The application of a supercritical antisolvent process for sustained drug delivery

Yulu Wang a, Yiping Wang b, Jun Yang a, Robert Pfeffer a, Rajesh Dave a,⁎, Bozena Michniak c

d a New Jersey Center for Engineering Particulates (NJCEP), New Jersey Institute of Technology, Newark, NJ, United States
b Department of Pharmaceutical Sciences, Rutgers-The State University of New Jersey, Piscataway, NJ, United States
c Department of Pharmacology and Physiology, UMDNJ-New Jersey Medical School, Newark, NJ, United States

Received 1 September 2005; received in revised form 23 February 2006; accepted 8 March 2006
Available online 2 May 2006

Abstract

Supercritical processes for drug delivery system design have attracted considerable attention recently. This present work investigates the application of a supercritical antisolvent coating process for controlled drug release design. Hydrocortisone as the host drug particles and poly(lactide-co-glycolide) (PLGA) as the polymer carrier were selected as the model system for this purpose. In this research the drug particles were suspended in a polymer solution of dichloromethane. The suspension was then sprayed into supercritical CO2 as an antisolvent. A parallel study of co-precipitation of the drug and polymer using the same supercritical antisolvent process at the same operating conditions was performed for comparison with the coating process. SEM images were used to characterize the drug particles before and after and the assay analysis was carried out using HPLC. The coated particles and co-precipitated particles were evaluated in terms of encapsulation efficiency and drug release profiles. The major advantage of this new approach is the ability to physically coat very fine (<30 μm) particles without having to dissolve them in an organic solvent. It was found that higher polymer to drug ratios produced higher encapsulation efficiencies and the coated drug particles did show sustained release behavior. The co-precipitation of the drug and polymer (at the same operating conditions), however, did not exhibit any sustained release.

© 2006 Elsevier B.V. All rights reserved.

Keywords: Encapsulation; Coating; Particle; Supercritical CO2; SAS; Sustained release

1. Introduction

The incorporation of a pharmaceutical ingredient into a polymer carrier is of great interest for controlled drug delivery systems. Each drug has a concentration range that provides optimal therapeutic effects. When the drug concentration falls out of this range (either higher or lower), it may cause toxic effects or become therapeutically ineffective. Therefore, it is desirable to release the drug content from a polymer carrier in a sustained or a controlled manner so as to eliminate the potential of either over-dosing or under-dosing. A polymer carrier can also provide protection for fragile drugs, such as proteins and peptides, from hydrolysis and degradation. In addition, a drug controlled release system can improve patient compliance by reducing the drug administration frequency.

Polymer-based microsphere controlled drug release has attracted significant attention recently because of its flexibility of administration. Microspheres less than 100 μm are suitable for intravenous delivery for absorption. When the particle size is less than 5 μm, the microspheres can be administered via inhalation drug delivery. In controlled drug release, polymer-based microspheres usually have either a matrix or a micro-encapsulated structure. In a matrix structure, the drug is uniformly dispersed in a polymer matrix whereas a microcapsule is composed of drug particles surrounded by a polymer coating film.

For both the matrix or microcapsule structure, drug release occurs by one (or both), of two primary mechanisms: diffusion release or degradation release. Diffusion release takes place when an incorporated drug passes through the polymer pores or through polymer chains. This drug controlled release system can be designed by using a “smart” polymer, whose permeability is dependent on environmental conditions, such
as pH, temperature, ionic strength, etc. [1]. For example, pH is the stimulant for an acidic or basic hydrogel, and temperature is the stimulant for a thermo-responsive hydrogel (poly-N-isopropylacrylamide). Degradation release occurs when a polymer degrades within the human body as a result of natural biological processes, such as hydrolysis. In this type of controlled release system, the selection of the polymer is critical since the degradation is dependent strongly on its chemical structure and molecular weight. The most popular biodegradable polymers for drug controlled release systems include poly(lactic acid), poly(glycolic acid) and their copolymers [2].

Drug-loaded polymer microspheres can be made by emulsion evaporation, phase separation, spray-drying, freeze-drying, and interfacial polymerization techniques. All of these methods involve the dissolution of the polymer and the drug in an organic solvent, dispersion of the solution under a strong force, and stabilization under certain temperature and pH conditions. However, problems of residual organic solvent in the final product and poor encapsulation of drugs due to partitioning of the pharmaceutical components between two immiscible liquid phases are frequently encountered. Moreover, harsh conditions, such as temperatures, pH conditions, and strong shear forces, may denature some bioactive agents. Also, extensive downstream processing is usually required when using these conventional methods.

Supercritical CO2 (SC CO2) is the most widely used supercritical fluid because of its mild critical conditions ($T_c=31.1$ °C, $P_c=73.8$ bars), non-toxicity, non-flammability, and low price. The low critical temperature of CO2 makes it attractive for processing heat-sensitive flavors, pharmaceuticals and labile lipids [3]. The use of SC CO2 for micro-particle preparation has been widely reported using rapid expansion of supercritical solution (RESS) [4–8] and a variety of antisolvent processes such as gas antisolvent (GAS) [9,10], supercritical antisolvent (SAS) [11–14], aerosol solvent extraction systems (ASES) [15] and solution enhanced dispersion by supercritical fluids (SEDS) [16].

The application of SC CO2 processes to prepare drug loaded polymer microspheres for controlled drug release has become a fast growing field. Tom and Debenedetti [17] investigated a SC CO2 process for the formation of drug-loaded microspheres for controlled drug release. In this pioneering work, a model system, the suspension was then sprayed through a capillary nozzle (280 μm). The results showed that the protein particles were successfully encapsulated in a polymer coating without agglomeration with a final size ranging from 6 to 62 μm. However, the application of RESS process is severely limited by the fact that most of the polymers and drugs of interest are not soluble in SC CO2 at any reasonable concentrations. There is another disadvantage in that it is very difficult to control the coating or encapsulation because the nucleation and precipitation of coating materials take place very fast (less than $10^{-5}$ s) during RESS [20]. As an alternative, antisolvent processes (GAS/SAS/ASES/SEDS) for drug delivery system design has attracted a lot of attention recently because of its flexibility in choosing a suitable solvent to dissolve the polymer that is also miscible with SC CO2.

Bleich and Müller [21] studied drug-loaded particle formation using the ASES process. PLA was used as the carrier and several different drugs, such as hyoscine butylbromide, indomethacin, piroxicam and thymopentin, were selected as model drugs for this study. The drugs and PLA were dissolved in methylene chloride and the solution was atomized into SC CO2 through a 400-μm nozzle at a flow rate of 6 ml/min. The solvation of SC CO2 in the organic solvent resulted in the formation of drug-loaded microparticles smaller than 50 μm. It was found that, with decreasing polarity of the incorporated drug, drug loading was lowered as a result of an increase in extraction by SC CO2, with the organic solvent acting as a co-solvent. Polar drugs, such as proteins and peptides, were successfully encapsulated by the ASES process, whereas non-polar drugs failed to be encapsulated and were completely extracted by the SC CO2 and the organic solvent.

Tu et al. [22] attempted the microencapsulation of para-hydroxybenzoic acid (β-HBA) and lysozyme with PLA using the ASES process. In this research the drug solution, polymer solution and SC CO2 were delivered through a specially designed coaxial multiple nozzle. A higher loading efficiency of 15.6% was achieved for lysozyme encapsulation, while β-HBA was poorly encapsulated with an efficiency of only 9.2%.

Falk et al. [23] proposed making drug-loaded microspheres using the SAS process. In this study, drugs such as gentamicin, naloxone and naltrexone and PLA were dissolved in methylene chloride using the hydrophobic ion-pairing (HIP) complexation method, which improved the solubility of the drugs considerably, to make a homogeneous solution. The prepared solutions were sprayed into SC CO2 through an ultrasonic nozzle vibrating at 120 kHz. The drug loaded microspheres (0.2–1.0 μm) formed due to the co-precipitation of the drugs and the PLA. Drug release tests showed that gentamycin was successfully incorporated into a PLA matrix, exhibiting diffusion controlled drug release. However, naltrexone and rifampin were found to be poorly incorporated because these
two drugs were more lipophilic and somewhat soluble in SC CO₂, resulting in drug surface bonding on the microspheres.

Elvassore et al. [24] studied the formation of protein loaded polymeric microcapsules in the SAS process. A model system of insulin and PLA was dissolved in a mixture of DMSO and dichloromethane. The prepared solution was then sprayed into SC CO₂ through a 50-μm fused silica nozzle. The results showed that insulin loaded microspheres with particle size from 0.5 to 2 μm were produced and the incorporation efficiency was as high as 80%.

Ghaderi et al. [25] studied the formation of microparticles with hydrocortisone loaded in DL-PLA polymer using a combination of SC N₂ and CO₂ as the antisolvent in the SEDS process. It was shown that microparticles of size less than 10 μm were produced. Hydrocortisone was successfully entrapped in DL-PLA microparticles with a loading efficiency up to 22%. The combination of SC N₂ and CO₂ was found to facilitate a more efficient dispersion of the polymer solutions than SC CO₂ alone.

Most of the reported research on the formation of drug-loaded microspheres for controlled drug release has focused on the co-precipitation of the solute of interest (drug) and the carrier polymer using an antisolvent process. However, since a SAS co-precipitation process requires the dissolution of both the drug and the polymer in a solvent, this creates a challenge for proteins since many proteins are insoluble in organic solvents. Also, many organic solvents can denature the protein’s bioactivity. Moreover, the co-precipitation of two different solutes is difficult to achieve except when the two solutes have similar thermodynamic properties and undergo similar precipitation pathways. For some materials, the co-precipitation may also lead to phase separation, unless special attention is paid to the selection of solvents and anti-solvents.

Motivated by the above-mentioned limitations of the co-precipitation approach, an alternative antisolvent process for particle coating or encapsulation was developed for drug delivery applications. Several notable reports on particle coating based on anti-solvent processes include work by Bertucco and Vaccaro [26], who did a preliminary study of particle encapsulation by polymer using a GAS process. In their study, particles of KCl (500 μm) were suspended in a solution of polymers (hydroxypropyl methylcellulose phthalate, Eudragit E 100, ethylcellulose) in various organic solvents (toluene, acetone, 1,4-dioxane, ethylacetate). Compressed CO₂ was introduced into a high-pressure vessel, in which the suspension was charged. The compressed CO₂ was dissolved in the organic solution, leading to the loss of solvent strength of the organic solvent. As a result, the polymer precipitated out and deposits on the surface of suspended KCl particles. The KCl particles were successfully encapsulated by ethylcellulose. However, when Eudragit 100 and HP-55 were used as the coating materials, aggregation took place due to insufficient stirring during precipitation.

Young et al. [30] studied the encapsulation of lysozyme in a biodegradable polymer by precipitation with a vapor-over-liquid antisolvent, which is simply a modification of the precipitation with a compressed antisolvent (PCA) process. In this work, a suspension of 1–10 μm lysozyme particles in a polymer solution was sprayed into CO₂ vapor over a CO₂ liquid phase (below supercritical conditions) through a nozzle. By delayed precipitation, polymer particles were allowed to grow large enough to encapsulate lysozyme. The process showed high encapsulation efficiency because the polymer precipitated onto the surface of protein particles in a small droplet.

We have previously film coated both nano and sub-micron “model” particles by a polymer film in a SAS type process [31] and were able to achieve non-agglomerated coating down to particles as small as 500 nm [32]. In this process, the host particles of interest are suspended in a coating polymer solution instead of being dissolved as in a co-precipitation process. The prepared suspension is either sprayed into SC CO₂ or SC CO₂ is injected into the suspension. As a result of the mutual diffusion between SC CO₂ and the organic solvent, the polymer becomes supersaturated, is driven out of solution, and deposits on the surface of the host particles producing a film coating. The main advantage of this approach is that the particles to be coated do not have to be dissolved in any solvents, which implies that there is no possibility of denaturing the host material, no need to find a solvent capable of adequately dissolving the host as well as the polymer, and the process can be purely physical without any reaction between the host particle and the polymer film.

The objective of this research is to apply the SAS process to coat or encapsulate fine drug particles (5–30 μm) to achieve controlled drug release. Drug particles less than 30 μm in size were chosen as hosts and a biodegradable polymer of PLGA (50:50) was used as the coating polymer. The SAS process requires good miscibility of the solvent and SC CO₂. Once the polymer solution containing drug particles in suspension contacts SC CO₂, very rapid mass transfer from the organic solvent to the bulk SC CO₂, and vice versa, takes place so that a high degree of supersaturation is achieved. The polymer nucleates and precipitates out of solution and deposits on the surface of the drug particles; a film coating can be expected if sufficient polymer is deposited on the surface of the hosts.

2. Materials and methods

2.1. Materials

The coating material was poly lactide-co-glycolide (PLGA) (Resomer® 502, MW 12,000, 50/50, Tg –40 to –55 °C) supplied by Boehringer Ingelheim Chemicals, Inc., USA. Acetone was purchased from Aldrich and used as received. Bone-dry liquid CO₂ was obtained from the Matheson Company, USA. Hydrocortisone (HC) (mean size less than 30 μm) was supplied by ICN Biomedical Inc., USA. It was used as received without further treatment.

2.2. Methods

The experimental set-up is schematically shown in Fig. 1. It consists of three major systems: a suspension delivery
system, a CO₂ supply system, and a stainless steel high pressure chamber with a volume of 1000 ml (Parr Instruments, USA). A water bath is used to keep the temperature at a desired value. A metering valve (Swagelok, SS-31RS4, R.S. Crum and Company, USA) was utilized to control the system pressure; the CO₂ inlet and outlet and a pressure gauge are located on the lid of the high-pressure chamber. The suspension is delivered by a HPLC pump (Beckman, 110B). To prevent clogging in delivering the suspension system, the pump was modified by taking the filters in the pump head out. While this may cause damage to the pump and the piston, because of the fine particle size and non-abrasive nature of the particles, we did not see any damage on the piston, which is made of stainless steel, or seals, which are made of sapphire. A capillary nozzle (254 μm ID) is used to spray the suspension into the high-pressure chamber and a metering pump (Model EL-1A, American Lewa®, USA) is used to deliver liquid CO₂ into the chamber from a CO₂ cylinder. The liquid CO₂ is chilled to about zero degrees Centigrade by a refrigerator (Neslab, RTE-111) to avoid cavitation. A heating tape (Berstead Thermolyne, BIH 171-100) is used to preheat the liquid CO₂ before it enters into the high-pressure chamber.

The experimental protocol used is as follows. The precipitation chamber is first charged with SC CO₂. After the predetermined operating conditions (temperature and pressure, 33 °C and 8.96 MPa) are reached, a steady flow of CO₂ (1.5 standard liters per minute) is established by adjusting the metering valve and the metering pump. PLGA and hydrocortisone, 150 mg of each (at a 1:1 ratio), are then weighed and added into 30 ml of dichloromethane (DCM). PLGA is dissolved in DCM while hydrocortisone is suspended in the polymer solution due to the very limited solubility of hydrocortisone in DCM. The suspension is then injected at a flow rate of 0.8 ml/min into the high-pressure chamber through the capillary nozzle by using the modified HPLC pump (Beckman, 110B) for about 10 min. After spraying, fresh CO₂ is supplied continuously to purge the chamber with about 1 equivalent volume of CO₂ in order to remove any remaining dichloromethane. After purging, the precipitation chamber is slowly depressurized and the coated drug particles collected for characterization.

In addition, a parallel study of co-precipitation of hydrocortisone and PLGA was performed for comparison purposes (Table 1). In the co-precipitation experiment, PLGA and hydrocortisone are both dissolved in either acetone or a mixture of methanol and DCM (volume ratio of 1:1) to make a homogeneous solution. The solution is then sprayed into the high-pressure chamber at the same operating conditions that were used in the SAS coating process. The operating conditions of the SAS coating and the co-precipitation experiments are listed in Table 1.

### 2.3. SEM microscopy

Field emission scanning electron microscopy (FE-SEM) (Leo, 1530VP) was used to observe any morphological changes before and after the coating treatment. The samples were simply spread on carbon tape for observation under SEM.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Operating conditions used in the SAS coating and co-precipitation experiments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experiments</td>
<td>Parameters</td>
</tr>
<tr>
<td>Solvent</td>
<td>Polymer conc. (mg/ml)</td>
</tr>
<tr>
<td>Coating of drug particles</td>
<td>DCM</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Co-precipitation of drug and PLGA</td>
<td>Acetone</td>
</tr>
<tr>
<td></td>
<td>Methanol</td>
</tr>
<tr>
<td></td>
<td>and DCM</td>
</tr>
</tbody>
</table>

All experiments were operated at 33 °C and 8.96 MPa, CO₂ flow-rate: 1.5 SLPM, liquid injection flow-rate: 0.8 ml/min.
2.4. HPLC analysis

HPLC assay analysis of hydrocortisone was performed using a Hewlett Packard 1100 equipped with a reverse phase C-18 column (Microsorb-MV 100, 150 × 4.6 mm, 5 μm, Varian). The mobile phase was made at a composition of acetonitrile/purified water (40:60 v/v) and the injection volume was 10 μl. The flow rate was 1.0 ml/min and hydrocortisone was detected at 242 nm by a UV detector. The run time for the assay was 4.0 min and the retention time for hydrocortisone was 2.9 min.

2.5. Determination of encapsulation efficiency (EE)

A known amount of coated drug samples was washed with ethanol, which is a good solvent for hydrocortisone but a poor solvent for PLGA, to dissolve the uncoated or partially coated drug particles. The suspension was centrifuged at 1500 rpm for 5 min. The supernatant fluid was sampled to determine the un-encapsulated drug content using HPLC. The sediment was then dissolved with a mixture of acetone and ethanol (50:50) and the drug content was determined using HPLC assay analysis. Each sample was analyzed in triplicate. The encapsulation efficiency (EE) was calculated using the following equation.

$$\text{%EE} = \frac{\text{encapsulated drug}}{\text{unencapsulated drug} + \text{encapsulated drug}} \times 100\%$$

The coated or encapsulated drug was weighed and was put into a test tube holding 30 ml of pH buffer solution (PBS, pH 7.4) containing 0.05% Brij 58. A small magnetic stirrer bar was used to improve the mixing. The test tubes were covered by parafilm. All samples were incubated at 37 °C while being agitated. At given time intervals the test tubes were centrifuged at 1500 rpm for 5 min and 200 μm of supernatant fluid was transferred into small vials for HPLC assay analysis, and was replaced with the same volume of fresh PBS. For each time interval the amount of drug removed in the 200-μl sample used for HPLC analysis was taken into account when calculating the

Fig. 2. Original uncoated hydrocortisone particles at different magnifications: (a) 1.5 KX, (b) 2.94 KX.

Fig. 3. Coated hydrocortisone particles at a polymer to drug ratio of 1:4 at two different magnifications: (a) 5.21 KX, (b) 10.0 KX.
release fraction. Dissolution tests of each sample were performed in three replicates.

3. Results and discussion

SEM pictures of the original hydrocortisone particles are shown in Fig. 2. Hydrocortisone is seen to be in crystal form with defined facets and sharp edges. The average particle size is less than 30 μm as seen from the scale bar. The coated hydrocortisone particles, at a polymer to hydrocortisone weight ratio of 1:4, are shown in Fig. 3. The coated particles have a different shape (morphology) and no clear sharp edges when compared with the uncoated drug particles. This indicates that some of the drug particles were partially coated with polymer during the SAS process but no film coating or encapsulation seemed to have occurred.

The difference in shape between the coated and uncoated drug particles may be attributed to the fact that some hydrocortisone (about 17% of the total) [33] dissolved in DCM, although DCM is not a good solvent for hydrocortisone. The dissolved drug may undergo nucleation and re-crystallization during the SAS process, resulting in different habit, which can be observed in the SEM pictures before and after SAS process. This can pose difficulties in coating.

When the polymer to drug ratio was increased to 1:2, more polymer precipitated out and deposited on the surface of the drug particles as seen in Fig. 4. The smaller drug particles seemed to be embedded or entrapped in the coating polymer. However, the larger drug particles appeared to have been left uncoated, indicating that large, irregular shaped particles may require even more polymer to encapsulate them.

In order to encapsulate the larger particles, the polymer loading was increased to a polymer to drug ratio of 1:1. SEM pictures of the coated drug particles are shown in Fig. 5. As observed in Fig. 5, more polymer coating took place on the surface of the drug particles as compared with drug particles coated at a 1:4 (Fig. 3) and a 1:2 ratio (Fig. 4). Some of the smaller drug particles were even encapsulated in polymer microspheres. However, it was found that the polymer coating on the surface of the drug particles was still unevenly distributed due to the irregularity of the drug particles. Thus it appears that uniformly coating or encapsulating irregular particles by SAS presents a major challenge.
A parallel study was performed to compare drug particle coating and co-precipitation using the SAS process. In the co-precipitation experiments, hydrocortisone and PLGA were both dissolved in acetone or a mixture of methanol and DCM. A clear solution instead of a suspension was sprayed into SC CO₂ in the SAS process.

SEM photographs of the co-precipitated particles of drug and polymer in Fig. 6 clearly show that the co-precipitated particles have a very different morphology and shape from the original particles. The re-crystallized drug particles have defined facets and the polymer appears to be simply attached to (rather than coating) the surface of the re-crystallized drug particles. It is apparent that there was a phase separation during the precipitation of polymer and drug from the acetone or mixture of DCM and methanol solutions. Therefore, it appears that no coating or encapsulation occurred in the SAS co-precipitation process.

The coated drug particles and co-precipitated drugs were analyzed to determine the encapsulation efficiency. The results are listed in Table 2. The coated drug particles at a polymer to drug ratio of 1:4 showed that drug particles were not encapsulated within the polymer. This supported the conclusion that the drug particles were only partially coated by polymer as shown in Fig. 3. In the encapsulation efficiency test, if an uncoated part of the surface of a drug particle is exposed to ethanol, the whole drug particle would be dissolved gradually. Therefore, partially coated drug particles did not show any encapsulation efficiency. When the polymer loading was increased to a ratio of 1:2, more polymer coating occurred on the surface of drug particles and the average encapsulation efficiency increased to 6.7%. When more polymer was used, the smaller drug particles were probably completely encapsulated by the polymer. Consequently, these encapsulated drug particles were not washed away by ethanol in the encapsulation efficiency test and they contributed to the encapsulation efficiency. However, the encapsulation rate was not improved considerably even though the polymer loading was doubled. This was probably due to the fact that the larger, irregular-shaped, high aspect ratio drug particles left some sharp edges or corners uncoated and therefore they were completely dissolved by the ethanol treatment.

When the polymer to particle ratio was further raised to 1:1, more drug particles were encapsulated and the encapsulation efficiency increased to 22.6%. This supported the observation in Fig. 5 that more of the drug particles were completely

<table>
<thead>
<tr>
<th>Ratio of PLGA to HC</th>
<th>SAS Process</th>
<th>Encapsulation efficiency (EE) (%)</th>
<th>Average EE (%)</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:4 Coating*</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1:2 Coating</td>
<td>8.4</td>
<td>6.7 ±1.4</td>
<td>6.3</td>
<td>5.4</td>
</tr>
<tr>
<td>1:1 Coating</td>
<td>21.5</td>
<td>22.6 ±2.3</td>
<td>25.2</td>
<td>21.2</td>
</tr>
<tr>
<td>1:1 Co-precipitation from methanol and DCM*</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>1:1 Co-precipitation from acetone*</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

* Experiments were performed in three replicates on each sample.
encapsulated or trapped in polymer microspheres. This suggests that the encapsulation efficiency could be further improved by either increasing the amount of polymer or reducing the size of host particles.

The co-precipitated drug and polymer particles from either acetone or a mixture of methanol and DCM showed no encapsulation of drug particles even at a polymer to drug ratio of 1:1. This is in good agreement with what was observed in Fig. 6 that the re-crystallized drug was not encapsulated with polymer and that the polymer was simply attached on the surface of the drug particles.

In vitro drug release tests were carried out to determine the release behavior of coated drug particles at different polymer to drug ratios. The release profiles are plotted in Fig. 7. The drug particles coated at a 1:4 ratio showed a fast release behavior; almost all of the drug content was released in about 1.5 h. This rapid release rate was attributed to the fast dissolution of the drug particles. The release behavior confirmed the result of the encapsulation test of the coated particles at a 1:4 polymer to drug ratio that no drug particle was entirely encapsulated.

The coated particles at a 1:2 ratio showed an initial release of about 90% of the drug content in about 1.5 h. After the initial burst, a second phase of much slower drug release (Fig. 7) occurred. At day 9 the PLGA started to degrade and the rest of the encapsulated drug was released in about 1 day. This suggested that about 10% of the drug particles were completely encapsulated, which was close to the encapsulation efficiency test result. The uncoated or partially coated drug particles were quickly dissolved in the release medium and this accounted for the burst release.

The drug particles coated at a 1:1 ratio showed a lower amount of fast release of drug than those coated at the 1:2 ratio. About 80% of drug was released during this phase. After this initial burst stage, a period of much slower drug release occurred before the onset of the polymer degradation stage. In about 9 days, PLGA started to degrade and the encapsulated drug was continuously released for about 3 days. This release behavior again supported the results of the encapsulation efficiency test on the coated drug particles at a 1:1 ratio. The

release profile exhibited by the drug articles coated at a 1:1 polymer to drug ratio was typical of polymer degradation controlled drug release [34,35]. By increasing the amount of polymer used for coating or reducing the size and aspect ratio of the drug particles, we would expect a larger fraction of drug particles to be incorporated into polymer microspheres. Thus, the initial burst release would be reduced and the release of drug would last longer.

To compare the SAS coating and co-precipitation processes, a drug release test of the co-precipitated sample from acetone was performed following the same procedure. The release profile is shown in Fig. 8 at a polymer to drug ratio of 1:1. It is clear from the figure that the re-crystallized drug and PLGA from the co-precipitation process exhibited a very fast release of the drug throughout the entire duration of the test. This suggests that no encapsulation occurred during the co-precipitation of drug and PLGA, even at the highest polymer to drug ratio of 1:1 that was studied. This release test result confirmed the encapsulation test result given previously.

4. Concluding remarks

Hydrocortisone particles were shown to be successfully coated with PLGA in the SAS coating process. At a low 1:4 polymer to drug weight ratio the drug surface was only partially coated and no encapsulation (encapsulation efficiency of zero) occurred. The encapsulation efficiency improved with an increase in polymer to drug ratio and increased to 22.6% when the polymer to drug ratio was 1:1. At polymer to drug ratios of 1:2 and 1:1, the coated drug particles exhibited a partial sustained release behavior. However, co-precipitations of drug and polymer (both in solution) failed to achieve encapsulation; the polymer appeared to be simply attached in chunks on the surface of the drug particles.

Although the encapsulation efficiency achieved was low and an initial burst stage was observed, an improvement in the drug sustained release properties could be obtained by increasing the polymer loading or either reducing the size or the aspect ratio of the drug particles because smaller, more spherical particles have a greater chance to be fully encapsulated or entrapped. Thus the SAS coating process is a promising technique for the design of drug delivery systems and might be especially useful for inhalation drugs where the particle size cannot be larger than a few microns. Since this process does not require dissolving the host particles, it can also be utilized for encapsulating proteins and other similar materials that may be adversely affected if they are dissolved in a solvent.

Acknowledgements

The authors would like to thank the National Science Foundation for financial support through Grant #CTS-9985618, and the New Jersey Commission of Science and Technology for financial support through Award #01-2042-007-24. Electron micrographs were taken at NJIT’s new electron microscopy facility, which was partially funded by the National Science Foundation through Grant #CTS-0116595.
References


