Microencapsulation of Solid Dispersions: Release of Griseofulvin from Griseofulvin:Phospholipid Coprecipitates in Microspheres

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The preparation, characteristics, and behavior of microspheres of poly(L-lactic acid) (PLA) containing griseofulvin (Gris) or Gris:phospholipid coprecipitates are described. Microspheres were spherical and increased in size from 17 μm (empty) to 30 μm, containing 22% Gris. The release of coprecipitated Gris after 60 min from 146,000 MW PLA microspheres in pH 2.0 buffer at 37°C was twofold greater than that from microspheres containing pure Gris. Also, the release profile from pure Gris microspheres was 25% lower than its dissolution profile, whereas the dissolution and microsphere release profiles of Gris coprecipitate were the same. Microspheres of Gris coprecipitate suspended in PEG 600 in hard gelatin capsules for 1 week released Gris at levels comparable to the dissolution of coprecipitate. Decreasing the MW of PLA substantially increased the release of Gris from microspheres of coprecipitate after 20 min but insignificantly from microspheres of pure Gris. These findings suggest that microsphere formulation offers some new opportunities in the development of solid dispersions which normally encounter processing difficulties.

KEY WORDS: microencapsulation; solid dispersions; coprecipitates; griseofulvin; phospholipid.

INTRODUCTION

The preparation of solid dispersions of drugs with water-soluble or water-dispersible carriers is intended either to increase the dissolution of the drug or, at least, to modify the kinetics of release of the drug in some predictable manner (1). One of the drawbacks of this type of formulation, however, has been the instability of the physical state of the powder during processing and during storage, i.e., the system ages (2,3). Attempts to resolve these problems have been very few. However, recently, the reduction of aging of a specific type of solid dispersion system has been demonstrated by modifying the carrier composition (4).

The application of microcapsule and microsphere technology has yielded better physical properties of drugs for manufacturing tablets or capsules because of having superior flow characteristics and compressibilities than the standard granulation. In addition, the microparticles processed in this manner can be formulated to yield drug release kinetics which are more uniform and prolonged (5–7). Another potential use of microencapsulation in the formation of small particles is believed to be the stabilization of solid dispersions, thereby increasing the utility of these dispersions both after processing and during storage. Therefore, a study was undertaken to prepare microencapsulated coprecipitates of the griseofulvin:phospholipid system which previously was shown to have superior dissolution behavior compared to micronized griseofulvin (8,9).

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MATERIALS AND METHODS

Poly(L-lactic acid) (PLA), MW 50,000 or 146,000, was obtained from ICN Biochemicals, OH, and Hexcel Medical, CA, respectively. Micronized griseofulvin (Gris, 99.3%; Glaxo, Canada), cholesterol (CHOL, 99%), L-α-dimyristoylphosphatidylcholine (DMPC, 99%), and polyvinyl alcohol (PVA; avg MW 10,000) were obtained from Sigma Chemical Co. Chloroform and methylene chloride were of analytical grade and used without further purification.

Microsphere Preparation

Microspheres were prepared under atmospheric conditions by a modified process of Beck *et al.* (10). The procedure involved dissolving the polymer (75%), drug, and lipids (25%; 4:1 Gris:lipid weight ratio, where the lipid component consisted of 1:0.33 DMPC:CHOL mole ratio) in chloroform (batch size, 1.2 g), adding a 0.5% PVA aqueous solution, then emulsifying with magnetic bar stirring at a constant rate of 300 rpm. The agitation was continued for 3 hr under atmospheric conditions allowing the solvent to evaporate. The microspheres formed were then allowed to settle and the supernatant was replaced with 1 *M* sodium chloride solution. The microspheres were agitated for a further 30 min, then filtered (Whatman No. 5 filter paper), washed with distilled water, rinsed with 10% ethanol (to remove excess Gris crystals), and dried under reduced pressure in a desiccator at 24°C for 16 hr. The 146,000 MW PLA was employed in all microsphere experiments except when the 50,000 MW PLA was used for comparison.

Microsphere Characterization

The loading of Gris in the microspheres was determined by dissolving 10 mg of microspheres in 1 ml of chloroform and then diluting to 10 ml with 95% ethanol. Solutions for analysis were obtained by a 1:10 dilution with pH 2.0 buffer solution, then absorbances were measured spectrophotometrically at 293 nm (Beckman Model 25 spectrophotometer) and the amount of Gris was determined from a standard calibration curve. The DMPC content of the microspheres was determined using a modified method of Raheja *et al.* (11).

Particle size distributions of the respective formulations were obtained by microscopic examination (1000× magnification). At least 600 microspheres were sized in each case using a calibrated graticule (British Standard graticule) placed adjacent to the eyepiece lens. Particle diameters corresponding to 50% cumulative frequency undersize were determined and averaged for triplicate lots. The volume specific surfaces were then calculated (12). Also, information

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about microsphere size and morphological characteristics was obtained using scanning electron microscopy (Philips SEM 505, Holland).

Drug Release Studies

Drug release from the microspheres was determined as a function of time using the spin-filter dissolution test apparatus (Magne Drive, Clow-Koffman Industries, KS) equipped with a 1-μm nominal porosity filter screen and 900 ml of 37°C HCl–KCl, pH 2.0, buffer stirred at 600 rpm. Unless otherwise specified, a weight of microspheres equivalent to 1.5 mg of Gris was suspended in the dissolution medium, which was circulated through the spectrophotometer, and the time-dependant release of Gris was determined from absorbances. Drug release and dissolution studies were also conducted using hard gelatin capsules (size 0) containing microspheres or Gris powder suspended in PEG 600, which had been stored for 1 week. Results are reported as the averages of triplicate experiments.

RESULTS AND DISCUSSION

Preparation of Microspheres

The optimum concentration of PVA as the emulsifier was determined to be 0.5%; higher concentrations of PVA led to excessive aggregation of microspheres, which is consistent with previous findings of others (13). The mean encapsulation efficiency of Gris in the microspheres varied between 64 and 86%, depending on the amount added and the solvent used as shown in Table I. The yield of microspheres was between 62 and 10%, decreasing with increased Gris loading. Microscopic observation revealed some crystals of Gris adhering to the surfaces of the microspheres even though they had been washed with 10% ethanol (Fig. 1C), which affected the yield. At higher Gris concentrations excess crystals actually interfered with microsphere formation. The adherence of crystals to microspheres is reported to be a common problem (14).

Characteristics of Microspheres

Typical scanning electron micrographs show that empty PLA microspheres had perfectly spherical shapes with smooth surfaces (Fig. 1A). In comparison, the Gris-loaded (17.1% loading) (Fig. 1B) or coprecipitate-loaded (10.6% Gris loading) (Fig. 1C) microspheres were also spherically shaped, but with rippled surfaces. Generally, the occurrence of free Gris crystals on the surfaces of the microspheres was low but this increased with Gris content (Table I).

The microsphere size increased and the volume specific surface decreased accordingly as a function of Gris content as shown in Table I, varying from 17.1 μm for empty microspheres to 30.3 μm for microspheres containing 21.6% Gris as a coprecipitate. The chloroform solvate of Gris was encapsulated to a lesser extent in PLA microspheres compared to when methylene chloride was used as a solvent, with a concomitant smaller mean microsphere diameter. Also, at equivalent Gris contents, the mean size was larger when methylene chloride was used.

Gris Release Studies

The time-dependent release of Gris from Gris coprecipitate-loaded microspheres relative to pure Gris is described in Fig. 2 as a function of the total Gris loading. These release profiles are typical of those obtained previously (8) (and shown in Fig. 3) in the dissolution of Gris from powdered coprecipitates, suggesting that the physical state of the coprecipitate in microspheres is similar to the unencapsulated coprecipitate. The amount of Gris released after 60 min from microspheres containing Gris coprecipitates was 1.6, 1.9, and 2.0 times more from batches of 8.1, 10.6, and 19.5% Gris loading, respectively, than from microspheres containing 17.1% Gris only. On the other hand, the amount of pure Gris released from microspheres was found to be slightly less than the amount of Gris in solution after dissolution of its powder (Fig. 3), whereas the release from microencapsulated Gris coprecipitates was the same as the dissolution of Gris from powdered coprecipitates of the same composition. This is further evidence that Gris coprecipitates can be

Table I. Characteristics of Griseofulvin-Loaded Poly(L-Lactic Acid) Microspheres[a]

Microsphere contents	Gris conc. (%)		Specific surface (cm^2/cm^3)[c]	Particle diameter (μm)[d]	Gris crystals[e]
	Theoretical	Observed[b]			
Empty	—	—	2919	17.1 ± 1.4	—
Gris:DMPC:CHOL					
[4:1(1:0.33)]	12.65	8.1 ± 1.7	2787	19.2 ± 1.9	+
[4:1(1:0.33)]	15.81	10.6 ± 3.1	1874	20.1 ± 2.1	+ +
[4:1(1:0.33)]	21.83	19.5 ± 2.0	1238	26.2 ± 2.0	+ +
[4:1(1:0.33)]	25.00	21.6 ± 2.2	1205	30.3 ± 2.8	+ + +
Gris-solvate	25.00	17.1 ± 2.8	961	28.1 ± 2.6	+ + +
Meth. chloride-treated Gris	25.00	21.4 ± 4.3	872	46.8 ± 3.4	—

[a] Mean MW 146,000.
[b] Mean ± SD, $n = 5$.
[c] Surface area per unit volume (12).
[d] Mean ± SD, $n = 3$.
[e] Extent of formation of free Gris crystals during preparation: —, none; +, low; + +, medium; + + +, high.

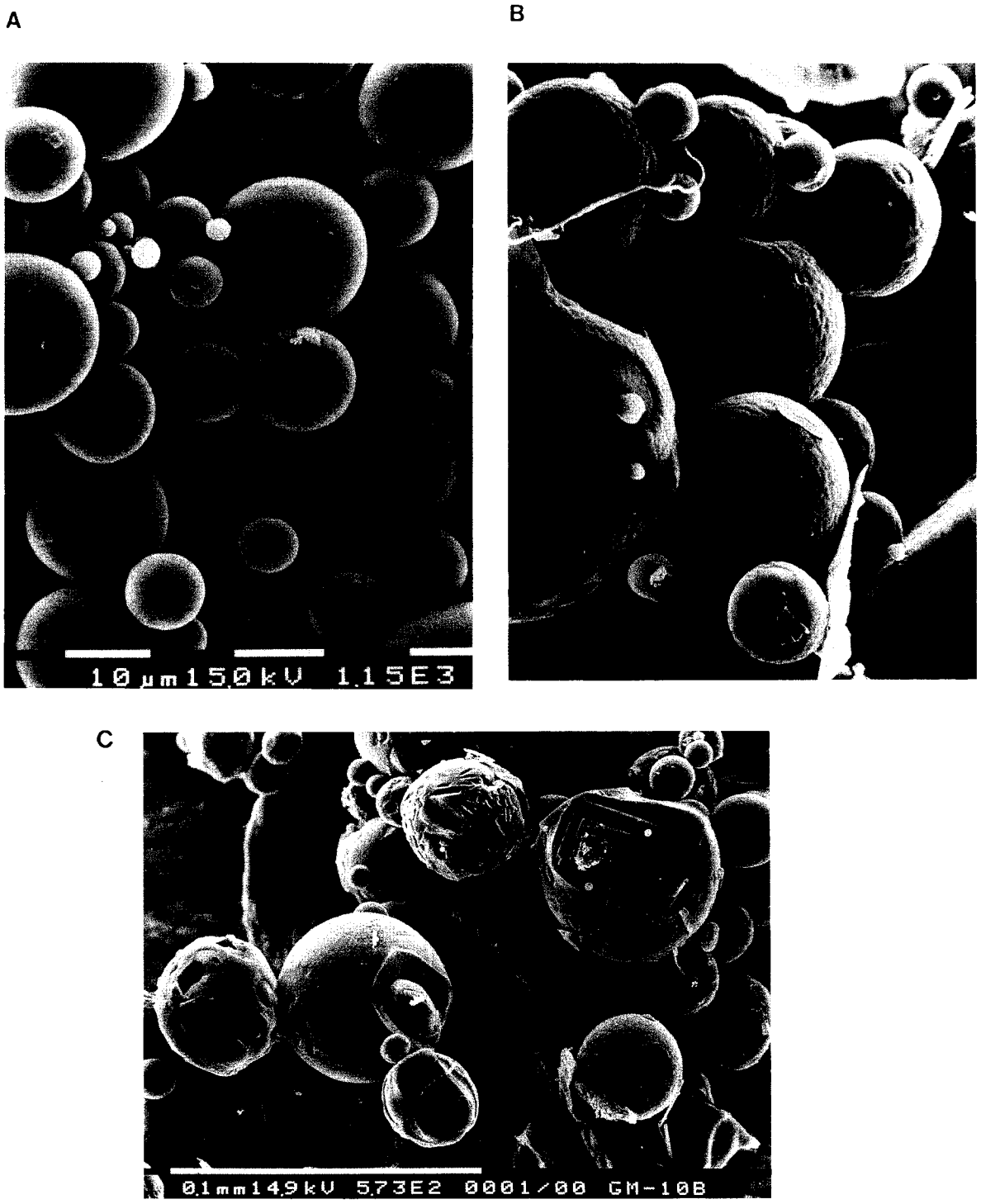

Fig. 1. Scanning electron micrographs of (A) empty 146,000 MW PLA microspheres; (B) microspheres containing 17.1% micronized Gris; (C) 10.6% Gris-loaded microspheres of Gris:DMPC:CHOL 4:1(1:0.33) coprecipitate.

loaded into microspheres without significant alteration of their dissolution properties. Analyses of DMPC in the microspheres exhibited large variations between samples (20–50% of the total drug content), but in spite of this, the enhanced release of coprecipitated Gris from the microspheres was not compromised.

The storage of hard gelatin capsules containing either Gris, microspheres of Gris, or microspheres of coprecipitated Gris suspended in PEG 600 for 1 week was intended to determine whether the coprecipitates would retain their dissolution characteristics. PEG 600 was selected as a nontoxic, relatively inert water-miscible organic solvent for this purpose. The solubility of Gris in PEG 600 at room temperature as determined from equilibration studies (results not

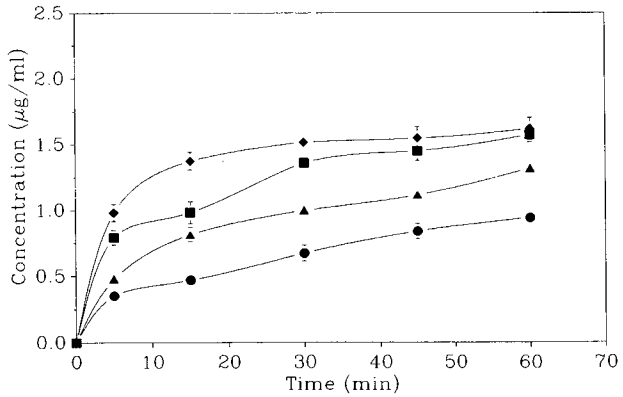

Fig. 2. Release of Gris from PLA microspheres containing Gris or Gris:DMPC:CHOL 4:1(1:0.33) coprecipitate (CP) as a function of Gris content in pH 2.0 buffer at 37°C: ▲, 8.1% Gris CP; ■, 10.6% Gris CP; ♦, 19.5% Gris CP; ●, 17.1% Gris only.

shown) was 15 mg/L (the same as in water at 37°C), from which it can be determined that 7.5 μg of Gris was dissolved in the 0.5 ml of PEG 600 in the hard gelatin capsule at the end of the storage period, leaving approximately 99.5% of the added Gris in suspension in the PEG 600. The corresponding release and dissolution data are shown in Fig. 4. It can be seen that in all cases of storage in PEG 600, concentrations of Gris in the dissolution medium rose to near-maximum or maximum levels within 15 min. This is likely due to both the solubilizing action of PEG 600 and the wetting of the particles. In the case of Gris only, the entire amount of drug had undergone dissolution within 30 min, whereas Gris-loaded coprecipitates continued to release Gris at a slow rate up to 60 min. Further, this is evidence that the integrity of the coprecipitate in the microspheres was maintained during the storage period in PEG 600. This is in contrast to preliminary tests which yielded results of loss of the improved dissolution behavior of Gris from coprecipitates suspended in PEG 600.

The release profiles of Gris from microspheres prepared with different molecular weight PLAs are shown in Fig. 5.

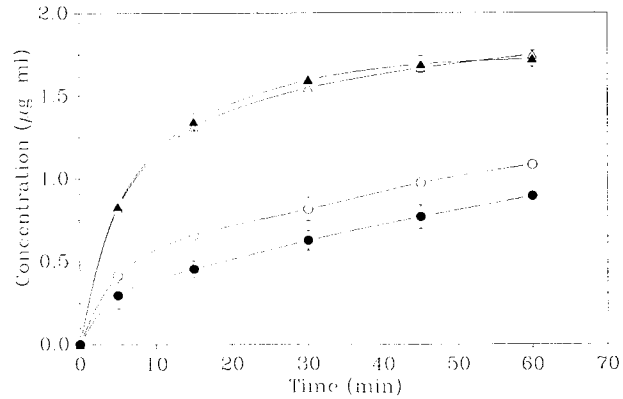

Fig. 3. Comparison of the release of Gris from PLA microspheres with dissolution of Gris formulations of the same composition in pH 2.0 buffer at 37°C: ○, micronized Gris; ●, 17.1% Gris-loaded microspheres; △, Gris coprecipitate; ▲, 10.6% Gris coprecipitate-loaded microspheres. One and five-tenths milligram equivalent of Gris was used.

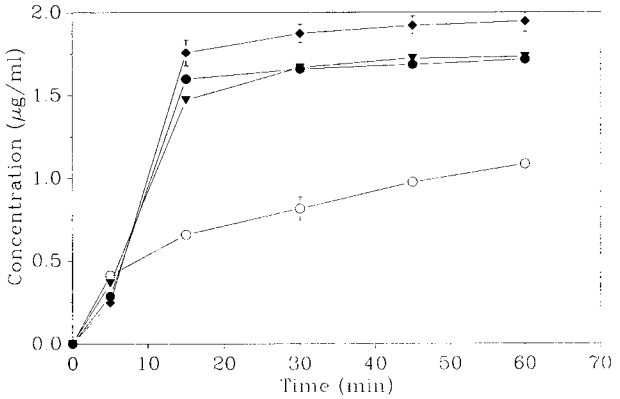

Fig. 4. Release of Gris from formulations suspended in PEG 600 in hard gelatin capsules after storage at room temperature for 1 week in pH 2.0 buffer at 37°C: ●, 17.1% Gris-loaded microspheres; ♦, 19.5% Gris coprecipitate-loaded microspheres; ▼, micronized Gris. The dissolution of micronized Gris (——○——) at pH 2.0, 37°C, which had not been suspended in PEG 600 is shown for comparison.

The differences in the release of Gris from 50,000 or 146,000 MW PLA microspheres was negligible whereas the release from Gris coprecipitate microspheres, after the initial rapid release phase (~20 min), became significantly greater with time from the 50,000 MW PLA microspheres.

CONCLUSIONS

The microencapsulation of an intact solid dispersion system in microspheres of PLA has been shown to be possible. The release of Gris from Gris:phospholipid coprecipitates exhibited similar behavior in microencapsulated and nonmicroencapsulated states. In comparison, the release profile of Gris from microencapsulated Gris was 20% less than that obtained from its dissolution. Furthermore, the integrity of coprecipitates in microspheres suspended in PEG 600 for 1 week appeared to be maintained. Decreasing the molecular weight of PLA significantly increased the release of Gris from microencapsulated coprecipitates but not pure Gris. It appears that microencapsulation may offer new

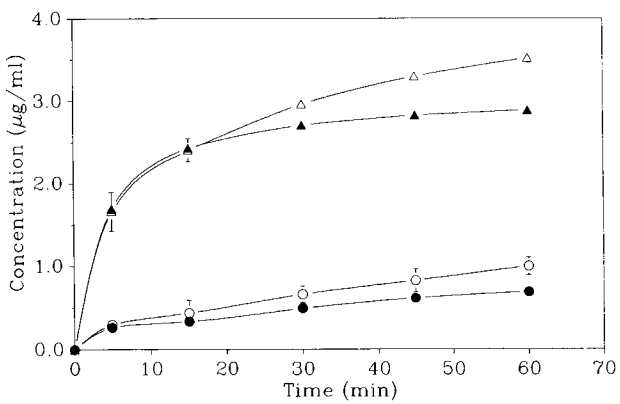

Fig. 5. Molecular weight dependence of the release of Gris from PLA microspheres containing 17.1% Gris or 19.5% Gris coprecipitate in pH 2.0 buffer at 37°C. (○, ●) Gris; (△, ▲) Gris coprecipitate. Open symbols, 50,000 MW; filled symbols, 146,000 MW. In this study, 6 mg equivalent of Gris in microspheres was added to the dissolution medium.

opportunities to exploit the solid dispersion formulation advantages of poorly water-soluble drugs. This could entail minimizing the difficulties encountered with these systems during processing as well as developing desirable controlled-release patterns.

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