Effect of Drug Loading and Molecular Weight of Cellulose Acetate Propionate on the Release Characteristics of Theophylline Microspheres

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Microspheres with 40, 50, and 60% drug loading of anhydrous theophylline core material were prepared by the emulsion-solvent evaporation method. Three different molecular weights of cellulose acetate propionate were used as encapsulating polymers. The geometric mean diameter of the microspheres increased with drug loading for all polymers. Dissolution rate for a given particle size fraction also increased with drug loading for all polymers. Higuchi/Baker-Lonsdale spherical matrix dissolution kinetics were followed by narrow particle size fractions of the microspheres. A linear relationship between the T-50% (time required for 50% of the drug to be released) and the square of microsphere diameter was observed with all three molecular weights of the encapsulants. The slowest drug release was obtained with the high molecular weight polymer, which also produced the smoothest microspheres.

KEY WORDS: microspheres; encapsulation; drug loading; dissolution; cellulose acetate propionate; molecular weight; theophylline.

INTRODUCTION

Matrix microspheres made by the solvent-evaporation process are versatile as sustained-release dosage forms suitable for many drugs. However, microsphere characteristics are greatly affected by processing and formulation variables, such as drug loading and molecular weight of the carrier polymer. An increase in drug loading in matrix microspheres usually increases the drug release rate (1–5), but may have little effect in certain cases (6). When drug release properties of two viscosity (molecular weight) grades of ethylcellulose in microcapsules were compared, slower release of drug was obtained with the higher viscosity grade (7). Dissolution from microspheres made with four different molecular weights of poly(*d,l*-lactide) was slower as molecular weight increased (1). However, increased molecular weight may result in polymer characteristics that are less suitable for the encapsulation process and may cause the formation of microparticles that have more rapid release (8).

The objectives of this investigation were to evaluate (a) the effect of drug loading on particle size and drug release of the microspheres, (b) the effect of polymer molecular weight (viscosity) grade on drug release properties of the microspheres, and (c) to observe morphological differences of the microspheres using scanning electron microscopy.

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MATERIALS AND METHODS

Preparation of Microspheres

Anhydrous theophylline (Sigma Chemical Company, St. Louis, MO) was micronized by grinding the drug using a glass mortar and pestle. The ground drug was then sieved through a 270-mesh screen. Microspheres with three different drug loadings, *viz.*, 40, 50, and 60% (w/w) were prepared by the emulsion-solvent evaporation method as described previously (9) with three different molecular weights of cellulose propionate (Scientific Polymer, Ontario, N.Y.) having intrinsic viscosities of 1.08 (low MW), 1.15 (medium MW), and 1.20 (high MW) in acetone. Particle size distribution of the microspheres was performed by sieving through a set of standard sieves with openings of 500, 355, 250, 177, 125, 88, and 63 μm. For the purpose of reporting microsphere particle size, those microspheres passing through a sieve and retained on the next smaller sieve were assigned a size midway between the two sieves, e.g., 428, 303, 214, 107, and 76 μm for the above-mentioned standard sieves.

Drug Content Analysis and *in Vitro* Dissolution

Drug content analysis was performed by placing a 5-mg sample of the microspheres in a 10-ml volumetric flask. Methylene chloride (J. T. Baker Chemical Co., Philipsburg, N.J.) was added to dissolve the polymer and the drug. The flask was sonicated for 10 min to facilitate the dissolution of the microspheres. Drug concentration in the flask was determined spectrophotometrically at a 274-nm wavelength.

In vitro dissolution studies were carried out on the microspheres at 37°C in 1000 ml of simulated intestinal fluid (SIF) USP and simulated gastric fluid (SGF) without enzyme at 100 rpm using a standard USP XXI dissolution apparatus with Teflon-coated paddles. Accurately weighed samples of microspheres (20–30 mg) were suspended in the dissolution media and an aliquot of dissolution fluid was withdrawn every hour for 12 hr to assay the released drug spectrophotometrically at 271 nm. The fluid was returned to the vessel after analysis.

Scanning Electron Microscopic Evaluation

Scanning electron microscopic examination of the microspheres prepared with all three molecular weight polymers was performed in order to evaluate the effect of polymer molecular weight on the surface characteristics.

RESULTS AND DISCUSSION

Particle Size Distribution

Three methods are commonly used to control the particle size distribution of microspheres prepared by the solvent-evaporation process. They are (a) altering the agitation intensity during the emulsification process, (b) varying the solvent–polymer ratio, and (c) changing the surfactant concentration. However, a change in the drug-to-polymer ratio also can have a substantial influence on particle size. In the present investigation, particle size distribution of the micro-

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Table I. Geometric Mean Diameters (d_g) of Microspheres at Three Drug Loadings

Drug loading	Polymer molecular weight					
	Low		Medium		High	
	d_g	$(\delta_g)^a$	d_g	$(\delta_g)^a$	d_g	$(\delta_g)^a$
40% (w/w)	164 μm	(1.43 μm)	165 μm	(1.54 μm)	132 μm	(1.61 μm)
50% (w/w)	190 μm	(1.61 μm)	Bimodal distribution[b]		160 μm	(1.67 μm)
60% (w/w)	220 μm	(1.59 μm)	300 μm	(1.85 μm)	205 μm	(1.80 μm)

[a] Geometric standard deviation.
[b] Forty-two percent of microspheres had d_g >175 μm, and 35% <125 μm.

spheres prepared with all the three molecular weights of the polymers could be changed simply by altering the drug-to-polymer ratio. This was observed when the polymer concentration was kept constant, and the amount of the drug to be encapsulated was increased. Other factors such as emulsification stirring speed, solvent-to-polymer ratio, and surfactant concentration were kept constant.

The geometric mean diameter and the geometric standard deviation (determined from log-probability plots) of the microspheres with three different drug loadings prepared with all three molecular weights of the polymer are shown in Table I. It is evident from the table that increasing the drug loading from 40 to 50% (w/w) and eventually to 60% (w/w) increased the geometric mean diameter of the microspheres.

Effect of Drug Loading on Dissolution Characteristics

Increasing the drug loading of the microspheres prepared with all the three molecular weights of the polymer increased the drug release for a given particle size range and consequently decreased the T-50% values (Table II). The T-50% values for the microspheres prepared with high molecular weight polymer with less than 50% released at 12 hr were estimated by extrapolation of Baker–Lonsdale plots. It is our experience that dissolution from narrow particle size fractions of this type of microspheres is reasonably well described by the Higuchi/Baker–Lonsdale spherical matrix model up to 85–95% release. The decrease in the T-50% values for microspheres prepared with low and medium molecular weight polymers was more than the decrease in T-50% value for the high molecular weight polymer. This decrease in the T-50% values or an increase in the release rates with increasing drug loading can be attributed to decreased tortuosity and decreased diffusion path lengths for the drug molecules to get out of the microspheres (10). The larger change noted with the lower molecular weight polymers can probably be attributed to the lower viscosity of the polymer solutions and the resulting processing phenomena noted in the section on scanning electron microscopy.

Table II. T-50% Values in Hours Estimated from Baker–Lonsdale Plots

Polymer (MW)	Drug loading		
	40% (w/w)	50% (w/w)	60% (w/w)
High	206.2	103.0	34.9
Medium	38.0	14.7	2.5
Low	27.2	6.2	0.6

Effect of Microsphere Size on Dissolution Characteristics

Drug dissolution profiles from microspheres with four different particle sizes, 428, 303, 214, and 107 μm, with 60% (w/w) drug loading can be seen in Figs. 1–3. It is evident from the figures that increased drug release with decreased particle size of the microspheres was more pronounced for microspheres prepared with medium and low molecular weight polymers compared to those prepared with the high molecular weight polymer.

The relationship of square of microsphere diameter versus T-50% (Fig. 4) was linear for the microspheres prepared with medium and low molecular weight polymers (the correlation coefficient for medium MW polymer was 0.990 and that for the low MW polymer was 0.999), as predicted by the Higuchi analysis for spherical matrices (10). The T-50% plot constructed from drug release data from microspheres prepared with high molecular weight polymer is less reliable since only 30% or less of the drug was released in the 12 hr that the dissolution was monitored and all T-50% values

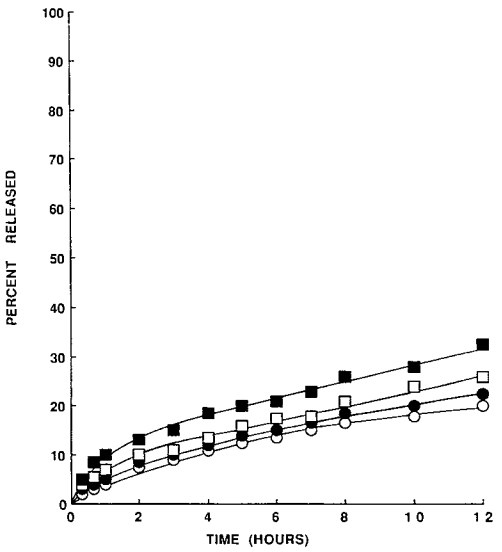

Fig. 1. Effect of microsphere particle size on dissolution of theophylline from microspheres prepared from high molecular weight cellulose acetate propionate: (○) 428 μm; (●) 303 μm; (□) 214 μm; (■) 107 μm. Drug content of microspheres, 60% (w/w); dissolution in SIF.

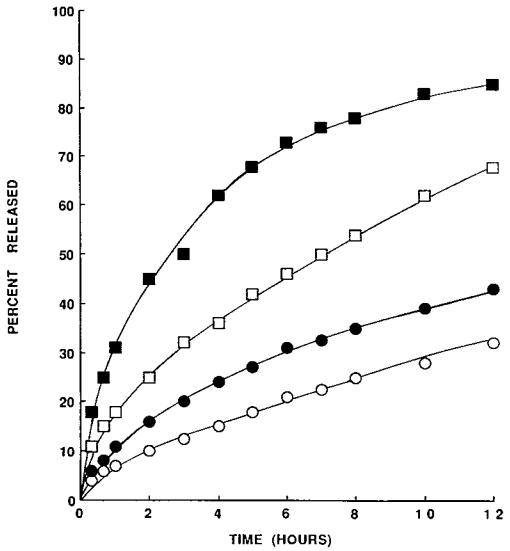

Fig. 2. Effect of microsphere particle size on dissolution of theophylline from microspheres prepared from medium molecular weight cellulose acetate propionate: (○) 428 μm; (●) 303 μm; (□) 214 μm; (■) 107 μm. Drug content of microspheres, 60% (w/w); dissolution in SIF.

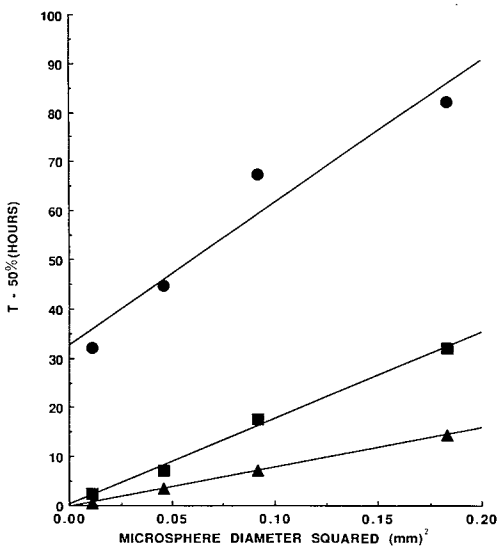

Fig. 4. Relationship between microsphere diameter squared versus T-50%: (●) high molecular weight polymer; (■) medium molecular weight polymer; (▲) low molecular weight polymer.

were estimated from extrapolated Baker–Lonsdale plots. For narrow sieve fractions of microspheres, dissolution from microspheres is reliably described by the models up to 85–95% release. Therefore, estimation of the 50% dissolution time of the largest microspheres from the data using the model is reasonable. Note that the dissolution characteristics from the estimated T-50% fall close to what would be predicted from more complete data obtained with smaller microspheres. If the larger particles were expected to be used in an oral dosage form, then more detailed information after 12 hr would be useful.

Comparison of Drug Dissolution in SIF and SGF from Microspheres

Comparison of drug dissolution from microspheres prepared with all three molecular weights in SIF (Fig. 5) and in SGF (Fig. 6) showed that the high molecular weight polymer was the most drug retardant, with about 31% of the drug released in 12 hr in SIF and 18% released in SGF. The low molecular weight polymer was the least retardant, with all

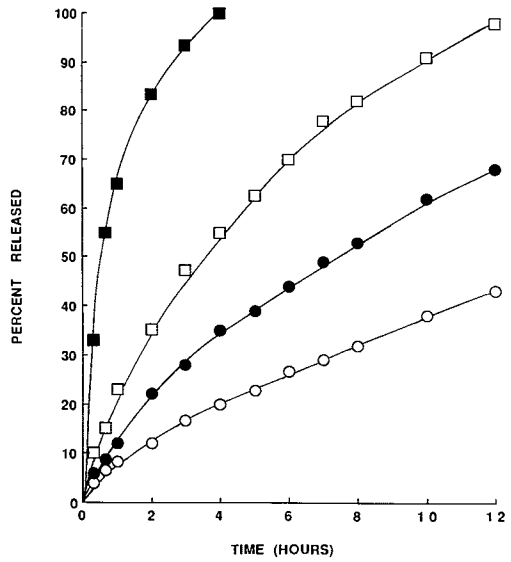

Fig. 3. Effect of microsphere particle size on dissolution of theophylline from microspheres prepared from low molecular weight cellulose acetate propionate: (○) 428 μm; (●) 303 μm; (□) 214 μm; (■) 107 μm. Drug content of microspheres, 60% (w/w); dissolution in SIF.

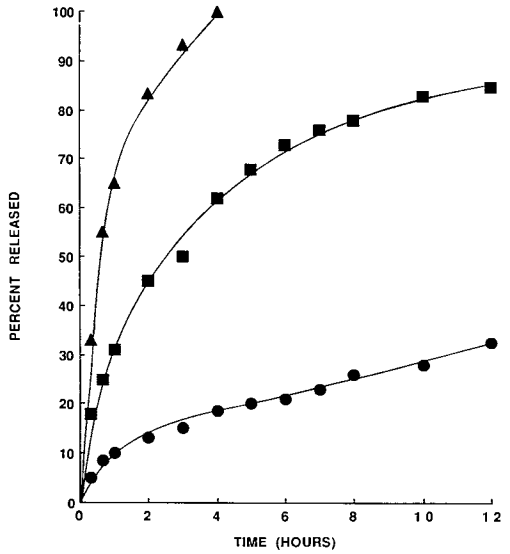

Fig. 5. Comparison of theophylline release in SIF from microspheres prepared with high, medium, and low molecular weight cellulose acetate propionate: (●) high molecular weight polymer; (■) medium molecular weight polymer; (▲) low molecular weight polymer. Drug content of microspheres, 60% (w/w). Microsphere diameter, 107 μm.

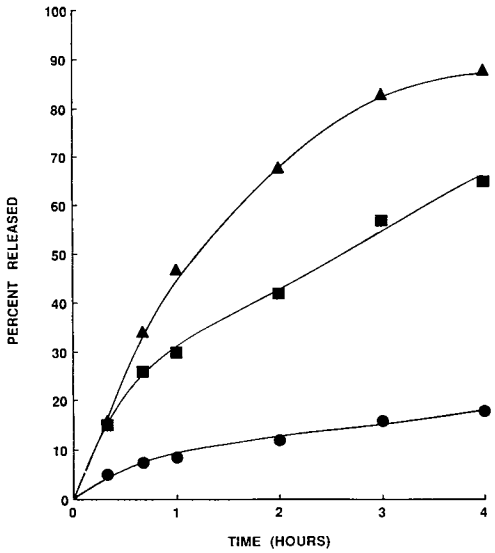

Fig 6. Comparison of theophylline release in SGF from microspheres prepared with high, medium, and low molecular weight cellulose acetate propionate: (●) high molecular weight polymer; (■) medium molecular weight polymer; (▲) low molecular weight polymer. Drug content of microspheres, 60% (w/w). Microsphere diameter, 107 μm.

the drug being released in 4 hr in SIF and about 92% of the drug released in SGF. The medium molecular weight had intermediate drug releasing properties, with about 85% drug released in SIF in 12 hr and 65% released in 4 hr in SGF.

The dissolution data fitted well to the Baker–Lonsdale model for drug release from spherical matrices (11) and Table III lists the slopes (with standard deviations) and the correlation coefficients obtained from the Baker–Lonsdale plots. Good fits from the narrow-particle size fractions indicate largely matrix release kinetics from the microspheres.

Scanning Electron Microscopy (SEM)

SEM studies performed on the microspheres revealed a smoother outer surface of the microspheres prepared with high molecular weight polymer compared to those prepared with medium and low molecular weight polymer (Figs. 7A–C). This phenomenon can be explained as follows.

Table III. Slopes and Correlation Coefficients of Baker–Lonsdale Plots of Drug Dissolution from Microspheres in SIF (107-μm-Diameter Microspheres)

Polymer MW	Drug content (%)	Slope (K) ± SD	Correlation coefficient
High	40	$0.000267 \pm 9.71 * 10^{-6}$	0.999
	50	$0.000537 \pm 2.02 * 10^{-5}$	0.997
	60	$0.001595 \pm 7.51 * 10^{-5}$	0.998
Medium	40	$0.001466 \pm 7.11 * 10^{-5}$	0.997
	50	$0.003930 \pm 2.45 * 10^{-4}$	0.993
	60	$0.019550 \pm 7.18 * 10^{-4}$	0.992
Low	40	$0.002082 \pm 6.97 * 10^{-5}$	0.995
	50	$0.009936 \pm 2.25 * 10^{-4}$	0.998
	60	$0.106380 \pm 6.68 * 10^{-3}$	0.999

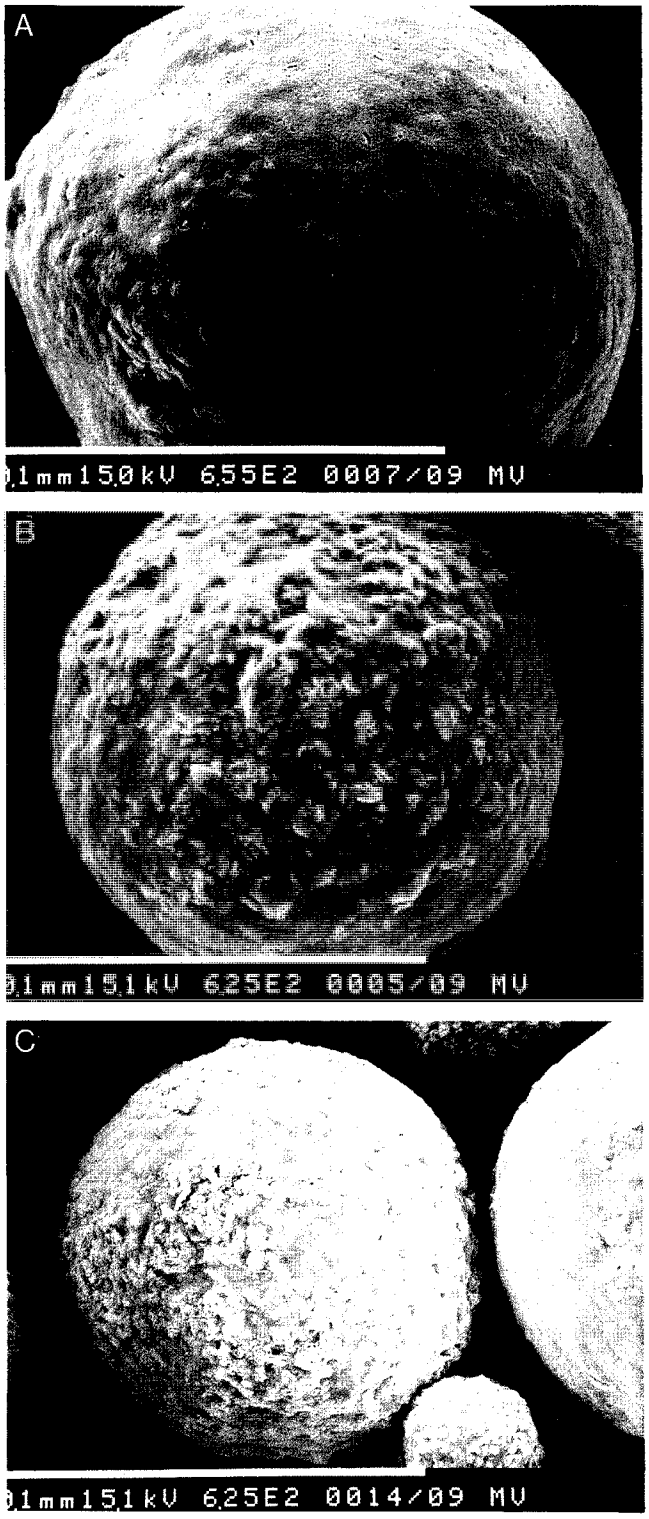

Fig. 7. (A) Scanning electron micrograph of microsphere made with high molecular weight polymer. (B) Scanning electron micrograph of microsphere made with medium molecular weight polymer. (C) Scanning electron micrograph of microsphere made with low molecular weight polymer. (A) 655× and (B, C) 625×; reduced 10% for reproduction.

As a globule of liquid suspension is sheared away from the main mass of the polymer solution phase during processing, the suspended particles are presumably randomly distributed in the globule. In the case where the suspended particles have a higher density than the polymer solution, spinning centrifugal forces cause movement of the suspended particles toward the interface at the same time that interfacial forces are causing the globule to minimize its surface area and to assume its spherical shape. The viscosity of the polymer solution affects the rate of migration of the suspended solid particles; higher viscosity decreases the rate of movement of the particles. The high molecular weight of polymer solution had the highest viscosity, and particles made from this polymer had the smoothest surfaces (the least number of particles near the surface). Another factor that minimizes the migration of particles is that, as the solvent evaporates, the high molecular weight polymer gels more quickly than the other polymer solutions, thus minimizing the time during which the suspended particles can move to the interface.

CONCLUSIONS

At drug loadings above 40%, increases in drug content can greatly affect fractional release rates of matrix microspheres of the same size range. With an increase from 40 to 60% drug loading, the observed change ranged from six times for the high molecular weight polymer to nearly 50 for the low molecular weight polymer. Thus, both lower release rates and smaller changes with drug loading can be expected for the high molecular weight polymer used in this investigation. Drug loading above 40% also affects microsphere size distribution; increased loading results in a shift to larger particle sizes.

REFERENCES

1. K. Suzuki and J. C. Price. Microencapsulation and dissolution properties of a neuroleptic in a biodegradable polymer, poly(dl-Lactide). *J. Pharm. Sci.* 74(1):21–24 (1985).
2. R. K. Chang, J. C. Price, and C. W. Whitworth. Control of drug release rate by use of mixtures of polycaprolactone and cellulose acetate butyrate polymers. *Drug Dev. Ind. Pharm.* 13(6):1119–1135 (1987).
3. R. K. Chang, J. C. Price, and C. W. Whitworth. Dissolution characteristics of polycaprolactone-polylactide microspheres of chlorpromazine. *Drug Dev. Ind. Pharm.* 12(14):2355–2380 (1986).
4. R. K. Chang and J. C. Price. Control of drug release rates through the use of mixtures of polycaprolactone and cellulose propionate polymers. *Pharm. Tech.* 10(10):24–33 (1986).
5. R. Bodmeier and J. W. McGinity. Preparation and evaluation of drug containing poly(dl-lactide) microspheres formed by the solvent evaporation method. *Pharm. Res.* 4(6):465–471 (1987).
6. Y. Pongpaibul, J. C. Price, and C. W. Whitworth. Preparation and evaluation of controlled release indomethacin microspheres. *Drug Dev. Ind. Pharm.* 10(10):1597–1616 (1984).
7. P. B. Deasy, M. R. Biophy, B. Ecanow, and M. Joy. Effect of ethylcellulose grade and sealant treatments on the production and *in vitro* release of microencapsulated sodium salicylate. *J. Pharm. Pharmacol.* 32:15–20 (1980).
8. J. Singh and D. H. Robinson. Controlled release of captopril microcapsule: Effect of ethylcellulose viscosity grade on the *in vitro* dissolution from microcapsules and tabletted microcapsules. *J. Microencap.* 7(1):67–76 (1990).
9. A. J. Shukla and J. C. Price. Effect of drug (core) particle size on the dissolution of theophylline from microspheres made from low molecular weight cellulose acetate propionate. *Pharm. Res.* 6(5):418–421 (1989).
10. T. Higuchi. Mechanism of sustained action medication. *J. Pharm. Sci.* 52(12):1145–1149 (1963).
11. R. W. Baker and H. S. Lonsdale. Controlled release: Mechanisms and rates. In A. C. Tanquary and R. E. Lacey (eds)., *Controlled Release of Biologically Active Agents*, Plenum Press, New York, 1974, pp. 15–71.