

2.1. Materials

Acetylsalicylic acid crystals (99%) and allyl alcohol (>99%) were obtained from Aldrich Chemical Company. Dichloromethane, chloroform and acetone, for the TLC experiments, were purchased from EM Science. Silica gel (20 × 20) polyester backed TLC plates of thickness 250 μm (Whatman Ltd.) were utilized in the TLC experiments. The pictures of the TLC plates

were taken by using a MultiImage Light Cabinet (Alpha Innotech Corporation).

2.2. Encapsulation of acetylsalicylic acid crystals

The apparatus and general procedures employed in operation of the 13.56 MHz RF pulsed-plasma reactor have been described previously (Panchalingam et al., 1993). In the present study, a 360° rotatable version of the plasma reactor was employed to help achieve uniform and complete coating of drug particles. The reactor was patterned after that described by Denes and co-workers (Martin et al., 2002). A cylindrical Pyrex glass reactor of 5 cm internal diameter and 45 cm in length was used as the plasma chamber. Complete rotation of the reactor chamber under vacuum conditions was achieved by ferrofluidic vacuum rotary feed through valves (Schoonover, Inc.) inserted at both ends of the reactor tube. Rotation of the particles provided agitation and continuous exposure of the crystal surfaces to the plasma gases thus helping to promote encapsulation of the crystals in polymeric films. The reactor chamber rotation rate was controlled with a variable speed motor (Dayton Model 4Z827D) connected by a pulley to the reactor.

Films were deposited onto acetylsalicylic acid particles. Each end of the reactor chamber was stoppered with glass wool in order to ensure that crystals remain in the chamber during coating. Acetylsalicylic acid crystals were ground, sieved and vacuum dried overnight before coating. The particle size distribution covered a range of values, extending from 1 to 100 microns, with mean size of ∼30 μm, as shown by light scattering measurements. Optical microscopy revealed a rather uniform needle-like structure for these crystals. The rotation rate was kept at 4 rev/min. The quantity of acetylsalicylic acid particles placed in the reaction chamber was 4 g in each run.

The pulsed plasma approach was used in all the coatings. The average power employed under pulsed plasma conditions is calculated according to the formula:

$$P_{\text{average}} = \frac{\tau_{\text{on}}}{\tau_{\text{on}} + \tau_{\text{off}}} \times P_{\text{peak}} \quad (1)$$

where τ_{on} and τ_{off} are the plasma on and off times and P_{peak} is the peak power. A major advantage of pulsed plasma polymerization is the fact that the average power employed during film formation can be much lower than the power employed under continuous wave conditions in view of the relatively longer plasma off times compared to plasma on times.

The present study included the evaluation of various plasma deposition conditions for use in achieving controlled drug release rates with the drug substrates. Plasma deposition variables examined were the duty cycle, the peak power input and the coating time period. Plasma on/off times were in the milli-second range and two different plasma on/off times were employed, namely: 1/3 and 1/5 ms. The peak powers examined were 25, 50 and 100 W. The coating period was varied between 30 min and 1 h. The allyl alcohol flow rate and the pressure of the reactor were kept constant at 1.5 cm^3 (STP)/min and 160 mTorr, respectively. The approach employed was to investigate different combinations of the reaction variables and study the effect of these changes on the release rates.

2.3. Characterization of plasma polymerized allyl alcohol

In order to measure film deposition rates and characterize film compositions spectroscopically, replicates of the polyallyl alcohol coatings performed with drug substrates were created using silicon wafers (thickness measurements) and KBr (infrared studies) substrates. These experiments were carried out in the same plasma reactor and under the same plasma deposition conditions as employed in the drug encapsulation runs. The FT-IR spectra were collected with a Bruker Vector 22 spectrophotometer using 4 cm^{-1} resolution. Spectra were recorded in absorption mode on films deposited on KBr discs. The thickness of the films deposited on silicon wafers was measured using a Tencor Alpha Step 200 profilometer.

2.4. Release experiments

The drug release measurements were carried out using a V-530 model UV–vis spectrophotometer (Jasco) at an absorption wavelength of 276 nm. The release experiments with acetyl salicylic acid were performed in pH 1 HCl solution (a simulated gastric fluid). The absorbance versus time measurements were taken periodically using 1 cm quartz cuvettes. A stock solution,

prepared with 25 mg of acetylsalicylic acid crystals in 100 ml of solution, was employed to generate a Beer's law calibration curve. This solution, along with subsequent dilutions, were at a pH of 1.0. The Beer's Law plot of absorbance versus concentration was linear over an aspirin concentration range of 0–13 mg/100 mL. Slight negative deviation was observed over the 13–25 mg/100 mL range. All drug release measurements involved aspirin concentrations in which the linear Beer's Law plot was applicable. The encapsulated drug crystals, sample size 10 mg, were stirred constantly in a 100 ml volumetric flask during the release rate measurements. Periodically, an aliquot was transferred into the cuvette and the liquid was returned to the volumetric flask as soon as the absorbance data were taken. All release experiments were conducted at room temperature (about 25 °C).

2.5. Kinetic study of release characteristics

All model fitting was performed using Microsoft Excel.

2.6. Thin-layer chromatography (TLC) experiments

TLC experiments were carried out to determine if aspirin molecules were converted to other products during the plasma encapsulation process. Solutions containing the free drug and selected encapsulated drug were prepared by dissolving 10 mg of the compound in 1 ml of dichloromethane. All drug solutions were freshly made and 5 μl aliquots were applied approximately 1 cm apart unto 5 cm × 17 cm silica gel TLC plates. Before use, the TLC plates were dried in an oven for 1 hour at 110 °C in order to remove any atmospheric moisture adsorbed. Each TLC plate contained one spot for the free drug and two spots corresponding to encapsulated drug substrates coated using different plasma variables. Chloroform–acetone (4 + 1) solvent system was placed into the TLC jars along with a filter paper, the jars were then sealed and the solutions were equilibrated for 30 min. The systems were run for about 15 cm from the base line, the solvent level was marked and the plates were air-dried. The dried plates were then subjected to iodine vapor and their pictures were taken. The retention factors calculated for each drug were compared to literature values (Stead et al., 1982).

3. Results

Previous work from this laboratory showed that very good film chemistry controllability was obtained in the films produced by pulsed plasma polymerization of allyl alcohol (Chen, 1995; Rinsch et al., 1996). In this prior work, XPS analysis and FT-IR analysis revealed that, as the RF duty cycle decreased, the retention of the monomer's oxygen content increased thus leading to an increase in the hydrophilicity of the coating. Among the findings of this work was also the fact that significant film growth occurred during the plasma off times. Deposition per pulse cycle was shown to increase at constant on time and power as the off time increased.

In the present study, FT-IR analysis of plasma polymerized allyl alcohol films was performed as a function of peak power. The results are displayed in Fig. 1. As can be observed from Fig. 1, there is an increase in the retention of the monomer's oxygen content from 100 to 25 W. This increase is easily detected by comparing the relative intensities of the O–H (∼3400 cm^{-1}) and C–H (∼2900 cm^{-1}) stretching vibrations as the peak power changes. These findings suggest an increase in the wettability of the films produced as the peak power decreases. Additionally, the presence of the C=O group (∼1700 cm^{-1}) is observed in the product films. Although there is a small C=O containing impurity in the starting monomer, it is seen that additional C=O is created at high peak power. Clearly, the extent of C=O formation, relative to OH incorporation, in the film, decreases with decreasing peak power.

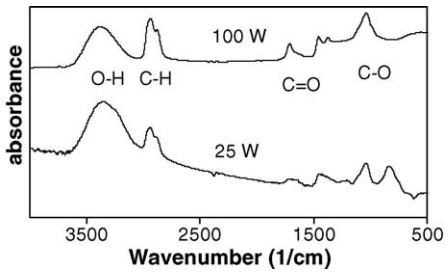

Fig. 1. FT-IR absorption spectra obtained for pulsed plasma polymerization of allyl alcohol at 1/5 ms and peak powers of 100 and 25 W.

Table 1
Conditions used in the different coatings of acetylsalicylic acid with allyl alcohol and the corresponding film thickness and film formation energy efficiency values

Coating	Monomer flowrate (cm^3(STP)/min)	Peak power (Watts)	RF duty cycle on/off (ms/ms)	Coating time (min)	Film thickness (kÅ)	Energy efficiency (mÅ/J)
1	1.5	100	1/5	30	4.9	160
2	1.5	50	1/5	30	5.9	390
3	1.5	25	1/5	30	4.0	530
4	1.5	25	1/5	60	7.4	500
5	1.5	25	1/3	60	4.0	180

The experimental conditions sued in the different coatings of acetylsalicylic acid with allyl alcohol and the corresponding film thickness and deposition rate values are displayed in Table 1. The film thicknesses and energy efficiencies of plasma polymerized allyl alcohol films were investigated as a function of peak power, coating time and duty cycle.

As the Table 1 film thickness data reveal, the energy efficiency of film formation (mÅ/J) increases with decreasing power input (samples 1, 2 and 3). This result indicates that ablation reactions may be significant at higher power inputs. Changing the coating time, with the other variables held constant, has a significant effect on the film thicknesses. When the coating time is doubled, the film thickness increases approximately by a factor of 2, indicating a linear relationship between deposition time and film thickness under the pulsed plasma conditions employed. This can be contrasted with continuous wave depositions in which non-linearity between deposition time and film thickness is frequently observed (Yasuda, 1985). Decreasing the duty cycle increases the energy efficiency of film formation, correlating with the previous findings that significant film growth occurs during plasma off periods (Rinsch et al., 1996).

In the present study, the effect of variations in three of the plasma variables used in the coatings was examined, namely: power, coating time and RF duty cycle. The results obtained are shown in Fig. 2 in terms of percent drug release versus immersion time. Also included in these and subsequent figures are the release rates for the uncoated crystals used as controls. All three plasma variables were found to affect the release rates of the drug molecules.

In Fig. 2(A), the release rates are shown as a function of the peak power employed during coating. The peak powers employed were 25, 50 and 100 W. Although the film thickness varies slightly for this sequence (see Table 1), the variation in coating thickness (from 4.0 to 5.9 Å) is relatively small compared to the magnitude of the drug release rates. Doubling the power input

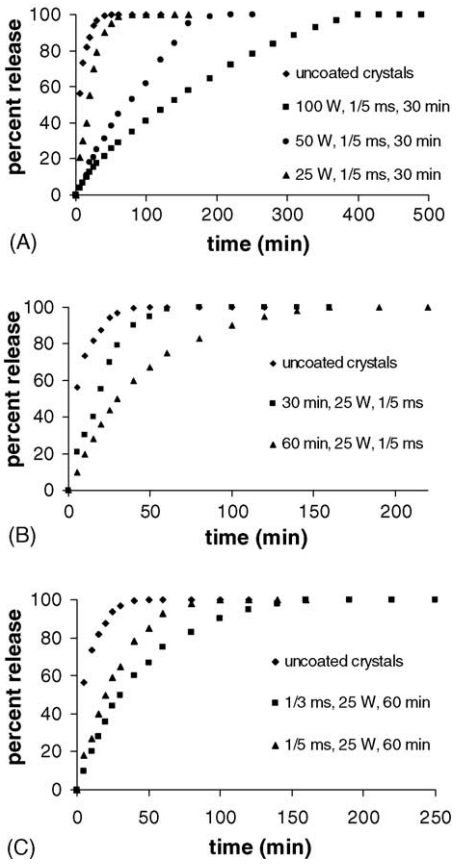

Fig. 2. Release profiles of polyallylalcohol coated acetylsalicylic acid crystals as a function of (A) peak power input (B) coating time (C) plasma duty cycle. Each variable was varied one at a time, with other variables held constant (as indicated above).

during coating results in an approximate two-fold increase in the time required for the completion of the drug release. These values are approximately 80 min for (25 W, 1/5 ms, 30 min), 220 min for (50 W, 1/5 ms, 30 min) and 400 min for (100 W, 1/5 ms, 30 min). A reasonable explanation for this result is that the extent of polymer cross-linking increases with increased peak power. This increased cross-linking would provide a less porous barrier to water permeation thus reducing the release rate. Increased cross-linking of the film at higher peak powers is consistent with FT-IR and XPS analysis of these films from allyl alcohol as well as results with numerous other monomers (Rinsch et al., 1996; Beyer et al., 1997; Han et al., 1997, 1998; Han and Timmons, 1998). Based on release rates during the first 20 min, the slopes of the initial rates for (25 W, 1/5 ms, 30 min); (50 W, 1/5 ms, 30 min) and (100 W, 1/5 ms, 30 min) are calculated to be 2.58, 0.866 and 0.616% release/min, respectively. Thus, changing the power from 100 to 50 W increases the slope of the initial rate by a factor of 1.4 whereas decreasing the power by the same ratio to 25 W results in a three-fold increase in the slope of the initial rate data.

The duration of the plasma coating time also affects the drug release rates. Two different coating times were used, namely 30 and 60 min. As shown in Fig 2(B), doubling the coating time increases the time required for the completion of the drug release by a factor of 2; from 80 min for (30 min, 25 W, 1/5 ms) to 160 min for (60 min, 25 W, 1/5 ms). The slopes of the initial rates for (30 min, 25 W, 1/5 ms) and (60 min, 25 W, 1/5 ms) undergo a change of approximately a 0.7 decrease, i.e. from 2.58 to 1.8% release/min.

Finally, the effect of duty cycle variation during plasma polymerization on drug release rates are illustrated in Fig. 2(C). Two different plasma duty cycles were employed, namely, 1/3 and 1/5 ms. Although both coating runs were of 60 min duration, the lower duty cycle film (1/5 ms) was significantly thicker, 7.45 versus 4.00 kÅ for the 1/3 ms run. Despite this greater thickness, it is interesting to note that the drug release rate of the 1/5 ms coating is approximately 1.4 times faster than that observed for samples coated during the 1/3 ms depositions. The higher duty cycle film is more cross-linked and this presumably accounts for the slower release rate (Rinsch et al., 1996). This observation is in accord with the peak power effects noted earlier and shown in Fig. 2.

4. Discussion

Overall the data presented in Fig. 2 are clearly supportive of using plasma generated polymer coatings to control the release rates of drug molecules from micron sized particles. Furthermore, as also shown by these experiments, the drug release rates can be modulated by changes in several, easily accessible, plasma parameters, namely: coating times, peak power inputs and pulsed plasma duty cycles. Specifically, the acetylsalicylic acid release rates decrease as the power input, the coating time and plasma duty cycles are increased. The plasma generated polymer film coatings on the drug crystals function as separation (i.e. permeation) barrier between the drug molecules and the solvent. Plasma polymer films are known to be porous in nature, thus permitting diffusion of solvent water molecules through these barriers with eventual dissolution of the drug molecules. The variations in drug release rates with plasma variable changes are in accord with this simple model. For example, increasing the plasma coating time will increase the thickness of the barrier layer thus reducing the drug release rates, as noted in these experiments. Also, it is speculated that increasing the power input or the plasma duty cycle during coating will reduce the porosity of the films. Certainly, it is well known from the plasma polymer literature that both of these variations increase the extent of cross-linking in plasma polymer films. The increased cross-linking has been shown to reduce moisture-penetration of plasma synthesized barrier films (Yasuda, 1985). Thus, it seems reasonable to assume that the same consideration is applicable in the variation in drug release rates observed in the present study.

In the present study, the polyallyl alcohol coated acetylsalicylic acid release rates were further subjected to kinetic analysis. The kinetic analysis was carried out over time periods corresponding to release of approximately the first 60% of the drug molecules. The kinetics of drug release is frequently analyzed in terms of either zero-order or first-order kinetics (Korsmeyer et al., 1983; Ritger and Peppas, 1987; Yang et al., 2001; Agrawal et al., 2003). In terms of zero-order kinetics, the proposed model involves initial diffusion of water into the drug containing capsule with formation and maintenance of a saturated solution in which both liquid and undissolved solid remain in equilibrium. On the other hand, first-order kinetics is interpreted as the

result of an initial, rapid solution process inside the capsule in which the drug molecules are solubilized, followed by slower diffusion of drug molecules out of the capsule thus generating a progressively less concentrated solution inside the capsule with time.

The release of acetylsalicylic acid molecules was examined in terms of both zero order and first order kinetics. A zero order process would obey the equation:

$$\frac{M_r}{M_0} = k_0 t \tag{2}$$

where M_r amount of drug released at time t, M_0 total amount of drug before dissolution, k_0 zero-order release constant and t time. The experimental data obtained with polyallyl alcohol coated acetylsalicylic acid crystals treated in terms of zero order kinetics are shown in Fig. 3. The R^2 (coefficient of determination) factors for these various plots were relatively poor ranging from a high of 0.977 to a low of 0.946.

In contrast, analyses of these data in terms of first order kinetics resulted in significantly better correlation factors. For the first order plots, the data were analyzed with respect to the equation:

$$\ln\left(\frac{M_t}{M_0}\right) = -k_1 t \tag{3}$$

where M_t amount of drug remaining at time t, M_0 total amount of drug before dissolution, k_1 first-order release constant and t time. These first order plots are shown in Fig. 4. The R^2 factors ranged from 0.9992 to 0.9788, again based on the first 60% drug release. Thus, based on the relative R^2 values obtained, the release rate data correlate significantly better with 1st order as opposed to zero order kinetics. However, in connection with this analysis, it is important to note that, since replicate runs were not carried out, the above results must be viewed as being only qualitative in scope. A more detailed analysis should involve replicate runs, as well as inclusion of an intercept since the origin (0,0) would be a statistically valid point and could have been included (Neter et al., 1996). In the present case, the inclusion of the origin would result in even better correlation with first order kinetics.

The first order rate constants ranging from 0.12 to 0.0054 min^{-1} for the various polyallyl alcohol coatings, represent a factor in excess of 20 for variation of release rates. Since the purpose of this study was simply to investigate the feasibility of modulating the release rates with plasma deposited coatings, no emphasis was placed on extending the release times to even longer durations. However, it seems reasonable to project that simply coating the particles for longer time periods, perhaps combined with higher power inputs, offers an opportunity to control release rates, in continuous fashion, over extremely long time periods. Such considerations would be of significant importance in cases where drugs are implanted in specific organs for desired release over extended periods of time.

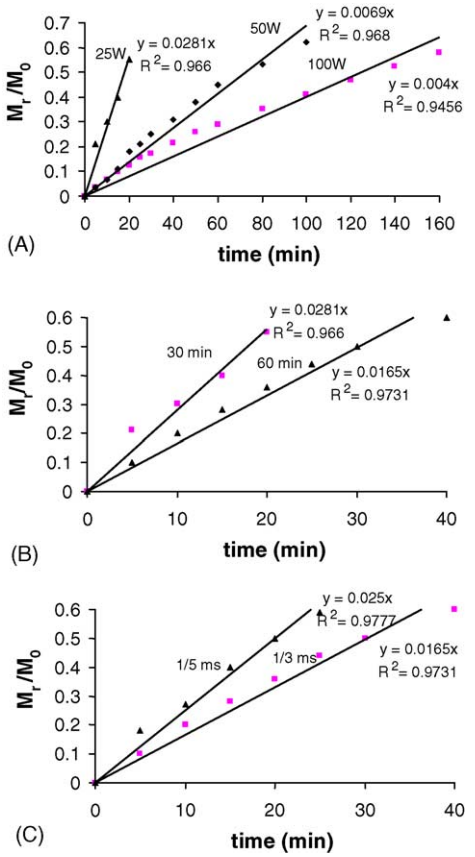

Fig. 3. Zero-order release kinetics analysis of polyallyl alcohol coated acetylsalicylic acid crystals as a function of (A) peak power input at 1/5 ms and 30 min (B) coating time at 25 W and 1/5 ms and (C) plasma duty cycle at 25 W and 60 min.

In the present investigation, thin-layer chromatography was used to determine if undesirable conversion of some drug molecules to other compounds occurred under plasma coating conditions. If appreciable conversions do take place then additional compounds, having RF values different from the drugs, were expected to

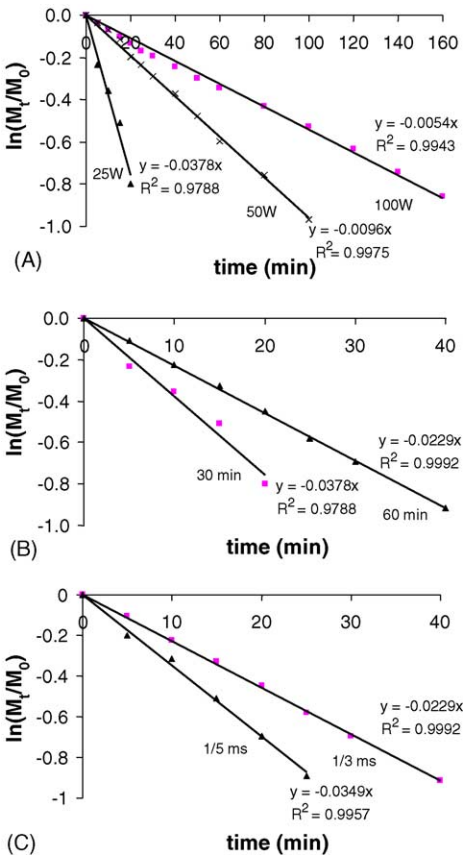

Fig. 4. First-order release kinetics analysis of polyallyl alcohol coated acetylsalicylic acid crystals as a function of (A) peak power input at 1/5 ms and 30 min (B) coating time at 25 W and 1/5 ms and (C) plasma duty cycle at 25 W and 60 min.

be detected under TLC analysis. For this purpose, a chloroform–acetone (4:1) solution was chosen as the mobile phase. With this choice of solvent and using silica as the adsorbent, literature indicates the retention factor for acetylsalicylic acid as 0.18 and the retention factor for ibuprofen as 0.46 (Stead et al., 1982). Four reference compounds were used for this type of system; methohexitone, quinalbarbitone, clonazepam and paracetamol. Only spots having exactly the same RF values were observed in comparing the TLC results of coated and uncoated aspirin. The retention factor of these was calculated to be 0.14 in good agreement with literature results for acetylsalicylic acid for TLC plates run under the same conditions. Thus the TLC results suggest that negligible amounts of drug molecules are converted to other compounds during the coating process. For the moment, it is emphasized that the pulsed plasma approach should be particularly useful in terms of minimizing degradation of drug particles. The film deposition rates are very high under pulsed conditions and include significant film formation during plasma off periods (Rinsch et al., 1996). During the plasma off periods, the chemistry is more selective and minimizes contributions from highly reactive species such as ion radicals. These factors, coupled with the absence of short wavelength photons during off times, help contribute to retention of the integrity of the drug molecules while promoting rapid coating of the particles.

5. Conclusions

Based on results of this initial investigation, the potential use of plasma polymerization processing represents a promising new route to control drug release. Key plasma deposition variables examined, specifically power input, coating time and pulsed plasma duty cycle, were found to be effective in providing control of the drug release rates. The release rate of acetylsalicylic acid from polyallyl alcohol coatings decreases as the peak power, coating time and plasma duty cycle increase. These initial studies indicate that it should be possible to prepare blends of coated drug particles to provide relatively constant drug release rates. The pulsed plasma approach employed helps minimize undesirable changes in drug compositions while providing better film thickness and film chemistry controllability. Future studies will involve extension of this approach to include other drug molecules as well as other polymer coatings.

References

Agrawal, A.M., Neau, S.H., Bonate, P.L., 2003. Wet granulation fine particle ethyl cellulose tablets: effect of production variables and mathematical modeling of drug release. AAPS Pharm. Sci. 5 (Article 13).

Bernkop-Schnürch, A., Scholler, S., Biebel, R.G., 2000. Development of controlled drug release systems based on thiolated polymers. J. Control. Release 66, 39–48.

Beyer, D., Knoll, W., Ringsdorf, H., Wang, J.H., Timmons, R.B., Sluka, P., 1997. Reduced protein adsorption on plastics via direct plasma deposition of triethylene glycol monoallyl ether. J. Biomed. Mater. Res. 36, 181–189.

Bottcher, H., Slowik, P., Sub, W., 1998. Sol–gel carrier systems for controlled drug delivery. J. Sol–Gel Sci. Technol. 13, 277–281.

Chen, X., 1995. Molecular Tailoring of Surfaces via Pulsed RF Plasma Deposition. Ph.D. thesis. University of Texas at Arlington, TX.

Fozza, A.C., Moisan, M., Wertheimer, M.R., 2000. Vacuum ultraviolet to visible emission from hydrogen plasma: effect of excitation frequency. J. Appl. Phys. 88, 20–33.

Han, L.M., Rajeshwar, K., Timmons, R.B., 1997. Film chemistry control and electrochemical properties of pulsed plasma polymerized ferrocene and vinylferrocene. Langmuir 13, 5941–5950.

Han, L.M., Timmons, R.B., 1998. Pulsed-plasma polymerization of 1-Vinyl-2-Pyrrolidone: synthesis of a linear polymer. J. Polym. Sci.: Part A Polym. Chem. 36, 3121–3129.

Han, L.M., Timmons, R.B., Lee, W.W., Chen, Y., Hu, Z., 1998. Pulsed plasma polymerization of pentafluorostyrene: synthesis of low dielectric constant films. J. Appl. Phys. 84, 439–444.

Korsmeyer, R.W., Gurny, R., Doelker, E., Buri, P., Peppas, N.A., 1983. Mechanisms of solute release from porous hydrophilic polymers. Int. J. Pharm. 15, 25–35.

Luo, Y., Kirker, K.R., Prestwich, G.D., 2000. Cross-linked hyaluronic acid hydrogel films: new biomaterials for drug delivery. J. Control. Rel. 69, 169–184.

Martin, A.R., Manolache, S., Denes, F.S., Mattoso, L.H.C., 2002. Functionalization of sisal fibers and high-density polyethylene by cold plasma treatment. J. Appl. Polym. Sci. 85, 2145–2154.

Neter, J., Kutner, M.H., Nachtsheim, C.J., Wasserman, W., 1996. Applied Linear Statistical Models, 4th ed. WCB/McGraw-Hill.

Panchalingam, V., Poon, B., Huo, H.-H., Savage, C.R., Timmons, R.B., Eberhart, R.C., 1993. Molecular surface tailoring of biomaterials via pulsed RF plasma discharges. J. Biomater. Sci. Polym. 5, 131–145.

Qiu, X., Leporatti, S., Donath, E., Möhwald, H., 2001. Studies on the drug release properties of polysaccharide multilayers encapsulated ibuprofen microparticles. Langmuir 17, 5375–5380.

Railkar, A.M., Schwartz, J.B., 2001. Use of a moist granulation technique (MGT) to develop controlled-release dosage forms of acetaminophen. Drug Dev. Ind. Pharm. 27, 337–343.

Rango Rao, K.V., Devi, K.P., 1988. Swelling controlled-release systems: recent developments and applications. Int. J. Pharm. 48, 1–13.

Rinsch, C.L., Chen, X., Panchalingam, V., Eberhart, R.C., Wang, J.H., Timmons, R.B., 1996. Pulsed radio frequency plasma polymerization of allyl alcohol: controlled deposition of surface hydroxyl groups. Langmuir 12, 2995–3002.

Ritger, P.L., Peppas, N.A., 1987. A simple equation for description of solute release I. Fickian and non-Fickian release from non-swellable devices in the form of slabs, spheres, cylinders or disks. J. Control. Release 5, 23–26.

Stead, A.H., Gill, R., Wright, T., Gibbs, J.P., Moffat, A.C., 1982. Standardized thin-layer chromatographic systems for the identification of drugs and poisons. Analyst 107, 106–168.

Sukhorukov, G.B., Donath, E., Lichtenfeld, H., Knippel, E., Knippel, M., Budde, A., Möhwald, H., 1998. Layer-by-layer self assembly of polyelectrolytes on colloidal particles. Colloids Surf. A: Physicochem. Eng. Aspects 137, 253–266.

Tamilvanan, S., Sa, B., 1999. Effect of production variables on the physical characteristics of ibuprofen-loaded polystyrene microparticles. J. Microencapsul. 16, 411–418.

Tamilvanan, S., Sa, B., 2000. Studies on the in vitro release characteristics of ibuprofen-loaded polystyrene microparticles. J. Microencapsul. 17, 57–67.

Uhrich, K.E., Cannizzaro, S.M., Langer, R.S., Shakesheff, K.M., 1999. Polymeric systems for controlled drug release. Chem. Rev. 99, 3181–3198.

Valenti, M., Fabiani, F., 2001. Acetylsalicylic acid controlled-drug release compositions. PCT Int. Appl., 22.

Yang, C.-Y., Tsay, S.-Y., Tsiang, C.-C., 2001. Encapsulating aspirin into a surfactant free ethyl cellulose microsphere using non toxic solvents by emulsion solvent-evaporation technique. J. Microencapsul. 18, 223–236.

Yasuda, H., 1985. Plasma Polymerization. Academic Press, Orlando.