Synthesis of Controlled-Release Products in Supercritical Medium

Ozge Guney and Aydin Akgerman
Chemical Engineering Dept., Texas A&M University, College Station, TX 77843

Controlled-delivery products have recently received considerable attention. They prolong the drug's therapeutic effect, keeping its concentration between the therapeutic and toxicity limit. The final product must be free of residual solvent, even with nontoxic solvents, to provide its constant property that does not change with natural evaporation of the solvent. A major cost item in the synthesis of controlled-release drugs is to remove this solvent to acceptable limits. To eliminate the production step involving the organic solvent from the overall process, the drug was introduced into the polymer matrix using supercritical carbon dioxide ($scCO_2$) as the carrier solvent and swelling agent. This study focuses on the impregnation of a biodegradable polymer matrix with 5-fluorouracil for chemotherapy and β-estradiol estrogen hormone therapy. Swelling of the polymer matrix, solubility of drug components in $scCO_2$ and the adsorption isotherm/partition coefficients in the presence of $scCO_2$ were studied. To investigate the single-component supercritical adsorptive synthesis of controlled-delivery products, accurate experimental techniques to measure drug-component solubilities in supercritical fluids and adsorption isotherms in the presence of supercritical fluids were developed. Solubility data of these drugs in $scCO_2$ at 35−55°C and 101−220-bar were reported. The adsorption equilibrium constants/partition coefficients were presented for these drug components on poly-dl-lactide-co-glycolide (PLGA) at the same conditions. To understand the effect of operating variables on the total drug loading and to predict the drug-loading breakthroughs, a flow over a flat plate model was developed that accounts for the polymer swelling, the partitioning of the drug component between the supercritical and polymer phases, and the polymer diffusivity. Experimental isotherm data with and without the polymer were incorporated into the model to isolate the system response from the polymer response to determine impregnation efficiencies.

Introduction

Controlled-release implants are now used for treatment of diseases ranging from diabetes to cancer. With the help of these new products, the total amount of effective drug is reduced, and still its effect is prolonged, avoiding the problems that can originate by the introduction of excessive dosages so the effect lasts as long. This is achieved through controlling the rate of introduction of the drug to the body. The formulation of these products requires the drug and a matrix capable of releasing the active drug. The matrix in controlled drug-release systems is consequently a polymer. There are three characteristics that describe an ideal polymer used for drug delivery (Leong and Langer, 1987). First, the polymer must be biocompatible and degradable. Second, the degradation products of the polymer must be nontoxic, noncarcinogenic, should be soluble in the body's fluids, and not create an inflammatory response or allergic reaction. Finally, the polymer must be metabolized within a reasonable period of time.

In the preparation of drug-release products, using a swelling agent stretches the polymer matrix and increases the

Correspondence concerning this article should be addressed to A. Akgerman.

porosity for easier and faster impregnation. The classic methods to prepare controlled-delivery products uses an organic solvent for this purpose, which, in addition, serves as the carrier solvent for the drug component, in order to introduce the required active pharmaceutical into the polymer matrix.

An alternative is the use of supercritical fluids for the synthesis, which will result in final products for human consumption that are completely free of any residual solvent contamination. Although supercritical fluids have seldom been explored for this purpose, they have properties that could make them nearly the ideal medium for conducting impregnations and adsorptive separations. Supercritical fluids are inert to most adsorbents, nontoxic, inexpensive, readily available, and environmentally acceptable. In addition, supercritical carbon dioxide is nonflammable, so its use does not introduce a safety hazard during operation.

Researchers have exploited this increase in solute mass-transfer rate in polymeric matrices for supercritical fluid extraction (Paulaitis et al., 1983; McHugh and Krunakis, 1986; Kumar et al., 1986), but there has been much less research on supercritical impregnation. Although not related to controlled-release drug synthesis, the pioneering studies on polymer swelling and impregnation concentrated on understanding the phase behavior of supercritical fluid, polymer, and solute systems (Shim and Johnston, 1989; 1991). The studies related to the synthesis of controlled-release drug products focused on using supercritical fluids as vehicles for the formation of fine particles, such as microspheres, fine peptide, and protein powders. The two techniques that have been used up to now are RESS and SAS or GAS, which are essentially the coprecipitation of the drug and the polymer matrix from a supercritical solvent, the ultimate objective being the microencapsulation of the drug in the polymer matrix (Debenedetti et al., 1993). In a very recent study SAS was used to produce spherical solute particles coated by the polymer (Taki et al., 2000). This is a *reservoir device* where the drug forms the central core, rather than a *monolithic device* where the drug is homogenously dispersed throughout the polymer matrix.

The possibility of using supercritical carbon dioxide ($scCO_2$) saturated with a drug for the impregnation of the polymers for the synthesis of controlled-release drugs has previously been examined (Alessi et al., 1998; Kikic and Sist, 1998). Drug loadings of 8–25% by weight were reported. However, it was not clear whether the polymer matrix was actually impregnated (drug deposited within the polymer network) or the drug was precipitated on the external surface of the beads. No supporting evidence was presented on the impregnation of the internal surface of the polymer beads. However, there are many studies on supercritical phase impregnation. The impregnation of polyethylene films with metal carbonyls has been studied (Poliakoff and Howdle, 1995). Impregnation of organic dyes into glassy polymers using supercritical fluids has been achieved (Kazarian et al., 1997). Similarly dyeing of textiles via supercritical impregnation has been investigated (Saus et al., 1993). It has been demonstrated recently that using supercritical fluids to impregnate wood with certain chemicals, such as polymers, preservatives, fire retardants, or silicon compounds, is a promising technique for wood preservation (Sahle-Demessie et al., 1998). Also, the possibility of toughening cement materials by impregnation using $scCO_2$ as a potential application has been investigated (Gibbs, 1996).

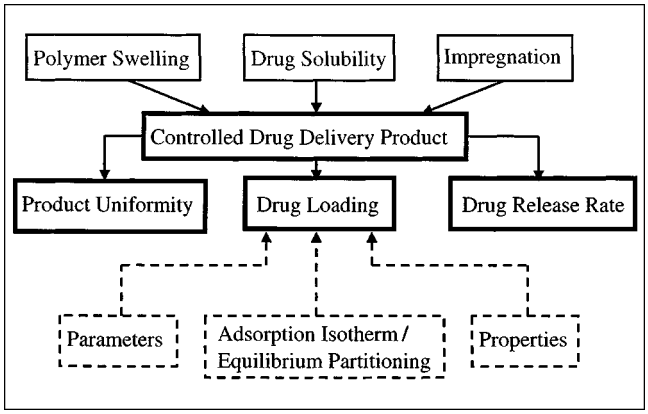

Figure 1. Tasks in this research: (– – –) predictive route; (——) experimental route.

Impregnation of a polymer matrix by a drug component dissolved in a supercritical fluid is a single-component supercritical adsorption or absorption process (depending on whether the polymer goes below glass transition temperature) governed by the solubility of the drug component in the supercritical fluid and the adsorption isotherm (for adsorption, the polymer stays above glass transition) or the partition coefficient (for absorption, the polymer goes below glass transition) of the drug component between the supercritical and polymer phases. Figure 1 summarizes the tasks for the adsorptive synthesis of controlled drug-delivery products.

(1) Determination of the solubilities of the drug components in $scCO_2$—The solubility controls the amount of drug component that can be carried by the mobile fluid phase.

(2) Determination of the extent of polymer matrix swelling with supercritical fluids—The extent of swelling determines the ease of impregnation.

(3) Determination of the adsorption isotherms and/or partition coefficients of the drug components on the polymer phase—The adsorption isotherm and/or partition coefficients determine the amount of active drug that can be placed in the matrix for controlled release of the drug.

The final product has to be tested for certain properties, such as *product uniformity*; the drug has to be homogeneously distributed in the polymeric matrix, called *drug loading*; the drug content within the polymer matrix has to meet specific standards to ensure a desired therapeutic effect and *release rate*; the final product has to present a favorable release profile.

Finally, the experimental techniques need to be perfected to receive reproducible and predictable results. This way the process control and optimization will be achieved. The tools necessary for this purpose are the measurement of some properties, such as column dimensions, porosity, the estimation of some parameters, such as mass-transfer coefficients, effective diffusivities, and the determination of adsorption isotherm or equilibrium partitioning.

In this study, the focus is on the impregnation of a biodegradable polymer matrix, poly-*dl*-lactide-*co*-glycolide, with 5-fluorouracil and β-estradiol, drugs that are used for

chemotherapy and estrogen hormone therapy, respectively. The first task is the determination of the solubilities of these drugs in supercritical carbon dioxide, which are already reported in the literature (Guney and Akgerman, 2000).

It has been observed that, like the solubility, the efficiency of swelling increases with increasing temperature at constant pressure. However, it cannot be so high that either the drug component or the polymer is degraded or adversely affected. The highest temperature is set by the nature of the impregnation agent and the polymer. Typically, temperatures from 40°C to about 60°C define the preferred range, since a temperature of at least 40°C needs to be employed in order to ensure a convenient rate of swelling (Sand, 1986). As mentioned before, swelling is a very important step in the adsorption/absorption process, because it determines the ease of impregnation of a polymer matrix. The greater the swelling, the quicker and more complete the diffusion of the impregnation agent. The solubility of carbon dioxide in many polymers is as high as that of typical organic liquid swelling agents, ranging from 10% to more than 30% by weight. Being a small linear molecule, it has high diffusivity in polymers, which is a characteristic of gases of similar molecular sizes. This allows an efficient impregnation process. In addition, carbon dioxide has a strong plasticizing effect; for example, concentrations of 8–10% by weight can depress the glass-transition temperature of common glassy polymers from 80 to 100°C to below room temperature. It has been found that amorphous polymers can absorb carbon dioxide to a greater extent than crystalline polymers, and that the plasticization is also very high (Shieh et al., 1996). Carbon dioxide also is preferred as a swelling agent because of its unusually high vapor pressure, its nonflammability, and its low cost. Furthermore, because carbon dioxide is physiologically and environmentally safe, and has no odor, any small amounts left in the final product have no adverse effects.

For the impregnation of the polymer matrix, the supercritical fluid saturated with the drug component is passed over the polymer at a constant volumetric flow rate. During this process, it diffuses into the polymer matrix, where the drug component is adsorbed on the polymer and entrapped as the system is depressurized. This process can be designed as a packed-column model, but in this study, a flow over a flat-plate model is preferred in order to decrease the loss of the final product on the column walls, to minimize the amount of polymer used in each run, and for easier handling of the final product.

Experimental Technique and Results

The impregnation experiments were carried out with the apparatus shown in Figure 2. The experimental setup includes a saturation column packed with the drug, and an im-

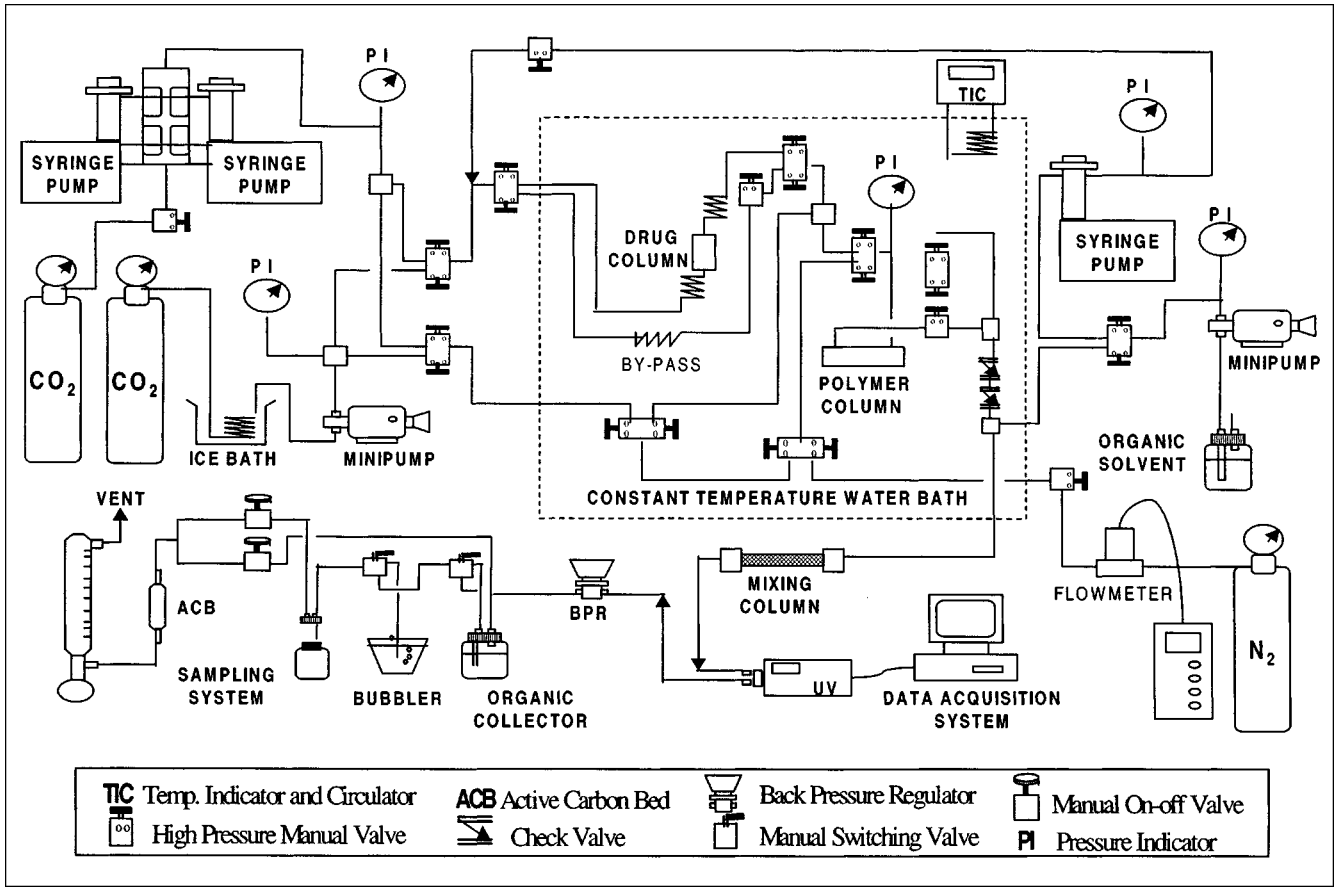

Figure 2. Impregnation of polymer matrices using supercritical carbon dioxide.

pregnation vessel, in which the polymer is placed. Sorption experiments require the introduction of a drug-saturated $scCO_2$ stream into the impregnation column. That is why the experiment consists of two sections: solubility measurement followed by impregnation. Before the solubility measurement, the polymer column is pressurized with pure CO_2 and heated to the required pressure and temperature for the experiment. While the $scCO_2$ phase is being saturated by the drug component, the polymer column is bypassed in order to let the polymer swell for ease of impregnation.

Several techniques for measuring polymer swelling are described in the literature. The basic principle of these techniques is to determine swelling by measuring the change in one or more dimensions of a polymer sample. In this study, the swelling was only qualitatively determined.

In order to comment on whether or not the polymer was swelled, a special polymer vessel was designed, as shown in Figure 3. This polymer column is equipped with two circular sapphire windows and a sliding bed on which the polymer is placed. The sliding bed is a rectangular prism; the top and the sides facing the sapphire windows are open. The state of the polymer can be monitored visually at all times, and with the help of the sliding bed, the final product is taken out, preserving the polymer particles' position within the polymer column during impregnation. This allows us to analyze the uniformity of the final product in terms of the drug concentration on the surface vs. within the polymer structure using scanning electron microscopy (SEM), or by dividing the final product into different parts and running a total drug-loading analysis on them separately.

In the polymer column, the $scCO_2$ is designed to flow over the surface of the polymer. The dimensions of the surface area of the polymer are fixed, but the polymer thickness, as monitored through the sapphire cells, can differ with gas sorption. Therefore the volume of the polymer in its swollen state can be roughly determined by measuring this thickness. Knowing the polymer density and the amount placed in the column, it is possible to calculate the polymer volume before swelling. A comparison of the two volumes will help determine whether or not swelling takes place.

The solubilities of the drug components in pure CO_2 under supercritical conditions were measured using a dynamic technique developed in our laboratories (Guney and Akgerman, 2000).

In impregnation experiments, the saturation column is initially bypassed to clean the system, to obtain a base line at the UV detector, and to stabilize the flow rates to reach steady state. Then the supercritical phase flow is directed through the drug-packed column. Due to small volume differences, minor flow adjustments are made after switching to the drug column. While the supercritical stream is being saturated with the drug, the pressure should be steady. After switching to the drug column, the UV signal starts to increase from the base line obtained with pure $scCO_2$, up to the saturation signal of the drug component in the form of an S-shaped curve. When a constant UV response is read, solute saturation is reached.

After drug saturation in the $scCO_2$ is reached, impregnation of the polymer can begin. While drug saturation is reached, the impregnation column has been kept pressurized with pure CO_2 in order to swell the polymer. The drug-saturated $scCO_2$ is then directed to the polymer column, after which the on-line UV signal drops sharply. In this part of the experiment, the on-line UV detector (Dynamax) serves for continuous monitoring of the breakthrough profiles, and the absorbance data are recorded by the data-acquisition system (Quick Log, Strawberry Tree Products) throughout the process. The column breakthrough is reached when the on-

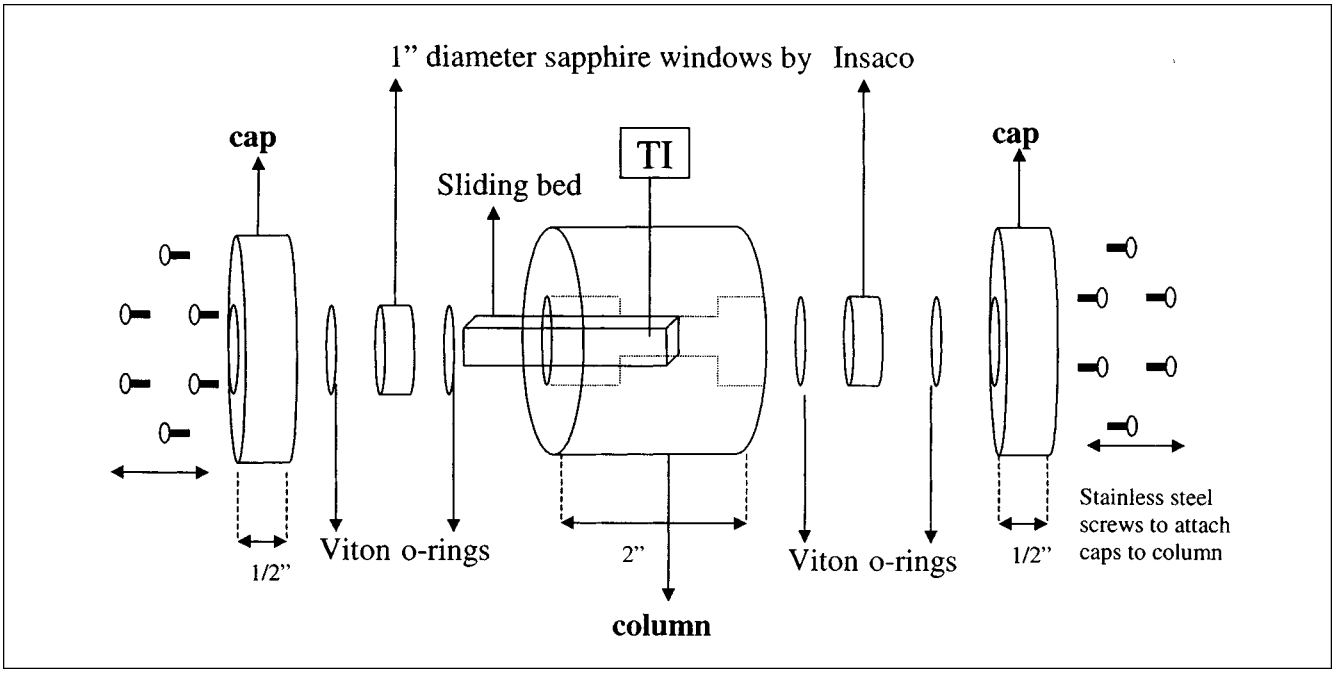

Figure 3. Polymer vessel.

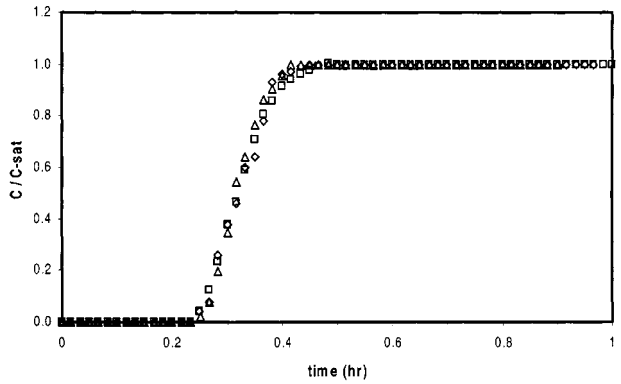

Figure 4. Saturation of supercritical carbon dioxide with β-estradiol at $T = 55$°C and $p = 207$ bar.

Each symbol represents a repeat run of the experiment.

line UV signal goes back up to the previously recorded saturation signal. The breakthrough data present an interesting U-shaped profile.

Since the impregnation experiments consist of two sections (solubility measurement followed by impregnation), the experiment times become considerably longer. That is why $scCO_2$ is delivered into the system via dual-deck ISCO Syringe Pumps, and the continuous flow is provided by the electric-valve package, an accessory that provides smooth and continuous switching between the two pumps.

Throughout this continuous-flow experiment, system pressure is safely taken down to the atmospheric pressure through a spring-hold backpressure regulator (Techne 1700 Series), and a separator is used to vent off the gas and collect samples in the organic solvent. The flow rate of the gas vented is continuously monitored with a digital flowmeter (Cole Parmer). Since the on-line UV detector serves only in a qualitative manner, the collected samples are analyzed off-line by another UV/vis detector operating in conjunction with software of Spectral Instruments (SI-4100). This way the saturation concentrations are determined, and the absorbance units recorded by the data-acquisition system are converted to concentration in $scCO_2$.

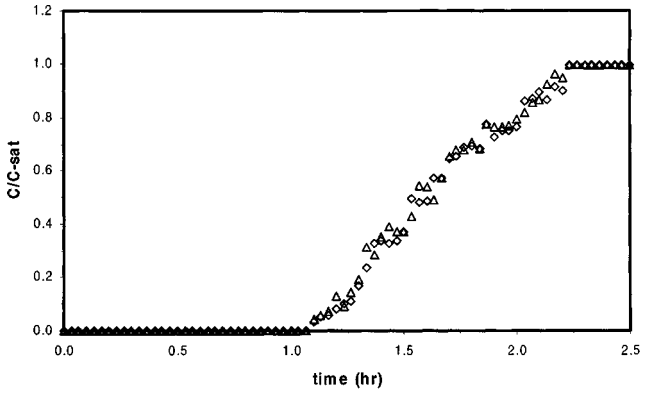

Figure 5. Saturation of supercritical carbon dioxide with 5-fluorouracil at $T = 35$°C and $p = 207$ bar.

Each symbol represents a repeat run of the experiment.

The first stage of the experimental procedure for the synthesis of controlled drug-delivery products is to determine that the drug component reaches its equilibrium concentration (solubility) in the supercritical phase. Figures 4 and 5 show the experimental data recorded by the data-acquisition system for the saturation of the drug component in $scCO_2$ at some selected temperatures and pressures plotted together with several repeat runs to ensure consistency. In these and the following figures that show data, the effluent concentrations, (C), are normalized with respect to the saturation concentration (or solubility, C-sat), and are plotted with respect to experiment time (where $t = 0$ corresponds to the time when pure supercritical carbon dioxide is directed through the drug column).

After drug-component saturation in the $scCO_2$ is reached, as previously described in the experimental procedure, the saturated supercritical stream is redirected through the polymer column for the continuous impregnation of the polymer matrix. The polymer matrix has been pressurized and heated to the experimental conditions in order to ensure sufficient swelling for ease of impregnation while $scCO_2$ was being saturated by the drug component.

The U-shaped impregnation profiles (Figure 6) results from the fact that initially the polymer vessel is pressurized with pure CO_2 in order to swell the polymer matrix before the drug-saturated flow is switched to the polymer column. On the other hand, the volume from the switching point through the detector to the final effluent is drug saturated before rerouting the flow through the polymer vessel (refer to Figure 2). Hence, the detector signal is that corresponding to the solubility value. When the flow is diverted to the polymer vessel and through the polymer vessel to the detector, it sweeps the pure CO_2 in the polymer column and the connecting line volume; therefore, the concentration in the effluent decreases due to this mixing and to the adsorption of the drug to the polymer. Hence the detector signal correspondingly decreases until the polymer starts getting saturated, at which time the effluent concentration equals the inlet concentration (from the saturator, at solubility value). Thus, the

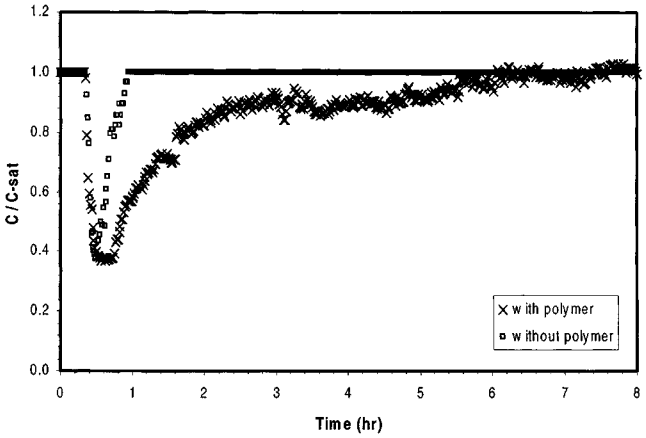

Figure 6. Impregnation of poly(lactide-*co*-glycolide) (~ 0.25 g) by β-estradiol via supercritical carbon dioxide at $T = 55$°C and $p = 207$ bar vs. blank run at the same conditions.

detector signal reaches its original value again (corresponding to solubility), indicating equilibration and termination of the experiment. That is why first the on-line UV detector picks up the signal for the pure CO_2 released from the polymer column, which is being pushed out of the polymer column with the incoming drug-saturated supercritical flow. Simultaneous to washing the pure carbon dioxide out of the polymer column, impregnation of the polymer matrix with the incoming drug-saturated $scCO_2$ stream takes place, during which time the on-line UV detector records a signal lower than the saturation signal. Thus, the response obtained after switching to the polymer vessel is the combined effect of system response and polymer vessel response to a step input.

The isolation of the polymer response to the impregnation process is necessary to determine the drug loading in the polymer matrix. To isolate the polymer response signal from the total response, system response was measured by carrying out the "blank runs." Blank runs are the experiments that are carried out following the exact same procedure as the impregnation experiments without the polymer in the polymer column. The data obtained from these experiments give the system response to this experimental procedure, and the difference between the profiles of the blank runs and the impregnation runs at the same condition gives the polymer response and drug loading in its matrix.

Figure 6 shows the typical polymer-column breakthrough data and the blank-run data with the interesting U-shaped profiles. The difference between the two responses would be the response of the polymer itself to drug loading, as shown in Figure 7. The area above the curve is the amount of drug adsorbed/impregnated to the polymer.

Modeling

Figure 7 shows the difference between the responses of the empty system and the system with the polymer to a step input at the solubility level, which is the response of the polymer to drug loading. The area above this curve is the amount of drug adsorbed/impregnated to the polymer. This can be shown by a mass balance on the drug component in the polymer column during impregnation

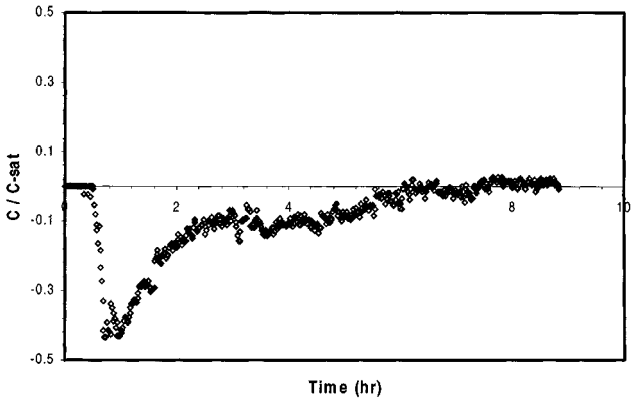

Figure 7. Differences of responses with and without polymer for the supercritical impregnation of poly(lactide-*co*-glycolide) (~ 0.25 g) by β-estradiol at $T = 55°C$ and $p = 207$ bar.

$$m_{\text{in}} - m_{\text{out}} = m_{\text{accumulated}} \tag{1}$$

where

$$m_{\text{in}} = \left[\int_0^{t_f} C_i \, dt\right] Mv = C_i M v t_f \tag{2}$$

$$m_{\text{out}} = \left[\int_0^{t_f} C_o(t) \, dt\right] Mv \tag{3}$$

Therefore

$$m_{\text{accumulated}} = \left[\int_0^{t_f} \left(1 - \frac{C_o(t)}{C_i}\right) dt\right] C_i M v \tag{4}$$

If the sorbent material (polymer phase) is nonporous, the accumulated mass (the amount of drug transferred to the polymer phase) is equal to the drug loading (the amount of

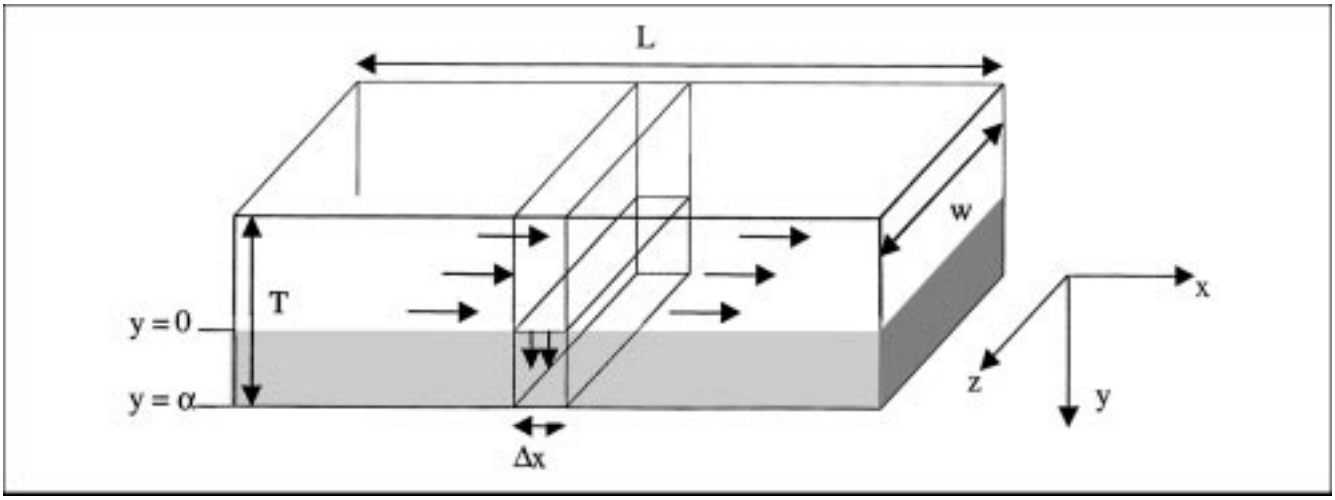

Figure 8. Impregnation on a nonporous polymer via flow over a flat plate.

drug component that is sorbed by the polymer).

$$m_{\text{sorbed}} = m_{\text{accumulated}} \tag{5}$$

If the sorbent material is porous, then the drug component is not only sorbed by the polymer but also trapped within the pores of the polymer matrix, and the mass sorbed is given by

$$m_{\text{sorbed}} = m_{\text{accumulated}} - \epsilon V C_i M \tag{6}$$

In the preceding set of equations (Eqs. 1 through 6), m is the mass of the drug component (mass), C_i and C_o are the initial and final concentrations of the drug component in the mobile phase and has units of mass per volume, t_f is the impregnation time and has time units, M is the molecular weight of the drug, υ is the volumetric flow rate (volume)/(time), and ϵ is the porosity of the sorbent.

The experimental drug-loading data have been calculated using the area above these curves, and converting the units to (mg-drug/*g*-polymer) using the equation below.

$$q = (\text{area}) \cdot (C_0) \cdot (\rho_{CO_2}) \cdot (\upsilon_{CO_2}) / (m_{\text{PLGA}}) \tag{7}$$

where q is drug loading (mg-drug/*g*-polymer), area has time units (h), C_0 is saturation concentration (mg-drug/*g*-CO2), ρ_{CO_2} is the density of $scCO_2$ (*g*-CO_2/mL-CO_2), υ_{CO_2} is the volumetric flow rate of $scCO_2$ (mL-CO_2/h), and m_{PLGA} is the mass of the polymer (PLGA) in the polymer vessel (*g*).

The model to fit the drug-loading data is derived by solving the mass-balance equation for the drug component for the system of the nonporous polymer phase using the boundary conditions as described below. In the polymer column, the $scCO_2$ is designed to flow over the surface of the polymer (see Figure 8). The polymer that is used for impregnation (PLGA) transforms into a dense molten state due to the glass temperature depression in contact with the $scCO_2$. The polymer is still able to swell with the $scCO_2$, but due to its molten state, loses its porous nature. The mass transfer of the drug component from the supercritical phase into the polymer matrix is perpendicular to the bulk motion of the supercritical fluid (see Figure 9).

Fick's law is the classic formulation of the rate of mass transfer. However, for sorption in polymeric materials, under certain conditions, non-Fickian mass-transport behavior has been observed. It has been discussed in the literature that the parameter, which determines the Fickian vs. non-Fickian behavior, is the diffusive Deborah number (Camera-Roda and Sarti, 1990). The characteristic of the non-Fickian behavior is that the sorption diffusivity relaxes from an initial value to a final value with time, oscillating around a final equilibrium value. The Deborah number (De) describes the time-scale ratio of relaxation to diffusion. At small Deborah numbers ($De < 1$), the relaxation occurs almost instantaneously, and a Fickian transport is observed. At large Deborah numbers ($De \gtrsim 100$), relaxation takes place much later, by which time diffusion already reaches equilibrium. The consideration of non-Fickian behavior is a concern only for intermediate Deborah numbers. The diffusivities in a supercritical adsorption process for the impregnation of a polymer matrix with a drug component are expected to be quite low, since the order of magnitudes for diffusivities of polymers and supercritical fluids are 10^{-10} and 10^{-4} to 10^{-5} (cm^2/s), respectively. In the supercritical adsorption process studied in this article, the impregnation times varied between 1.5 and 4 h. Even though the relaxation times were not determined, the Deborah numbers were calculated to check the validity of the Fickian behavior assumption. Even when the upper bound of the impregnation times (4 h) was used as the relaxation time, the Deborah numbers were low enough ($De < 1$) to assume Fickian behavior. Therefore material balance for the polymer phase is expressed by Fick's Law:

$$\frac{\partial q}{\partial t} = D_p \frac{\partial^2 q}{\partial y^2} \tag{8}$$

with the initial condition

$$t = o \quad q = 0 \tag{9a}$$

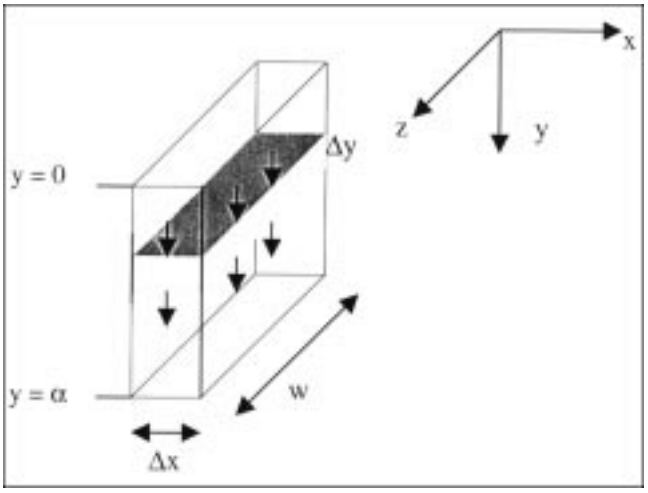

Figure 9. Impregnation on differential volume element of a nonporous polymer.

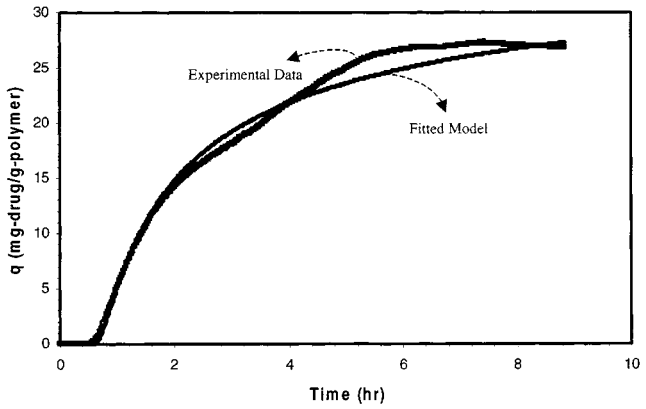

Figure 10. The model fit to the experimental impregnation data on PLGA with β-estradiol at $T = 55°C$ and $p = 207$ bar; $D_p = 7.5 \times 10^{-6}$ m^2/h $= 2.08 \times 10^{-5}$ cm^2/s.

and the boundary conditions

$$y = 0 \quad q = KC_0 \tag{9b}$$

$$y \to \infty \begin{cases} q \text{ is finite} \\ \dfrac{\partial q}{\partial y} = 0 \end{cases} \tag{9c}$$

The first boundary condition implies that equilibrium is established at the surface at all times, or that film mass transfer is negligible compared to diffusion into the polymer phase. The solution to Eq. 8 is given by

$$q = KC_0 \text{erfc}\left(\frac{y}{2\sqrt{D_p t}}\right) \tag{10}$$

In Eq. 10, q is the drug loading (mg-drug/g-polymer); K is the partition coefficient (gr-CO_2/gr-polymer); C_0 is the mobile-phase concentration, in this case, the saturation concentration or solubility in scCO_2 (mg-drug/g-CO_2); y is polymer thickness (m), t is experiment time (h); and D_p is the drug diffusivity in the polymer phase (m^2/h). All the parameters in Eq. 10, except D_p, are either measured or calculated variables. Thus, D_p is the only fitted parameter in this model. Figure 7 is the response of the polymer to a step input, so integration of the data in Figure 7 will give the breakthrough curve for a step response (as shown in Figure 10), which is defined by Eq. 10. The area in Figure 7 gives the total amount absorbed (Eq. 7), and K is obtained by dividing that with C_0 (the units for C_0 mg-drug/g-CO_2), which assumes linear partitioning. Then D_p is obtained by fitting Eq. 10 to the data given in Figure 10.

Table 1 gives the data on the total absorbed amounts for β-estradiol and 5-fluorouracil. In Table 1, the impregnated amount (q) has been reported in units of *mg*-drug/g-PLGA. Table 2 is a list of all the variables and parameters used in

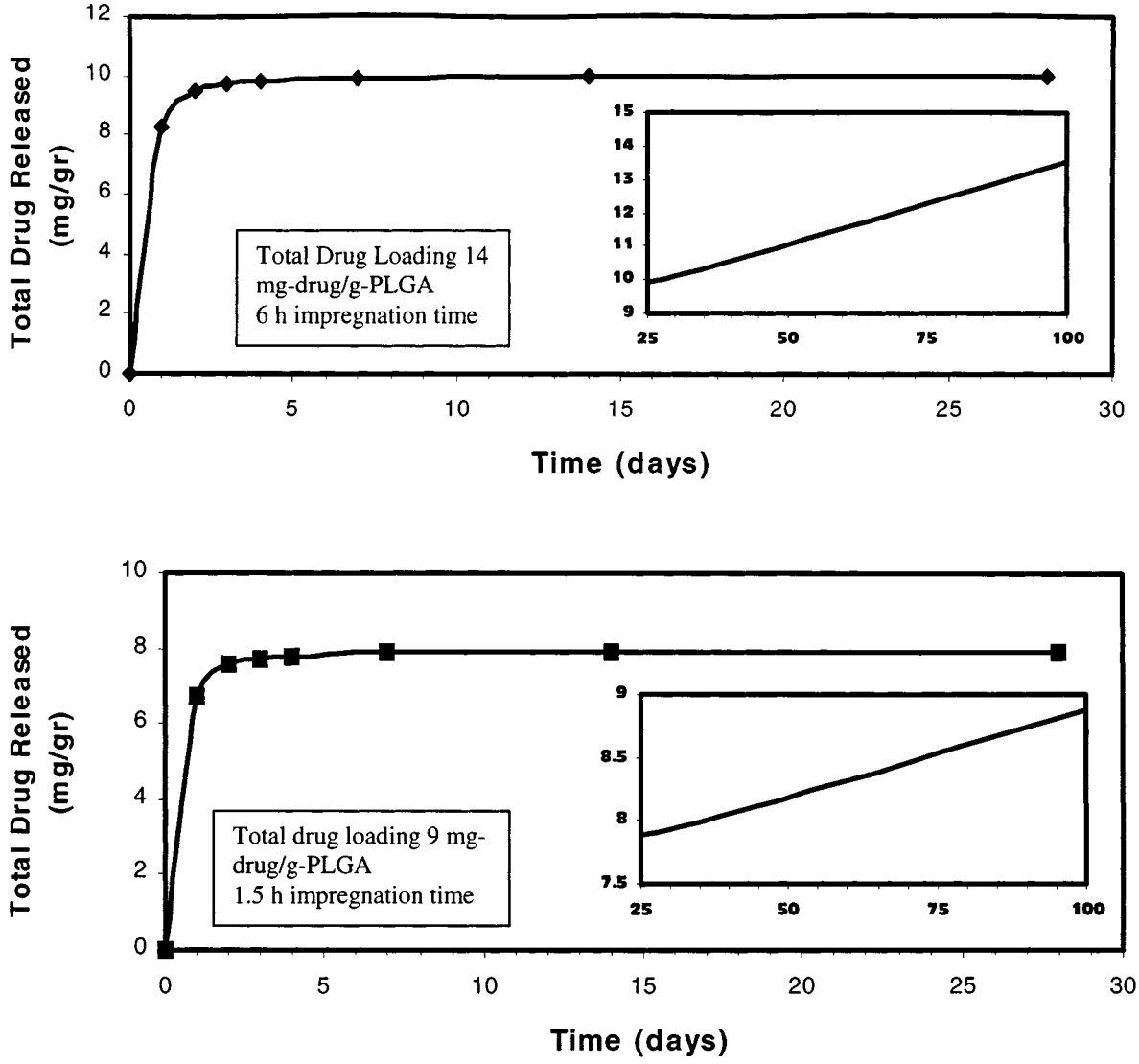

Figure 11. Release profiles and total drug loading for samples synthesized at $T = 35°C$ and $p = 207$ bar for β-estradiol impregnation on PLGA.

Eq. 10. The partition coefficient, K, is calculated as the ratio of the amount of drug in the polymer phase to the amount of the drug component in the supercritical phase. The polymer thickness was measured during the experiment with the help of the sapphire cells, and found to be consistent for the repeat runs at the same conditions. D_p is the only fitted parameter in this model. Then, using Eq. 10, the impregnated amount (q) has been calculated and also reported in Table 2, where it can be seen that the predicted values are very close to the experimental values.

To determine the release profiles of the final products (PLGA impregnated with drug via supercritical carbon dioxide), and to validate the results of the experimental work that was successfully predicted by the model developed for this system, the Bioengineering Research Group at Texas A&M University has conducted drug-release and total-drug-loading studies on some of the samples. These release profiles and the total-drug-content analysis results for these samples are given in Figure 11. We now emphasize that the total loadings reported in Figure 11 are obtained by analyzing the polymer and not from the analysis of step-response data.

When these release profiles are analyzed, it is observed that there is a rapid release of a certain amount of the drug component (~8 mg-β-estradiol/g-PLGA in the first profile) and (~6 mg-β-estradiol/g-PLGA in the second profile) within the first day, which suggests these values correspond to the amount of drug precipitated on the surface of the polymer rather than being impregnated within the polymer matrix. The release then continues linearly. The difference between the total drug loading and the amount that has precipitated on the surface is the amount of drug that has been impregnated within the polymer matrix.

The surface precipitation results from the experimental design of the impregnation process. According to the experimental procedure, once the polymer matrix is saturated with the drug component, the polymer column is isolated from the system, still at the experimental temperature and pressure. In order to get the final product out, the vent line on the polymer column is used to depressurize the polymer column. The depressurization conditions are of critical importance in defining the final characteristics of the impregnated polymer.

If the depressurization is fast, then the final form of the polymer will be more foamlike, with large pores. This property can be considered advantageous for implant applications, since the tissues will have more external surface area to attach themselves to, in which case both the drug release and the polymer biodegradation will be favored. The disadvantage is that the foamlike form of the polymer will result in higher concentrations of the impregnated drug close to the surface, resulting in faster release rates with less control. Instead, if the depressurization is done slowly, waiting for equilibration after each incremental decrease in pressure, the polymer will be in the form of a cluster of small particles, each ideally having a uniform drug loading. Therefore, the initial form of the polymer will be preserved. In order to accomplish this and to ensure a decrease in the solvency power of the supercritical phase so that back-extraction of the impregnated drug component will not take place, the heater of the polymer column is turned off before depressurization, and the temperature, and consequently the pressure, in the polymer column is decreased. Then the carbon dioxide is released slowly through the vent line with small pressure increments, waiting for equilibrium after each step. As a consequence of this depressurization procedure, the drug dissolved in CO_2 confined to the polymer vessel starts to come off the supercritical phase, precipitating on the polymer surface. The amount of dissolved drug in the supercritical phase within this confined volume will set the maximum limit of the surface precipitation for the drug, which would be equivalent to the amount released within the first day of the release study. The surface precipitation should always be equal or less than this value, depending on the specific depressurization procedure followed for that experiment.

To calculate the amount of drug in the supercritical phase within the volume of the polymer vessel (the amount that will precipitate on the polymer surface after expansion), the resi-

Table 1. Experimental Determination of Impregnated Drug Amount (q)

Variables in Eq. 7	β-Estradiol on PLGA $T = 35$°C $p = 207$ bar	β-Estradiol on PLGA $T = 55$°C $p = 207$ bar	5-Fluorouracil on PLGA $T = 55$°C $p = 207$ bar
Total Area (h)	0.68324	0.80732	1.24818
ρ_{CO_2}(g-CO_2/mL-CO_2)	0.8721	0.7633	0.7633
v_{CO_2}(mL-CO_2/h)	40	40	40
m_{PLGA}(g-PLGA)	0.2180	0.2564	0.2174
q_{DATA}	10.04	26.80	0.49

Table 2. Model Prediction for Drug Amount Impregnated in Polymer Matrix

Variables in Eq. 10	β-Estradiol on PLGA $T = 35$°C $p = 207$ bar	β-Estradiol on PLGA $T = 55$°C $p = 207$ bar	5-Fluorouracil on PLGA $T = 55$°C $p = 207$ bar
K (gr-CO_2/gr-PLGA)	122	137	292
y (m)	0.003	0.004	0.004
t_i(h)	(0 −6)	(0 −7)	(0 −9)
D_p (m^2/h)	6×10^{-6}	7.5×10^{-6}	5.5×10^{-6}
q_{MODEL}	9.88	26.24	0.5135

dence time of the drug component in the supercritical phase in the polymer column, and the temperature, pressure, and flow rate of the supercritical phase are needed. The temperature and pressure give the solvency power of the supercritical phase as well as the density of the $scCO_2$. The solvency power as a function of temperature and pressure is tabulated in the literature in mass-fraction units, for example, gr-drug/gr-$scCO_2$ (Guney and Akgerman, 2000), and can be converted to gr-drug/mL-$scCO_2$ units using $scCO_2$ density. The volumetric flow rate of the supercritical phase and the residence time give the volume of the polymer column. Therefore, it is possible to calculate the exact amount of drug in the supercritical phase trapped in the polymer column. Table 3 lists the results of this calculation for selected conditions at which impregnation experiments were performed, and the data from the drug-release study (refer to Figure 11; ~ 8 and ~ 6 mg-drug/gr-PLGA as data points for first-day release) are compared to these calculated values for the surface precipitation. Even though the results were consistent with the surface-precipitation theory, there was not enough release study data for conclusive results. It is important to note here that the units given in Table 3 for surface precipitation have units *mg*-drug, whereas the release study data are tabulated in Figure 11 as mg-drug/gr-PLGA.

The release profiles in Figure 11 are for two different experiments run under the same conditions ($T = 35$°C and $p =$ 207 bar) and both with ~ 0.35 gr-PLGA. In the first graph, the experimental impregnation time was 9 h, and in the second the experimental impregnation time was 1.5 h. When the total drug-loading data for these two graphs are compared, the second one being lower suggests that the polymer was not fully saturated with the drug component in 1.5 h. This experiment was designed to study the consistency of the impregnated drug content in the polymer matrix for different impregnation times. The reported total drug loading data for both of these experiments include the amount of drug that has precipitated on the polymer surface during expansion (refer to Table 3). Since the focus is on the impregnated drug content in the polymer matrix, the amount that is precipitated on the surface, for example, the first day release data, is subtracted from the total drug loading, and the results are reported as "Release Study Data" in *mg*-drug units in Table 4 in. These columns report the results of two different experiments ran under the same conditions (repeat runs). The surface precipitation is estimated to be an average of the values reported in Table 3. This experiment was designed to study the effect of the polymer amount on the impregnated-drug content. The results reported as "Release Study Data" in Table 4 are based on the total drug-content analysis, which is run on the end product. In the column titled "Experimental Data" in Table 4, the results obtained from the data collected during the experiment are reported. The data collected during the experiment are free of the surface-precipitation effect, since surface precipitation occurs only during depressurization of the polymer column. Figure 10 is a representative total drug-loading graph that is constructed using the data collected during the experiment. The values in the "Experimental Data" column in Table 4 are basically the data read off of this graph, at $t = 1.5$ h and $t = 6$ h, respectively. The units in Figure 10 are converted from mg-drug/gr-polymer to *mg*-drug in Table 4. The "Model Results" column in Table 4 shows the drug loadings determined by the model (see Eq.

Table 3. Surface Precipitation of Drug Component vs. Amount Determined by Release Study

	β-Estradiol on PLGA $T = 35$°C $p = 207$ bar	β-Estradiol on PLGA $T = 55$°C $p = 207$ bar	5-Fluorouracil on PLGA $T = 55$°C $p = 207$ bar
v_{CO_2}(mL-CO_2/h)	40	40	40
τ_1(h)	0.8	0.6	2.9
V_{CO_2} in vessel (mL)	32	24	116
$m_{PPT\text{-}MAX}$(mg-drug)	3	5.13	0.25
$m_{day\text{-}1\text{-}release}$(mg-drug)	2.1-2.8	N/A	N/A

Table 4. Consistency of Drug Content Impregnated in Polymer Matrix for Different Impregnation Times at 35°C and 207 bar.

Impregnation Time (h)	β-Estradiol 0.2180 g-PLGA **Experimental Data** (mg-drug)	β-Estradiol 0.35 g-PLGA **Release Study Data** (mg-drug)	β-Estradiol 0.2717 g-PLGA **Rlease Study Data** (mg-drug)	β-Estradiol 0.2180 g-PLGA **Model Results** (mg-drug)
1.5	1.02	1.05	1.01	1.17
6	2.25	2.1	N/A	2.15

Table 5. Consistency of Drug Content Impregnated in Polymer Matrix at 55°C and 207 bar

Impregnation Time (h)	β-Estradiol 0.2564 g-PLGA Exp. (mg-drug)	β-Estradiol 0.2559 g-PLGA Release Study (mg-drug)	β-Estradiol 0.2545 g-PLGA Release Study (mg-drug)	β-Estradiol 0.2564 g-PLGA Model (mg-drug)
1.5	2.73	2.815	2.97	2.96

10) which is also shown in Figure 10. Consequently, Table 4 is a comparison of the results of the experimental data, the release study, and the results calculated by the model. Table 5 is a replica of Table 4 at 55°C and 207 bar instead of 35°C and 207 bar.

Tables 4 and 5 clearly show that the release study results and the experimental data are in excellent agreement. The model slightly overpredicts the data earlier during impregnation, but predicts the data quite accurately as the experiment proceeds.

Conclusion

The feasibility study on the synthesis of controlled-delivery substances by impregnation via $scCO_2$ has been investigated. This process is governed by the solubility of the drug component in $scCO_2$ and the adsorption isotherms/equilibrium partitioning between the polymer and supercritical phases. It has been found feasible to dissolve a drug component and load it in a polymer matrix in $scCO_2$. This procedure resulted in satisfactory drug loading, even when the solubilities were low. When thermodynamic/transport parameters are known, drug loading can be predicted. It was concluded that different expansion procedures can be used to yield the polymer in a desired form, such as foam with larger pores or microporous spherical particles.

Although the overall loaded amounts are not high for the specific applications where these products will be used, the drug loadings are even higher than necessary. These products are going to be used for localized treatments where the drug concentrations needed to achieve therapeutic effect are much lower. More importantly, this study provided a recipe for the solvent-free synthesis of controlled-drug delivery products.

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Manuscript received June 26, 2001, and revision received Aug. 20, 2001.