

IJP 01462

# Solvent selection in the preparation of poly(DL-lactide) microspheres prepared by the solvent evaporation method

R. Bodmeier and J.W. McGinity

*College of Pharmacy, The University of Texas at Austin, Austin, TX 78712-1074 (U.S.A.)*

(Received 17 July 1987)

(Modified version received 30 October 1987)

(Accepted 2 November 1987)

**Key words:** Poly(DL-lactide); Quinidine sulfate; Biodegradation; Solvent evaporation method; Microencapsulation; Microsphere; Drug delivery system

---

## Summary

Poly(DL-lactide) (PLA) microspheres containing quinidine or quinidine sulfate were prepared by the solvent evaporation technique. The successful entrapment of drug within the microspheres was associated with: (a) a fast rate of precipitation of the polymer from the organic solvent phase; (b) a low water solubility of the drug in the aqueous phase; and (c) a high concentration of the polymer in the organic phase. The rate of polymer precipitation was strongly affected by the rate of diffusion of the organic solvent into the aqueous phase. Organic solvents of low water solubility resulted in a slow polymer precipitation, causing the drug to partition completely into the aqueous phase. Water-miscible organic solvents when added to the organic phase further enhanced the drug content in the microspheres. The construction of a solubility envelope for PLA and an envelope for microsphere formation based on the three-dimensional solubility parameter concept was found to be useful in the selection of suitable solvent mixtures and in the interpretation of solvent–non-solvent–polymer interactions and the formation of PLA microspheres.

---

## Introduction

Within the past 20 years, controlled release technology has emerged as an important new field in the development of pharmaceutical dosage forms. Drug delivery systems that can be either implanted, injected or inserted, provide a continuous release of drug independent of gastrointestinal absorption and/or first-pass effects. Early investigations centered on non-biodegradable but biocompatible polymers such as silicone rubber (Roseman and Higuchi, 1970). Even though these matrices are effective delivery systems, their suitability

as an implant is severely limited because the devices require surgical removal after they have fulfilled their function. This led to the development of drug delivery systems consisting of biodegradable polymers as carrier materials. The polymers of lactic and glycolic acid have been proved to be highly suitable as biodegradable carrier materials in drug delivery systems. The early applications of PLA and other polyesters included a wide range of polymer/drug composites of different size and shape (Yolles et al., 1975; Anderson et al., 1976). Novel biodegradable microparticulate drug delivery systems were prepared by phase separation techniques such as non-solvent addition (Vidmar et al., 1984; Sanders et al., 1984) or solvent evaporation (Beck et al., 1979).

---

*Correspondence:* R. Bodmeier, College of Pharmacy, The University of Texas at Austin, Austin, TX 78712-1074, U.S.A.

The solvent evaporation process was the method of choice for forming PLA microspheres in the present investigation. In this method, the core material and the polymer are codissolved or dispersed in a suitable water-immiscible and volatile organic solvent. This solution or dispersion is emulsified in an aqueous medium to form microdroplets. The microdroplets solidify and solid, free-flowing microspheres are obtained after complete evaporation, filtration, and drying.

Although the solvent evaporation process is conceptually simple, many variables can influence the final product (Bodmeier and McGinity, 1987a and b; Benita et al., 1984). These process variables include among others, the solubility of the drug, type of organic solvent or solvent mixtures, phase ratio of the emulsion system, polymer/solvent/non-solvent interactions, temperature, rates of solvent diffusion, type and concentration of emulsifier, polymer composition, viscosity, and drug loading. The applicability of the solvent evaporation process depends on the successful entrapment of the active agent within the microspheres. The solvent evaporation process is most successful for drugs that are insoluble in the aqueous medium. Otherwise, the drug will favorably partition into the aqueous phase resulting in low core loadings.

Microsphere formation is a phase separation process in which a polymer solution is transformed into precipitated, solid spheres. Polymer precipitation induced by non-solvents depends to a great extent on the polymer/solvent/precipitant interactions. The objectives of this investigation were to study the influence of the organic solvent system on the solvent evaporation process and to discuss the formation mechanism of the microspheres.

## Materials and Methods

### Materials

The polymers evaluated for microsphere preparation were two batches of poly(DL-lactide) with inherent viscosities of 1.2 and 1.7 dl/g (PLA I, PLA II) in chloroform at a concentration of 5 mg/ml (Southern Research Institute, Birmingham,

AL). The drugs, organic solvents, and chemicals used for microsphere preparation and analytical procedures were purchased from commercial suppliers and used without further purification. The following chemicals were used in this investigation: quinidine, quinidine sulfate, polyoxyethylene sorbitan mono-oleate (Sigma Chemical Co., St. Louis, MO), acetonitrile, benzaldehyde, carbon tetrachloride, chlorobenzene, chloroform, cyclohexane, dimethylformamide (DMF), dimethylsulfoxide (DMSO), ethanol, glycerol, hexane, 2-pentanol, tetrahydrofuran, xylene (MCB Manufacturing Chemist, Gibbstown, NJ), acetone, acetophenone, ethyl acetate, methanol, methylene chloride, *n*-butyl acetate, *n*-butyl lactate (Fisher Scientific Co., Fair Lawn, NJ), 1-propanol, ethylene dichloride (J.T. Baker Chemical Co., Rochester, NY), benzene (Mallinckrodt Chemical Works, St. Louis, MO).

### Methods

Microspheres were prepared by the solvent evaporation process. Experimental details were reported earlier (Bodmeier and McGinity, 1986). The polymer (0.35 g) and drug (0.15 g) were codissolved in an organic solvent (7.5–22.5 g). The organic solution was poured into the aqueous phase (1.4 liters) containing 0.05% polyoxyethylene sorbitan mono-oleate. The resulting o/w emulsion was agitated continuously for 3 h at room temperature and under ambient pressure. The microspheres were collected by filtration, washed with deionized water, and dried in a desiccator for at least 48 h. The dried spheres were sieved through a 60 mesh stainless-steel sieve and stored at room temperature.

Duplicate samples of drug-loaded microspheres (45–75  $\mu\text{m}$ ) of approximately 30 mg were accurately weighed and extracted in 100 ml of methanol for 24 h. The samples were filtered, if necessary, and then assayed for drug content by UV-spectroscopy at the wavelength of maximum absorbance ( $\lambda = 334 \text{ nm}$ ). The theoretical drug content within the microspheres was 30% unless otherwise mentioned.

The solubility of the polymer in various organic solvents and solvent mixtures was determined at room temperature. The polymer was stored in a

desiccator under vacuum before use. Dried polymer (400 mg) was added to glass vials containing 10 ml of solvent. The vials were sealed with aluminum foil and agitated for at least 48 h at room temperature ( $22 \pm 1^\circ\text{C}$ ) in a horizontal shaker. Solubility of the polymer in a particular solvent was indicated by clear solutions. All samples were weighed before and after each experiment to check for any potential solvent loss. Samples exceeding a 1% solvent loss were repeated.

Multicomponent solubility parameters have been introduced by Hansen (1967) to predict the solubility of polymers. He divided the total solubility parameter,  $\delta^2$ , into contributions from dispersion forces,  $\delta_d^2$ , polar interactions,  $\delta_p^2$ , and hydrogen bonding,  $\delta_h^2$ .

$$\delta^2 = \delta_d^2 + \delta_p^2 + \delta_h^2$$

These terms are partial solubility parameters. The partial solubility parameters for mixtures of solvents,  $\delta_{i,m}$ , are calculated as follows.

$$\delta_{i,m} = \phi_1 \delta_{i,1} + \phi_2 \delta_{i,2}$$

where  $i = d, p, h$  and  $\phi$ 's are the volume fractions of the individual components. A triangular plotting technique of the Hansen parameters was developed by Teas (1968). The following equation was used to calculate the fractional solubility parameters.

$$f_i = 100 \delta_i / (\delta_d + \delta_p + \delta_h) \quad \text{where } i = d, p, \text{ or } h$$

The fractional parameters,  $f_i$ , represent the coordinates of a triangular chart. The solubility envelope was constructed graphically from solvents dissolving the polymer. The boundary regions of the solubility envelope were established by increasing the non-solvent concentration in a binary mixture up to the point where no clear polymer solution occurred. The values of the solubility parameter and Hansen's partial solubility parameters were taken from the literature (Barton, 1975).

Viscosities were obtained by using uncalibrated Cannon-type capillary viscometers (size 25, 100, 300; Sargent-Welch Scientific Co.) at  $22 \pm 0.5^\circ\text{C}$ . The viscometers were calibrated with certified

viscosity standards (Cannon Instrument Co.). Viscosities were measured after shaking the solution for 48 h for the concentration range of 0.075–2.000 g/dl of PLA in methylene chloride, acetone, chloroform, and benzene. The viscosity of the polymer solution in centipoise was determined by substituting the experimental values into the following equation:

$$\eta_1 = \eta_2 \varphi_1 t_1 / (\varphi_2 t_2)$$

where  $\eta_1$  and  $\eta_2$  are the viscosities of the unknown and the standard liquid respectively,  $\varphi_1$  and  $\varphi_2$  are the densities, and  $t_1$  and  $t_2$  are the respective flow times in seconds. The relative viscosity was calculated as  $\eta_{rel} = \eta / \eta_0$  where  $\eta$  and  $\eta_0$  are the viscosities of the polymer solution and the solvent, respectively. All measurements were performed in triplicate. Flow times exceeded 120 s in all cases.

## Results and Discussion

PLA microspheres containing quinidine or quinidine sulfate were prepared by the solvent evaporation method. Microsphere formation is a phase separation process. Four major diffusional motions have to be considered during the formation of microspheres: solvent out, non-solvent in, drug out and probably low molecular weight fractions of PLA out. The direction, magnitude, and rate of solvent–non-solvent diffusion depend on the solvent/non-solvent/polymer/drug interactions and polymer concentration. The solvent loss from the surface of the droplet results in an increase in the concentration of the polymer. Once the limiting concentration for polymer precipitation is reached, phase separation will occur.

The data in Table 1 show the influence of different organic solvents on microsphere formation and drug content. Although the toxicity of the solvent system chosen has a major impact on the final product, it was not considered to be a key parameter in studying the mechanism of microsphere formation. The basic requirement for microsphere formation was the water immiscibility of the organic solvent. Water-miscible solvents

TABLE 1

*Influence of organic solvents on microsphere formation and on the quinidine sulfate content in the microspheres (30% theoretical drug loading)*

Solvent (8 ml)	Microspheres	Quinidine sulfate content (wt. %)	H <sub>2</sub> O solubility of org. solvents (wt. %) (25 °C) <sup>a</sup>
methylene chloride	spheres	23.3	1.961
chloroform	spheres	0.4	0.815
benzene	spheres	0.2	0.175
acetone	no spheres		
dimethyl sulfoxide	no spheres		
ethanol	no spheres		

<sup>a</sup> From Horvath (1982).

such as acetone or DMSO did not form droplets but large irregular polymer agglomerates upon emulsification due to rapid solvent exchange. The drug content was also highly dependent on the type of organic solvent used. By considering the solubility of the drug in each phase during drug partitioning between two immiscible phases, it was initially expected that favorable solubility of the drug in the organic solvent would enhance the drug content in the microspheres. The solubilities of quinidine sulfate in methylene chloride and chloroform were determined to be 9.16 and 97.57 g/l, respectively. Although the solubility of quinidine sulfate in chloroform was 10 times higher than in methylene chloride, it was not possible to successfully entrap quinidine sulfate with chloroform as the solvent. Thus, other factors had to predominate in the formation of the microspheres.

The change in drug content with changes in the solvent could be explained by the influence of the solvents on the rate of polymer precipitation at the droplet interface. The drug partitioned into the aqueous phase as long as the droplet was in a liquid, non-precipitated state. Further drug loss did not occur, once the polymer at the droplet surface precipitated. This concept was illustrated by investigating the time-dependent partitioning and loss of quinidine sulfate to the aqueous phase as shown in Table 2. Analysis of the aqueous phase for drug content during the initial stages of

microsphere formation was not possible since the suspended droplets were still in the non-precipitated liquid state. This problem was circumvented by changing the solubility of the ionizable drug, quinidine sulfate, in the external aqueous phase through a pH-change after different time intervals had elapsed after the initial emulsification step. The drug solubility in the external aqueous phase had to be minimized in order to entrap the drug within the microspheres (Bodmeier and McGinity, 1987a). The solubility of quinidine sulfate decreased with increasing pH, and under regular experimental conditions, quinidine sulfate-free microspheres were obtained at pH 7 (high drug solubility in the external phase) due to complete drug loss, while quinidine sulfate could be successfully entrapped at pH 12 (low drug solubility in the external phase). Microspheres were then prepared in aqueous media that had been initially adjusted to either pH 7 or pH 12. The pH-value of the aqueous phase of different batches was changed at different time intervals after the emulsification step from low to high aqueous drug solubility (pH 12 → pH 7) and from high to low drug solubility (pH 7 → pH 12). As can be seen in both cases, the drug content within the microspheres stabilized almost instantaneously. The time-dependent pH-changes showed that diffusion and drug loss across the droplet interface occurred only during the first minutes after the emulsification step. The drug content in the microspheres did not change in batches where the pH of the aqueous phase and hence the drug solubility was

TABLE 2

*Effect of pH-changes in the aqueous phase at different time intervals after the emulsification step on the quinidine sulfate content in the microspheres*

Time (min)	Quinidine sulfate content (wt. %)	
	pH 12 → pH 7	pH 7 → pH 12
0.5	6.0	2.3
1.0	18.3	0.9
1.5	21.2	0.5
2.0	22.7	0.4
3.0	22.9	0.3
5.0	23.4	0.5
180.0	23.3	0.4

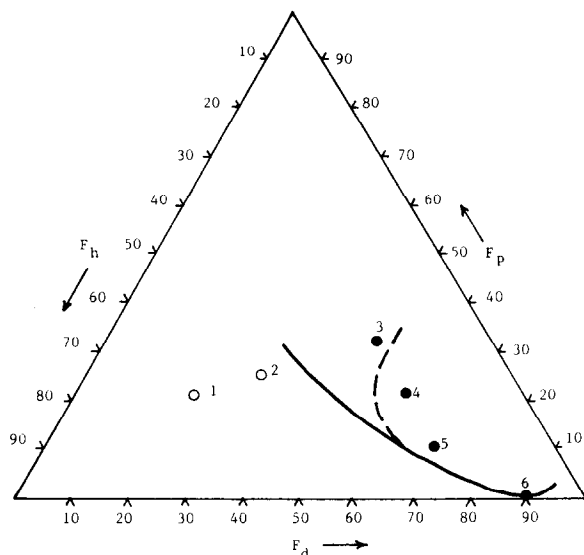


Fig. 1. Solubility plot for poly(DL-lactide): —, area of solubility; - - - - -, envelope of solvents suitable for microsphere preparation; ●, solvents; ○, nonsolvents; 1 = water; 2 = methanol; 3 = acetone; 4 = methylene chloride; 5 = chloroform; 6 = benzene.

changed later than 2 min after the emulsification step. The polymer precipitated rapidly at the outer surface hindering any further drug diffusion into the aqueous phase.

The rate of precipitation depended on the solvent/non-solvent/polymer interactions. In order to explain and describe polymer/solvent/non-solvent interactions and the selection of solvents for the preparation of microspheres, the three-dimensional solubility parameter concept of Hansen (1967) was used. The solubility of the polymer in different solvents characterized by their partial solubility parameters was determined. Various graphing techniques are available to express the solubility of the polymer in terms of the solubility parameters. A triangular plotting technique developed by Teas (1968) was found to be useful. The solubility envelope for PLA is shown in Fig. 1. A wide range of solvents dissolved PLA. However, not every solvent which dissolved the polymer formed microspheres upon emulsification. Therefore, an envelope of solvents suitable for microsphere preparation was established. This envelope was smaller than the solubility envelope

for PLA and excluded solvents of high water miscibility.

The polymer/solvent interaction and thus the solvation power of the solvent can be explained in terms of the difference,  $\Delta\delta$ , in the solubility parameter of the polymer,  $\delta_{ip}$ , and of the solvent,  $\delta_{is}$ ,  $\Delta\delta = \Sigma(\delta_{is}^2 - \delta_{ip}^2)$ . The solvation power of the solvent increases with a decrease in  $\Delta\delta$ . In general, the higher the solvation power of the solvent, the slower the rate of precipitation and the more the non-solvent required for polymer precipitation. The solvent power increases towards the center of the solubility envelope. According to this rule, methylene chloride was a better solvent for PLA than benzene or chloroform, which were located close to the solubility boundary. Drug partitioning into the aqueous phase occurred during the initial stages of microsphere formation prior to polymer precipitation. The droplet was expected to be longer in the non-precipitated or liquid state in good rather than in poor solvents, a higher drug content within the microspheres was initially expected from poor solvents of the polymer. However, this concept is limited to solvent systems, whereby solvent and non-solvent are mutually soluble in each other. This was not the case in the solvent evaporation method. An important factor in determining the rate of precipitation was the water solubility of the organic solvent used for the preparation of microspheres. Solvent diffusion into the aqueous phase depended on the water solubility of the organic solvent and its removal from the water/air interface by evaporation. Table 1 lists the water solubility of organic solvents (Horvath, 1982), which were considered for microsphere preparation. The only organic solvent which could be successfully used for the entrapment of drug under the selected experimental conditions was methylene chloride. Methylene chloride has the highest water solubility of the organic solvents forming microspheres as well as the lowest heat of evaporation. These results suggested that the rate of solvent diffusion in the aqueous phase and hence the rate of polymer precipitation were related to the water solubility of the organic solvent. Solvents with very low water solubility like benzene and chloroform diffused very slowly into the aqueous phase. The droplets were in the liquid

state for a long period of time and drug could easily diffuse across the non-precipitated droplet surface along its concentration gradient. This resulted in the complete loss of drug to the aqueous phase prior to precipitation. Benzene, although being a poor solvent for PLA, required a greater amount of aqueous phase for precipitation than methylene chloride, a good solvent.

The disposition of the polymer molecule at the point of precipitation depends on solvent/polymer interactions, and it might also be influential on the successful entrapment of drug in the microspheres. Polymer molecules show different chain conformations depending on the quality of the solvent. Good solvents enhance polymer/solvent interactions and the polymer chain will be in a more expanded state than in a poor solvent. This should reduce drug diffusion and hence drug loss to the aqueous phase. An attempt was made to characterize polymer/solvent interactions by relating the viscosity of polymer solutions to the solvent power of the solvent. Generally, in dilute solutions viscosity increases with increasing solvent power. A crossover point is reached at higher polymer concentrations where the viscosity is higher in poor solvents than in good solvents. This could not be verified by comparing the results presented in Fig. 2. The relative viscosities of the PLA solutions may be arranged for the concentration range investigated as follows: acetone < benzene

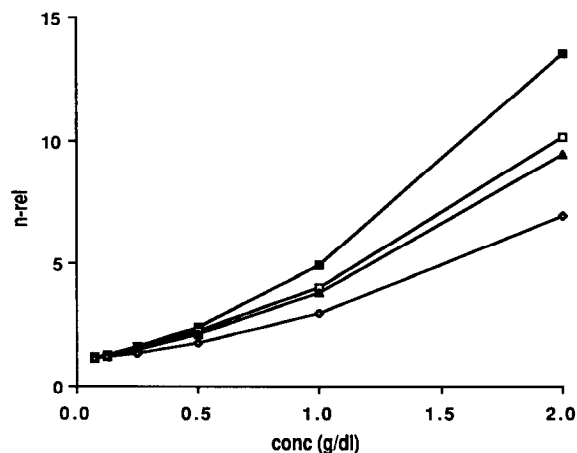


Fig. 2. Relative viscosities of solutions of poly(DL-lactide) in different organic solvents: ■, chloroform; □, methylene chloride; ▲, benzene; ◇, acetone.

< methylene chloride < chloroform. This order did not confirm the location of the solvents in the solubility envelope, where methylene chloride appeared to be a better solvent than benzene or chloroform. Viscosity studies did not give a good measure of solvent/polymer interactions in the case of PLA solutions and studies on mixed solvent systems were not undertaken.

Several solvent systems were selected and evaluated with respect to drug content within the microspheres. As concluded earlier, rapid polymer precipitation at the droplet surface was of primary importance for the successful encapsulation of drug. The longer the time for precipitation to occur, the longer the drug had to diffuse into the aqueous phase, resulting in empty microspheres. A high rate of precipitation was associated with a higher affinity of the solvent and of the non-solvent to interact with each other. For rapid precipitation to occur, solvents or solvent mixtures of higher water solubility near the boundary of the microsphere formation envelope facing the aqueous side were chosen. These solvents will rapidly diffuse out of the microspheres into the aqueous phase. Smaller amounts of non-solvent would be necessary to induce phase separation. Care had to be taken with solvent mixtures since loss of one solvent might actually move the composition back into the solubility envelope rather than out of it. The influence of solvent mixtures on the drug content in the microspheres is shown in Table 3. As expected, the addition of highly water-immiscible solvents such as chloroform or benzene retarded the phase separation. This was indicated by a drop in drug content, when compared with microspheres prepared from methylene chloride. The addition of water-miscible cosolvents such as acetone or methanol resulted in an increase in drug content. The higher drug content could be attributed to the faster precipitation of PLA induced by the cosolvents.

Table 4 shows the effect of organic solvent addition to the aqueous phase on drug content. In the case of methylene chloride, a water-immiscible solvent for the polymer, the gradient in organic solvent concentration and hence the difference in chemical potential between the organic and the aqueous phase was reduced. Solvent diffusion and

TABLE 3

*Influence of organic solvent mixtures on the quinidine content in the microspheres (40% theoretical drug loading)*

Solvent (10 ml)	Quinidine content (wt. %)
methylene chloride	24.3
methylene chloride/acetone (9:1)	28.4
methylene chloride/acetone (8:2)	31.3
methylene chloride/acetone (7:3)	32.9
methylene chloride/ethylacetate (9:1)	26.8
methylene chloride/ethylacetate (8:2)	29.1
methylene chloride/ethylacetate (7:3)	29.7
methylene chloride/methanol (9:1)	26.1
methylene chloride/methanol (8:2)	31.7
methylene chloride/methanol (7:3)	32.9
methylene chloride/DMSO (9:1)	29.9
methylene chloride/DMSO (8:2)	32.5
methylene chloride/DMSO (7:3)	32.9
methylene chloride/chloroform (9:1)	16.5
methylene chloride/benzene (9:1)	2.1

hence the rate of precipitation was retarded. This resulted in a complete loss of drug into the aqueous phase. Acetone, although being a solvent for the polymer, did not reduce the drug content significantly due to its high water solubility.

Quinidine sulfate dissolved in methylene chloride required heat to increase the concentration of dissolved drug to approximately 15 g/l. Drug loadings exceeding this concentration had to be prepared from a suspension of quinidine sulfate in methylene chloride. The yield of microspheres prepared from suspensions decreased with increasing payload. The addition of small amounts of methanol, an excellent solvent for quinidine

TABLE 4

*Effect of organic solvent addition to the aqueous phase on the drug content in the microspheres (30% theoretical drug loading)*

Solvent added (15 ml)	Quinidine sulfate content (wt. %)
no solvent	23.3
methylene chloride	0.9
acetone	21.8
methanol	23.0

TABLE 5

*Effect of the physical state of the drug at preparation and of methanol addition to the organic phase on the quinidine sulfate content in the microspheres*

Theoretical quinidine sulfate content (wt. %)	Solvent (g) <sup>a</sup>	Quinidine sulfate content (wt. %)
30	mc-solution (10.0)	24.4
	mc-suspension (10.0)	24.9
	mc + methanol (9.0 + 1.0)	24.5
50	mc-suspension (10.0)	42.2
	mc + methanol (9.0 + 1.0)	42.0

<sup>a</sup> mc = methylene chloride

sulfate, to the organic phase allowed the formation of a clear solution and the possibility of encapsulating higher amounts of quinidine sulfate with higher yields within the microspheres (Table 5). Insignificant differences in drug content were observed between samples prepared from a drug solution or drug suspension. The addition of suitable good solvents for the drug as cosolvents to the organic phase can avoid the emulsification of drug suspensions which may be advantageous in certain cases.

The effect of the volume of methylene chloride on drug content is shown in Fig. 3. Higher polymer/organic solvent ratios at constant volume of

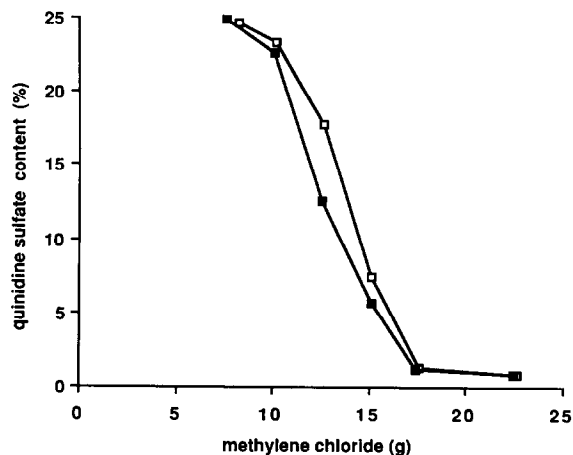


Fig. 3. Effect of the amount of methylene chloride on the quinidine sulfate content in the microspheres: ■, PLA I; □, PLA II.

the aqueous phase increased the drug content. Higher ratios resulted in higher polymer concentrations at the droplet boundary at the point of precipitation. Precipitation occurred faster at the surface of the droplet, thus inhibiting drug diffusion across the phase boundary. Additionally, higher polymer concentrations resulted in higher solution viscosities, which slowed down the rate of diffusion of solvent, non-solvent, and drug. A reduction in the amount of organic solvent is desirable with respect to increasing the payload of the microspheres. However, the higher polymer solution viscosity would require a different method of organic phase addition to the aqueous phase. Microspheres prepared with the higher molecular weight (MW) polymer, PLA II, showed slightly higher drug contents when compared with the lower MW polymer, PLA I. More non-solvent was required to induce phase separation with the lower MW polymer, resulting in slower precipitation and lower drug contents.

In conclusion, it was shown that the successful entrapment of drug and other properties depended to a great extent on the organic solvent used. Future studies will investigate the influence of drugs and polymers with different physicochemical properties on the formation mechanism of microspheres.

### Acknowledgements

This work was partially supported by a grant from the FMC Corporation, Philadelphia, PA, U.S.A.

### References

- Anderson, L.C., Wise, D.L. and Howes, J.F., An injectable sustained release fertility control system. *Contraception*, 13 (1976) 375–384.
- Barton, A.F.M., Solubility parameters, *Chem. Rev.*, 75 (1975) 731–753.
- Beck, L.R., Cowsar, D.R., Lewis, D.H., Cosgrove, R.J., Riddle, C.T., Lowry, S.L. and Epperly, T., A new long-acting injectable microcapsule system for the administration of progesterone. *Fertility and Sterility*, 31 (1979) 545–551.
- Benita, S., Benoit, J.P., Puisieux, F. and Thies, C., Characterization of drug-loaded poly(D,L-lactide) microspheres. *J. Pharm. Sci.*, 73 (1984) 1721–1724.
- Bodmeier, R. and McGinity, J.W., Preparation Variables of dl-Polylactic Acid Microspheres. *Proceedings of the 4th International Conference on Pharmaceutical Technology, Paris, France, Vol. II*, 1986, pp. 168–172.
- Bodmeier, R. and McGinity, J.W., Polylactic acid microspheres containing quinidine base and quinidine sulfate prepared by the solvent evaporation technique. I. Methods and morphology. *J. Microencapsulation*, 4 (1987a) 279–288.
- Bodmeier, R. and McGinity, J.W., Polylactic acid microspheres containing quinidine base and quinidine sulfate prepared by the solvent evaporation technique: II. Some process parameters influencing the preparation and properties of microspheres. *J. Microencapsulation*, 4 (1987b) 289–297.
- Hansen, C.M., The three dimensional solubility parameter—key to paint component affinities: II and III, *J. Paint Technol.*, 39 (1967) 505–514.
- Horvath, A.L., *Halogenated Hydrocarbons*, Marcel Dekker, New York, pp. 473–572.
- Roseman, T.J. and Higuchi, W.I., Release from medroxyprogesterone acetate from a silicone polymer. *J. Pharm. Sci.*, 59 (1970) 353–357.
- Sanders, L.M., Kent, J.S., McRae, G.I., Vickery, B.H., Tice, T.R., and Lewis, D.H., Controlled release of a luteinizing hormone-releasing hormone analogue from poly(D,L)lactide-co-glycolide microspheres. *J. Pharm. Sci.*, 73 (1984) 1294–1297.
- Teas, J.P., Graphic analysis of resin solubilities, *J. Paint Technol.*, 40 (1968) 19–25.
- Vidmar, V., Smolcic-Bubalo, A. and Jalsenjak, I., Poly(lactid acid) microencapsulated oxytetracycline: in vitro and in vivo evaluation. *J. Microencapsulation*, 1 (1984) 131–136.
- Yolles, S., Leafe, D.I., and Meyer, F.J., Timed-release depot for anticancer agents. *J. Pharm. Sci.*, 64 (1975) 115–116.