Water Migration from Soft Gelatin Capsule Shell to Fill Material and Its Effect on Drug Solubility

ABU T. M. SERAJUDDIN[x], PAI-CHANG SHEEN, AND MATTHEW A. AUGUSTINE

Received July 15, 1985, from the *Pharmacy R&D Department, Revlon Health Care Research, Tuckahoe, NY 10707.* Accepted for publication October 8, 1985.

Abstract □ The bioavailability of some poorly water-soluble drugs was reported to increase due to a change in dosage form from a tablet to a solution encapsulated in soft gelatin capsules. However, the objective of increasing the bioavailability may be defeated if the drug crystallizes from a solution inside the capsule. In this study, a water-insoluble drug [α-pentyl-3-(2-quinolinylmethoxy)benzenemethanol; REV 5901] was solubilized in both polyethylene glycol 400 (PEG 400) and a 6:1 mixture of Gelucire 44/14:PEG 400. The solutions were then encapsulated in soft elastic gelatin capsules with a fill weight of 700 mg (drug, 125 mg), and water migration from the capsule shell into the fill material and its effect on the solubility of the drug were investigated. Gelucire 44/14 is a mixture of hydrogenated fatty acid esters with a mp of 44°C; PEG 400 was added to reduce the mp of solution to ~36°C for easier encapsulation. After equilibration of capsules at ambient condition, the amount of water in the PEG 400 solution was 6.3%. This reduced the solubility of the drug by 45%, resulting in drug crystallization. The solubility decreased exponentially with the increase in water content. The water in the encapsulated Gelucire:PEG solution was only 1.1%, which did not affect the solubility significantly.

The advantages of drugs in soft gelatin capsules over conventional dosage forms, e.g., tablets, hard gelatin capsules, solutions, etc., have been reported in the literature. The advantages include increased bioavailability,[1-3] consumer preference,[4] better stability,[1,5] easier processibility,[1,5] and reduced side effects.[6] In recent years, there has been a renewed interest in soft gelatin capsules after it was shown that the bioavailability of digoxin, a poorly water-soluble and erratically bioavailable drug, could be increased significantly by a change in dosage form from a tablet to a soft gelatin capsule.[7-9] In most cases, the primary reason for increased bioavailability was that the drug was encapsulated in a solubilized form. Following oral intake of capsules, the drug dissolves or disperses rapidly in the GI fluid.

The physicochemical characteristics of soft gelatin capsules are different from those of other conventional dosage forms, and, therefore, special considerations are necessary in formulating this dosage form.[5,10] Properties of the drug and the vehicle, solubility of the drug, processibility of the vehicle, compatibility of the drug, the vehicle, and the gelatin shell, and stability of these three components after encapsulation must be carefully evaluated during formulation. However, little on the development of bioavailable soft gelatin capsule formulations has been reported in the literature.

Due to the high initial water content of the soft gelatin capsule shell (>20%),[10] water migrates from the shell to the fill material during the drying and subsequent equilibration periods.[5,10] The objective of increasing the bioavailability of a drug by solubilization may be defeated if the drug crystallizes inside the capsule due to water migration. In this study, the effect of water migration on the solubility of α-pentyl-3-(2-quinolinylmethyoxy)benzenemethanol (1), a water-insoluble drug (solubility in water at 37°C ~0.002 mg/mL),[11] in water-miscible vehicles was investigated. Attempts were made to minimize water migration by the selection of a suitable vehicle. A method of formulating a semisolid solution of 1 in a soft gelatin capsule is also described.

Experimental Section

Chemicals—Compound 1 was synthesized by the Process Chemistry R&D Department of Revlon Health Care Research, Tuckahoe, N.Y.[12] Polyethylene glycol (PEG) 400 was purchased from Ruger Chemical Co., Irvington, NJ. Gelucire 44/14 was supplied by Gattefossé Corp., Hawthorne, NY. This proprietary material is a mixture of glyceryl and PEG 1500 esters of fatty acids; the fatty acids are produced by the hydrolysis of hydrogenated copra and palm kernel oils. It is amphiphilic in nature and, as indicated by the associated numbers, has a melting point of 44°C and an HLB value of 14.[13] Gelatin and plasticizers used for encapsulation were supplied by R. P. Scherer, Clearwater, FL.

Determination of Solubility—The solubility of 1 in PEG 400 and in PEG 400–water mixtures were determined by equilibrating the drug with solvents at 20°C for ~18 h. A wrist action shaker was used to equilibrate the solutions. The solutions were then centrifuged, and weighed amounts of supernatant liquids were analyzed spectrophotometrically at 239 nm after suitable dilution with acidified methanol (1 M HCl:methanol, 1:9).

In the case of Gelucire 44/14, which is a solid at room temperature, a direct determination of solubility was not possible. In this case, solutions with varying concentrations of 1 were prepared at 45°C. The solutions were then allowed to solidify at room temperature (~22°C) and the solid solutions were observed periodically for up to 3 months under a polarized-light microscope for the presence of any drug crystal. The concentration at which a few crystals first appeared was estimated to be the drug solubility.

Thermal Analysis—Thermal analysis of Gelucire 44/14-based fill materials was conducted by using a Du Pont 990 thermal analyzer fitted with a differential scanning calorimeter (DSC). The samples tions were: sample size, 5 mg; temperature range, from ~10°C to ~80°C; heating rate, 10°C/min; and sensitivity, 0.5 mcal/s/in. (0.2 mcal/s/cm).

Encapsulation of Drug—Solutions of 1 (drug, 125 mg plus vehicle, 575 mg) were encapsulated in oblong soft gelatin capsules using an R. P. Scherer rotary die encapsulation machine. The process is essentially similar to that described earlier.[1,5,10] The solution of 1 in PEG 400 was encapsulated at room temperature. The solution in the Gelucire 44/14:PEG 400 mixture was filled at 38 ± 1°C. Identical gelatin shell composition (gelatin, plasticizer and water) was used in all capsules. The capsules were equilibrated with 20–30% relative humidity at room temperature for 7 d by placing them on open trays. They were then packaged in high density polyethylene bottles.

Evaluation of Capsules—The water content of the capsule shell and the fill material was determined by Karl Fischer analysis. To determine the water content of the capsule shell, the solution adhering to the inner surface of the shell was scraped out. A stability-indicating HPLC method was used to determine the content uniformity of the capsules. The possible crystallization of 1 in the fill material was studied by using a polarized-light microscope.

Results and Discussion

Solubility in Polyethylene Glycol 400–Water System—The solubility of 1 in PEG 400 and PEG 400–water mixtures at 20°C are plotted in Fig. 1(A). Since the solubility of 1 decreases with an increasing percentage of water, the amount of solvent per unit volume of solution differs. Therefore, the drug concentration was expressed with respect to a constant weight of solvent (milligrams of solute per grams of solvent); this is analogous to expressing the concentration in molality and has the advantage that a solution may be

0022-3549/86/0100-0062$01.00/0
© 1986, American Pharmaceutical Association

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

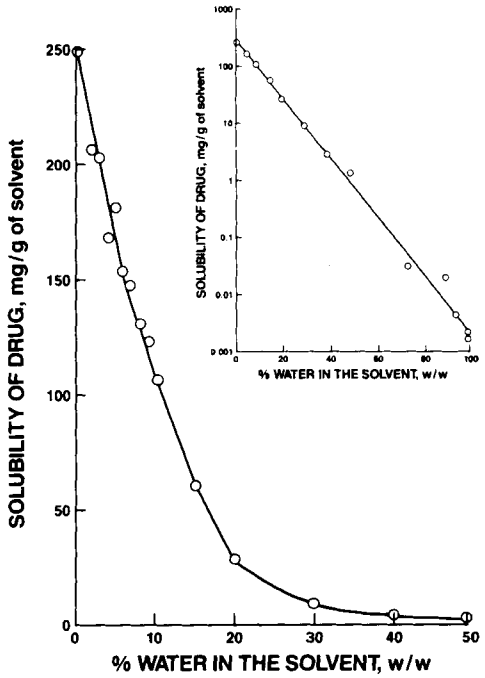

Figure 1—(A) *Solubility of α-pentyl-3-(2-quinolinylmethoxy)benzenemethanol (1) in PEG 400–water cosolvent system at 20 °C. Data points at >50% water remain at the baseline.* (B) *Semilogarithmic plot of solubility of 1 in PEG 400–water cosolvent system at 20 °C. At <20% water, data points at 5% intervals only are shown for the sake of clarity.*

prepared by accurate weighing. The solubility of 1 in PEG 400 at 20°C is 250 mg/g of solvent. The solubility decreases sharply with the incorporation of water in the system. For example, the solubility drops to ~100 and ~1.5 mg/g of solvent in the presence of 10 and 50% water, respectively. A semilogarithmic plot of the data in Fig. 1(B) shows a log-linear[14] decrease in solubility with the increase in percentage of water in the solvent. Recently, Groves et al.[15] also observed a similar log-linear decrease in solubility of a poorly water-soluble compound in PEG 400–water mixtures, except at a low percentage of water (<10%). The deviation from the theoretical relationship at a low concentration of water was attributed to a possible chemical interaction between the compound and PEG 400. Although a high solubility of 1 in PEG 400 indicates a high solute–solvent affinity, no deviation from the theoretical relationship is observed.

Solubility in Gelucire 44/14 and Gelucire 44/14–Polyethylene Glycol 400 Mixtures—The solubility of 1 in Gelucire 44/14 at room temperature (~22°C), as determined by the microscopic method, was found to be 200 mg/g of vehicle; a progressively greater number of 1 crystals were observed with the increase in drug concentration above this level. No crystals of 1 were, however, observed at room temperature for at least 3 months when 217 mg of the drug was dissolved per gram of a 6:1 mixture of Gelucire 44/14 and PEG 400. The latter concentration of drug was used in the fill material to maximize the amount of drug per capsule. Since the solubilities of 1 in Gelucire 44/14 and PEG 400 at 20–22°C were ~200 and 250 mg/g, respectively, a concentration of 217 mg/g of a 6:1 mixture of Gelucire 44/14 and PEG 400 was considered to be in the region of saturation solubility.

Reduction of Melting Point of Gelucire 44/14—Gelucire 44/14 has a melting point of 44°C (range: 42–46°C). Since the turing is 37–40°C,[5,10] 1 dissolved in a melt of Gelucire 44/14 could not be encapsulated due to its high melting point relative to the sealing temperature. The melting point at the drug solution was, therefore, reduced by the incorporation of PEG 400 in the vehicle. The drug was dissolved by melting the vehicle at ~45°C. The concentration of the drug ws adjusted such that 575 mg of vehicle contains 125 mg of 1 (217 mg/g of vehicle). The thermal properties of drug solutions and vehicles were studied after equilibrating the samples at room temperature for ~24 h. The results are shown in Fig. 2. The DSC thermogram of the fill material of a soft gelatin capsule, determined 3 weeks after preparation, is also shown in this figure. Since the onsets of melting endotherms were not sharp, the melting peaks were compared. The samples melted completely within 2°C above the melting peak.

Figure 2 shows that Gelucire 44/14 has its melting peak at 42°C (thermogram A). This temperature remains unchanged when 1 is dissolved in Gelucire 44/14 (thermogram B). The melting peak of a 6:1 mixture of Gelucire 44/14–PEG 400 without drug is 41°C (thermogram C). However, when PEG 400 is incorporated into the drug formulation, the peak melting temperature decreases progressively with the increase in PEG 400 concentration. The thermogram D shows that the peak melting temperature of a solution of 1 in a 6:1 Gelucire 44/14–PEG 400 mixture is 36°C. The reason that 1 decreased the melting temperature of a Gelucire 44/14–PEG 400 mixture, but not of Gelucire 44/14 alone, is not clear from this study. It is possible that a eutectic mixture was formed in the presence of PEG 400. Based on this study, a temperature of 38°C was selected for encapsulating the drug solution. As indicated by thermogram E, the thermal properties of the fill material do not change after encapsulation.

Soft Gelatin Encapsulation and Effect of Water Migration—The drug contents of the capsules containing PEG 400 and a 6:1 Gelucire 44/14–PEG 400 mixture as vehicles were found to be 121.9 ± 0.9 mg (SD, n = 10) and 128.0 ± 0.6 mg (SD, n = 10), respectively, thus showing good content uniformity. The yields of capsules were 89.5 and 85.4%, respectively, which is satisfactory for batch sizes of 10,000 capsules; most of the losses occurred during the initial setting of

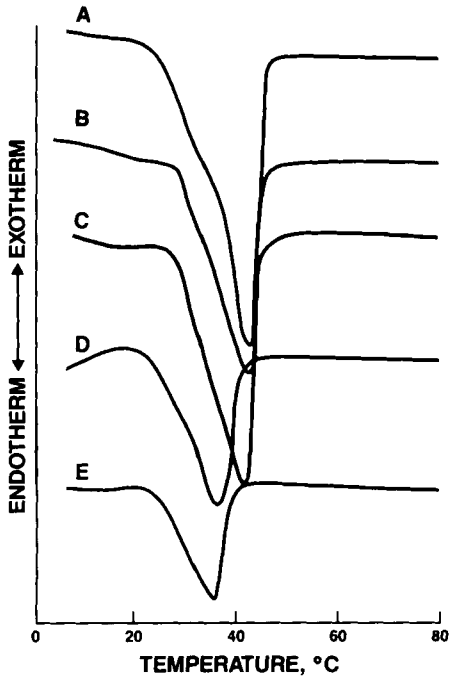

Figure 2—*Differential scanning calorimetry thermograms of various formulations of fill material with and without drug. Key:* (A) *Gelucire 44/14;* (B) *drug in Gelucire 44/14 (17.9% w/w);* (C) *6:1 mixture of Gelucire 44/14–PEG 400;* (D) *drug in 6:1 mixture of Gelucire 44/14–PEG 400 (17.9% w/w);* (E) *fill material after encapsulation.*

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

machines. Although the Gelucire 44/14 based formulation was encapsulated at or near the temperature necessary to seal the gelatin shells, there was no significant loss of capsules due to defective sealing.

The water content of fill materials and capsule shells was analyzed 3–4 weeks after preparing the capsules. When a solution of 1 in PEG 400 was used, the amount of water in the fill material was 6.4 ± 0.1% of the initial fill weight. In contrast, the water content of the fill material where Gelucire 44/14–PEG 400 was used to dissolve the drug was 1.1 ± 0% of the fill weight. The water contents of the capsule shells were 9.6 ± 0.2 and 5.6 ± 0.1%, respectively.

The initial microscopic analysis of the contents of soft gelatin capsules for the presence of 1 crystals was made 3–4 weeks after the preparation of the capsules. The capsules, after initial equilibration at 20–30% relative humidity for 1 week, were stored at 22°C, protected from moisture. Gross crystallization of 1 was observed in soft gelatin capsules containing only PEG 400 as a vehicle. Initial concentration of the 1 solution inside the capsule was 17.9% w/w, which is below its saturation limit in PEG 400 (20% w/w at 20°C). The observed crystallization was, therefore, due to a lowering of solubility by the migration of water to the fill material. Only ~80 mg of 1 remained in solution inside the capsule, which is in general agreement with Fig. 1. For comparison, a 17.9% w/w solution of 1 in PEG 400 was filled manually in hard gelatin capsules or glass vials, and stored under identical environmental conditions. No crystallization of drug was observed during 3 months of observation. Since, unlike a solution in PEG 400, the migration of water into the drug solution in Gelucire 44/14–PEG 400 was minimal, no crystallization of 1 was observed in this fill material for 3 months.

The gelatin mass used to prepare soft gelatin capsule shells may contain 30–40% water.[1] During drying and subsequent equilibration of capsules, the water may partially migrate into the fill material. The extent of such a migration of water may depend on the nature of the solvent or matrix used in the fill material. The lower water content of the fill material containing a mixture of Gelucire 44/14–PEG 400 as compared to PEG 400 alone may be related to the lower hydrophilicity of Gelucire 44/14 compared to that of PEG 400 (HLB: 14 versus ~20) and the low diffusion coefficient of water in the semisolid matrix.

The water contents determined in the present study are essentially the equilibrium values. There was no significant change in the amount and shell-to-fill ratio of water in Gelucire 44/14 based capsules when stored in closed 45-mL high-density polyethylene bottles (20 capsules/bottle) under varying conditions (4°C, 25°C, and 35°C) for an additional 3 months. Due to gross crystallization of the drug, the stability of PEG 400 based capsules was not studied for an extended period of time.

Another major difference between PEG 400 and Gelucire 44/14–PEG 400 was in the particle sizes of drugs crystallizing out of these vehicles. The majority of crystals in the PEG 400 based formulation were 500–1000 μm. On the other hand, all crystals observed in the formulation containing the Gelucire 44/14–PEG 400 mixture by reducing its temperature to ~4°C or by increasing the initial concentration of drug were <15 μm. This is possibly due to a difference in crystal growth in liquid and semisolid vehicles.

One major limitation of soft gelatin capsules is the amount of drug that may be encapsulated as a solution. This is of particular concern if a high dose of drug is necessary. Sometimes the required amount of drug may not be solubilized in the best suitable solvent. The results of the present investigation show that this situation might be further complicated by a lowering of solubility due to water migration. The migration of water, and thus the crystallization of 1, can be minimized by changing, among other possible factors, the vehicle.

In conclusion, the results of the present investigation highlight the importance of a critical evaluation of shell-to-fill water migration in formulating soft gelatin capsules.

References and Notes

1. Seager, H. *Pharm. Tech.* **1985**, *9(9)*, 84–104.
2. Batemann, N.; Uccellini, D. A. *J. Pharm. Pharmacol.* **1984**, *36*, 461–464.
3. Berry, I. R. *Drug Cosm. Ind.* **1983**, *133*, 32.
4. Delaney, R. *Pharm. Exec.* **1982**, *2*, 34–38.
5. Ebert, W. R. *Pharm. Tech.* **1977**, *1(5)*, 44–50.
6. Caldwell, L.; Cargill, R.; Ebert, W. R.; Windheuser, J. J. *Pharm. Tech.* **1979**, *3(7)*, 52–56.
7. Mallis, G. I.; Schmidt, D. H.; Lindenbaum, J. *Clin. Pharmacol. Ther.* **1975**, *18*, 761–768.
8. Marcus, F. E.; Dickerson, J.; Pippin, S.; Stafford, M.; Bressler, R. *Clin. Pharmacol. Ther.* **1976**, *20*, 253–259.
9. Johnson, B. F.; Bye, C.; Jones, G.; Sabey, G. A. *Clin. Pharmacol. Ther.* **1976**, *19*, 746–751.
10. Stanley, J. P. in "The Theory and Practice of Industrial Pharmacy"; Lachman, L.; Lieberman, H. A.; Kanig, J. L., Eds.; Lea & Febiger: Philadelphia, 1976; pp 404–420.
11. Serajuddin, A. T. M.; Sheen, P. C.; Bernstein, D. F.; Mufson, D.; Augustine, M. A. *J. Pharm. Sci.* in press.
12. Compound 1 is also known as REV 5901.
13. Waginaire, L.; Glas, B. "Gelucire", technical literature, No. 74, Gattefossé Co.: 1981; pp 3–8.
14. Yalkowsky, S. H.; Flynn, G. L.; Amidon, G. L. *J. Pharm. Sci.* **1972**, *61*, 983–984.
15. Groves, M. J.; Bassett, B.; Sheth, V. *J. Pharm. Pharmacol.* **1984**, *36*, 799–802.

Acknowledgments

The authors thank R. P. Scherer North America, Clearwater, FL, for the use of its facilities in encapsulating soft gelatin capsules. The assistance of Ms. E. Eger in the preparation of this manuscript is gratefully acknowledged.

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.