Drug Development and Industrial Pharmacy, 35:297–304, 2009

ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040802302157

informa
healthcare

Preparation and Characterization of Spironolactone-Loaded Gelucire Microparticles Using Spray-Drying Technique

Alaa Edeen B. Yassin, Fars K. Alanazi, Mahmoud El-Badry, Ibrahim A. Alsarra, and Nahla S. Barakat
Department of Pharmaceutics, King Saud University, Riyadh, Saudi Arabia

Fars K. Alanazi
Al-Kayyali Chair for Pharmaceutical Technology, King Saud University, Riyadh, Saudi Arabia

The basic objectives of this study were to prepare and characterize solid dispersions of poorly soluble drug spironolactone (SP) using gelucire carriers by spray-drying technique. The properties of the microparticles produced were studied by differential scanning calorimetry (DSC), scanning electron microscopy, saturation solubility, encapsulation efficiency, and dissolution studies. The absence of SP peaks in DSC profiles of microparticles suggests the transformation of crystalline SP into an amorphous form. The in vitro dissolution test showed a significant increase in the dissolution rate of microparticles as compared with pure SP and physical mixtures (PMs) of drug with gelucire carriers. Therefore, the dissolution rate of poorly water-soluble drug SP can be significantly enhanced by the preparation of solid dispersion using spray-drying technique.

Keywords spironolactone; spray drying; gelucires; microparticles; aerosil; differential scanning colorimeter

INTRODUCTION

Spray-drying technique is extensively used in the pharmaceutical industry to produce raw drug or excipients or microparticles, as an alternative to emulsification methods (Billon, Bataile, Cassanas, & Jacob, 2000; Giunchedi & Conte, 1995; He, Davis, & Illim, 1999; Lee, Kim, & Kim, 1999). This technique transforms liquid feed into dry powder in one step that is feasible for the scaling-up of the microencapsulation, continuous particle processing operation and can be used to a wide variety of materials (Broadhead, Rouan, & Rhodes, 1992).

The colloidal drug-entrapped particles could be prepared from a variety of both water-soluble and water-insoluble polymers of synthetic, semisynthetic, and natural origin. Spray drying is a very useful technique that can be successful in the preparation of a wide variety of medications including heat-sensitive, heat-resistant, water-soluble, and water-insoluble drugs as well as hydrophilic and hydrophobic polymers. This is meaningful for the development of pharmaceutical carriers specifically for the delivery of hydrophobic drug which represents one of the major challenges in the field of new drug delivery (Torchilin, Lukyanov, Gao, & Papahadjopoulos-Sternberg, 2003). The polymeric drug delivery systems produced by spray drying have a potential to provide new types of administered routes, such as oral dosage forms (dry powder, granules, or agglomerates), targeting systems to organs and tissues and long-acting parenteral biodegradable systems (He et al., 1999). (Also, spray drying can be used to enhance the solubility and particulate design [Asada, Takahashi, Okamoto, Tanino, & Danjo, 2004; Dollo et al., 2004; Moretti, Gavini, Juliano, Pirisino, & Giunchedi, 2001; Muller et al., 2000].) It is possible to improve water solubility by combining insoluble drugs with other water-soluble materials (Chiou & Riegelman, 1971; Ford, 1986).

Spray drying is characterized by important features such as reliability, reproducibility and possible control of particle size and release. Though spray-dried (SD) particulate systems suffer from thermodynamic instability, the use of antiplasticizing agents and improvement of Tg by using polymers like polyvinylpyrrolidone (PVP) have shown promising results (Paradkar, Chauhan, Yamamura, & Pawar, 2003). Low-melting point excipients like polyethylene glycols (PEG) and polyglycolized glycol esters like gelucires have been used widely as excipients in SD particles. These excipients have shown to cause faster drug dissolution by improving wettability of the drug particles, significant reduction in particle size during the formation of SD particles, or the inherently higher rate of dissolution of the soluble component of SD particles, which would pull along the more insoluble but finely mixed drug into the dissolution medium (Dordunoo, Ford, & Rubinstein, 1991; Leuner & Dressman, 2000; Passerini et al., 2002).

Despite the main advantages of spray drying, processing variables must be well controlled to avoid difficulties such as low yield, sticking, or high moisture content which are often

Address correspondence to Nahla S. Barakat, Department of Pharmaceutics, King Saud University, P. O. Box: 22452, Riyadh 11495, Saudi Arabia. E-mail: nsybarakat@yahoo.com

encountered with laboratory-scale spray dryers (Masters, 1991). Previous reports showed that stickiness is imparted by those low-melting point excipients causing processing problems. Silicon dioxide (Aerosil® 200) is a nonporous hydrophilic form of silica. Aerosil is one of the important carriers because of the presence of surface silanol groups and may be able to form hydrogen bonds with drug molecules during formulation of SD particles which cause faster drug dissolution by improving wettability of the drug particles (Chauhan, Shimpi, & Paradkar, 2005b).

Spironolactone (SP) is a specific aldosterone antagonist that is used as a potassium sparing diuretic; it shows poor solubility in gastrointestinal (GI) fluids, which can give rise to variation in its dissolution rate and incomplete and/or unpredictable bioavailability. To enhance SP bioavailability, several trials are made to improve both its solubility and its dissolution rate. Indeed, it was proven that SP dissolution rate could be enhanced by micronization (Chaumeil, 1998) or by complexation of SP with cyclodextrin (Kaukonen, Kilpeläinen, & Mannermaa, 1997; Soliman et al., 1997).

The objectives of this work are to: (a) formulate dry powder particulate system loaded with SP using polyglycolized glycerides (Gelucire 50/13 [G50], 44/14 [G44]) with silicon dioxide as pharmaceutical excipients and (b) investigate the influence of the matrices composition on the characteristics of the particulate formulation, namely, drug solubility evaluations, in vitro dissolution studies, particle size, and surface morphology.

MATERIALS AND METHODS

Materials

SP was generously supplied from (Kahira Pharmaceuticals & Chemical Industries Company, Cairo, Egypt). G50 (stearyl macroglycerides EP, solid pastilles, nominal mp = 47–50°C, HLB = 13) and G44 (lauroyl macroglycerides EP, semisolid, nominal mp = 38–44°C, HLB = 14) were a generous gift from Gattefosse s.a. (St. Priest, Cedex, France). Aerosil 200 was supplied by ICN Biomedicals, Inc. (OH, USA). All other chemicals and solvents were of analytical grade.

Preparation of Spironolactone Microparticles

A Buchi mini spray dryer model B-191 (Buchi Laboratoriums-Tecknik AG, Flawil, Switzerland) with standard nozzle was used to produce the dry powders of various formulations. SP in combination with G50 or G44 in different ratios was dissolved in sufficient amount of dichloromethane. To these clear solutions various silicon dioxide and propylene glycol (PG) amounts were slowly added to obtain uniform suspensions. The liquid feed was pumped continuously with the rate 5.0 mL/min. Both the inlet and the outlet temperatures were measured and controlled: inlet air temperature, 45°C; outlet temperature, 32°C. The suspensions were sprayed as atomized droplets by the force of the compressed air (air flow rate of 4 pound per square inch). The solution or suspensions were spray dried until no more particle powder could be obtained. The dried product was then collected, further dried and kept in a vacuum desiccator at room temperature. Placebo particle sample without drug entrapped was prepared using the same procedure. The composition of the different formulations is shown in Table 1.

Spray-Dried Particles Characterization Particle Size Distribution

The size distribution of the SD particles was evaluated by sieve analysis, using a vibrating shaker (AR400; Retsch, Haan, Germany) and six standard sieves (Scientific Instruments, UK) of 315, 250, 160, 100, 63, and 36 μm.

Entrapment Efficiency

The amount of SP that was entrapped in the particle powder after microencapsulation process was measured in triplicate using spectrophotometer (Ultrospec 2100 pro Spectrophotometer, England). The encapsulation efficiency of SP in particles was determined as the mass ratio of the entrapped SP to the theoretical amount of SP used in the preparation. SD particles equivalent to 25 mg of SP were weighed accurately and dissolved in suitable quantity of dichloromethane. The drug content was determined at 238 nm by spectrophotometer with suitable dilutions.

Scanning Electron Microscopic Analysis

The prepared microparticles' morphologies were examined under the scanning electron microscope (JSM-6360LV Scanning Microscope; Jeol, Tokyo, Japan). Before microscopy, the microparticle powders were mounted at carbon tape and were sputter-coated using gold (JFC-1100 fine coat ion sputter; Jeol). The photomicrographs were taken at an acceleration voltage of 20 kV (Alanazi, 2007).

Differential Scanning Calorimeter

Samples weighing approximately 5 mg were sealed in aluminum pans and analyzed using a TA 501 PC system with Shimadzu software programs (Tokyo, Japan). The samples were heated in an atmosphere of nitrogen and thermograms were obtained by heating at a constant heating rate of 10°C/min, in the 25–250°C temperature range. Indium was used as standard. Thermograms for SP, microparticles, and physical mixture (PM) were obtained.

Solubility Studies

Saturation solubility measurements of SP were carried out as follows: known excess amount of SP, its spray-drying particles, and PM were placed in glass stoppered flasks and 20 mL water was added to ach flask. The flasks were shaken at 40 strokes/min in a water bath at 25 ± 0.3°C for 48 h. The solutions were filtered through a membrane filter (0.45 μm),

TABLE 1
The Particulate Samples and Their Properties

Formulation ID	Composition SP : Gel : Aerosil : PG	Mean Diameter (μm)	Encapsulation Efficiency (%)	Production Yield (%)
F1	2:2:1:0	109.6	93.9	75.2
F2	1:2:2:0	53.8	94.9	73.1
F3	1:3:2:0	60.6	92.5	72.0
F4	1:0:1:0	83.8	96.7	70.0
F5	2:4:1:0	Aggregate	99.5	—
F6	2:0:1:0	50.4	95.7	71.3
F7	1:1:1:0	42.5	93.7	72.5
F8	2:2:3:0	77.3	96.8	70.0
F9	1:1:1:1	128.6	94.7	68.5
F10	1:1:1:1.5	65.9	93.8	71.5
F11	1:1:1:0.5	96.4	92.8	70.5
F12	1:1:1	22.3	90.5	73.2
F13	1:2:2	79.2	97.7	72.8
F14	1:3:1	74.8	94.7	73.0
F15	2:2:1	125.6	95.7	71.5
F16	2:2:3	27.5	98.3	72.8

Formulation 1–11 containing G44/14, Formulation 12–16 containing G50/13, prepared using spray-drying technique.

diluted suitably, and the dissolved drug was analyzed spectrophotometrically at 238 nm. This experiment was done in triplicate.

In Vitro Dissolution Studies

The dissolution profiles of SP from spray-drying particles were examined in triplicate using a dissolution tester (DT6, Erweka, Germany). The samples equivalent to 25 mg SP were placed in the dissolution vessel containing 1,000 mL of 0.1 N HCl maintained at 37 ± 0.5°C and stirred at 75 rpm (USP 23). Samples were collected periodically and replaced with a fresh dissolution medium. After filtration through a membrane filter (0.45 μm), concentration of SP was determined spectrophotometrically at 238 nm.

RESULTS AND DISCUSSION

The SD particulate system showed good flow properties with yield of 68.5–75.2% wt/wt. The entrapment efficiency was found to be in the range from 90.5 to 99.5% (data are shown in Table 1). Therefore, the spray-drying method used in this study appears applicable for the preparation of solid dispersions without affecting drug content.

The microphotographs of SD particulate formulations are shown in Figure 1. Pure SP consisted of a mixture of some large crystal with microparticles (data not shown), which might have been generated because of micronization or any other size reduction process at the time of manufacturing. SD particles, on the other hand, appeared as irregular-shaped clusters of waxy matrices. All the presented images in Figure 1 are clearly made of particle aggregates. In images C (F4), E (F10), and F (F13), small portions of separated monoparticles are seen. Based on the scale, they all lie in a size range of around 2–3 μm but with irregular shapes.

The thermal behavior of mixtures of drug and excipients are of important interests in pharmaceutical technology, and this can normally be processed by differential scanning calorimetry (DSC). The obtained information such as melting, recrystallization, decomposition, or a change in heat capacity could help to ascertain the physicochemical status of the entrapped drug inside the excipient and assess the interaction amongst different components during the fabrication process and may help to explain relevant properties of in vitro release. Figure 2A–C depicted the DSC thermograms of pure material including SP, Aerosil, G44 and G50, PMs, as well as various drug-loaded particulate formulations. All the pure material gave the peak relevant to the phase transition temperatures, for instance, the endothermic peak of melting pure SP at about 216°C, the melting transition temperature of G44 and G50 at about 46 and 52°C. Although Aerosil® did not display any thermal event in the examined temperature range, the result of no detectable melting endotherm peak of SP in all types of SD particulate formulations indicated that the spray-drying process resulted in higher energy amorphous products showing amorphous characteristics over a wider composition range. The drug formulated existed in an amorphous or disordered-crystalline drug

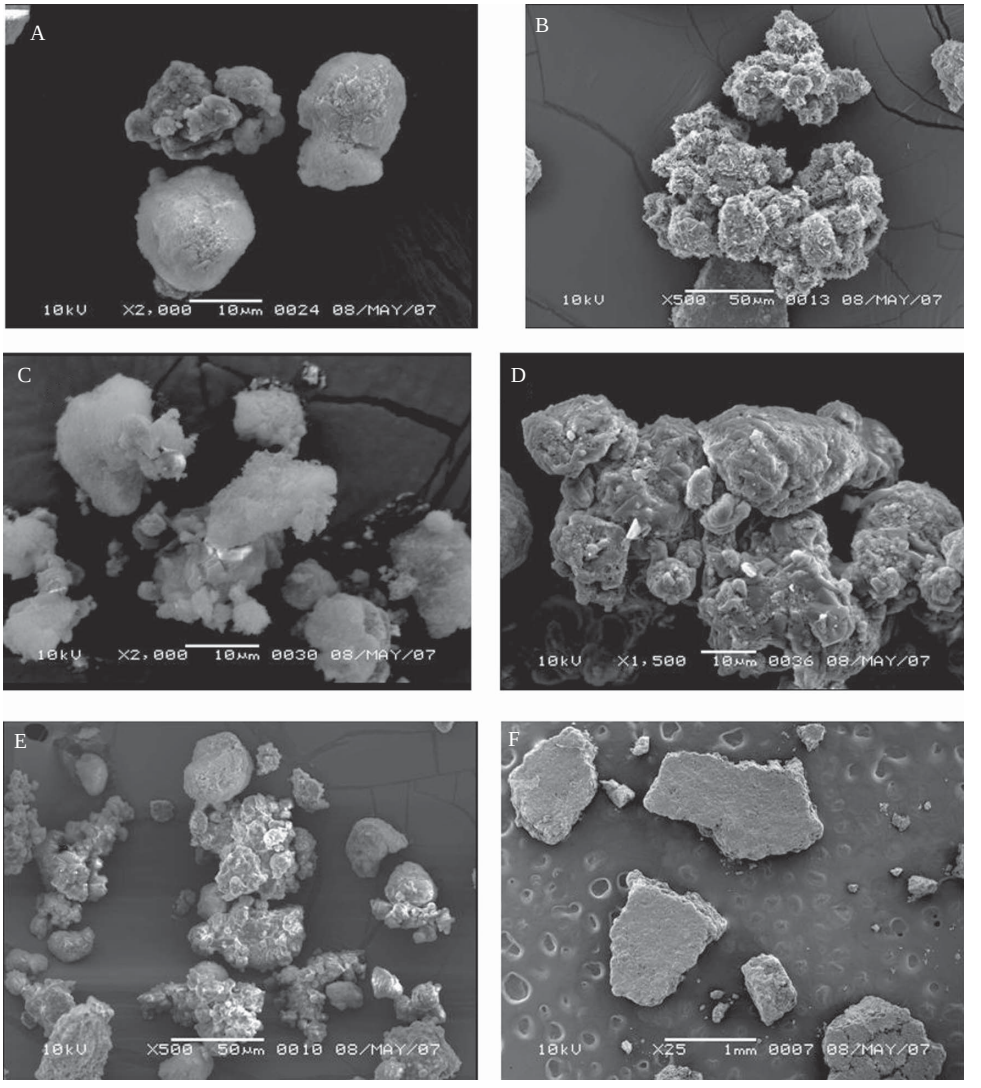

FIGURE 1. Photomicrographs taken by scanning electron microscopy for the spray-dried microparticles. (A) F1, (B) F3, (C) F4, (D) F7, (E) F10, (F) F13.

phase of a molecular dispersion or a solid solution state in matrix during rapid drying of the slurry droplets that was agreed with the general results of spray drying (Corrigan, 1995).

The DSC thermograms after 1 year of storage in desiccators at ambient temperature remained almost unchanged and no significant difference in their enthalpy change was determined. This indicates that such SD formulae of SP obviate the major potential problem of recrystallization in the polymer matrix which leads to loss of much of the achieved dissolution enhancement (data were not shown due to the high similarity in the DSC curves).

All the tested samples showed increase in drug solubility over crystalline SP (Table 2). F16 (2:2:3, SP:G50:Aerosil) and F8 (2:2:3, SP:G44:Aerosil) showed the highest saturation solubilities of 52.21 and 42.9 µg/mL, respectively. Both shared the same composition ratio and vary only in the type of fatty material.

The increase in the saturation solubility of SP from the SD particulate system might be attributed to factors such as a reduction in the particle size of the drug in the matrix, increase in the surface area, decrease in crystallinity, and an increase in the solubility of the drug in the presence of the lipid carriers (Barakat, 2006a; Chauhan, Shimpi, & Paradkar, 2005a; Serajuddin, 1999). Similar observations have been reported for solid dispersions of naproxen in PEG s and nifedipine in G50 with Pluronic F-68 (Mura, Manerioli, Bramanti, & Ceccarelli, 1996; Vippagunta, Maul, Tallavajhala, & Grant, 2002). Pluronic F-68 and G50 may enhance the solubility of poorly water-soluble drug in spray drying or PM either by micellar solubilization or by reducing the hydrophobic interaction or by both processes.

Dissolution profiles of crystalline SP and SD particulate system in 0.1 N HCl are shown in Figures 3–5. There is a significant increase in the dissolution rate as compared with SP. The cumulative percent amount dissolved in 60 min in the case of pure SP was only 45%, whereas it was 72–100% for SD particles containing G44 and Aerosil, and 92–100% for those containing G50 and Aerosil.

Figure 3 represents the dissolution profiles of F1–F8 compared with the same dose of pure SP powder. All the tested formulae showed significant enhancement in both the extent and the rate of dissolution except for F5 which comprises a low G44:Aerosil ratio of 4:1. Comparing the dissolution profiles of F1, F7, and F8, one can conclude that as the Aerosil ratio increases, the enhancement of dissolution profiles increases too and a minimum of 1:1 G44:Aerosil ratio is required for the enhancement. The tremendous enhancement in the dissolution profile of F2 (1:2:2; SP:G44:Aerosil) over F5 (2:4:1, SP:G44:Aerosil) ensures this important role of Aerosil. It was found that the addition of PG did not improve the dissolution behavior generally. F7 (with no PG) exhibited superior

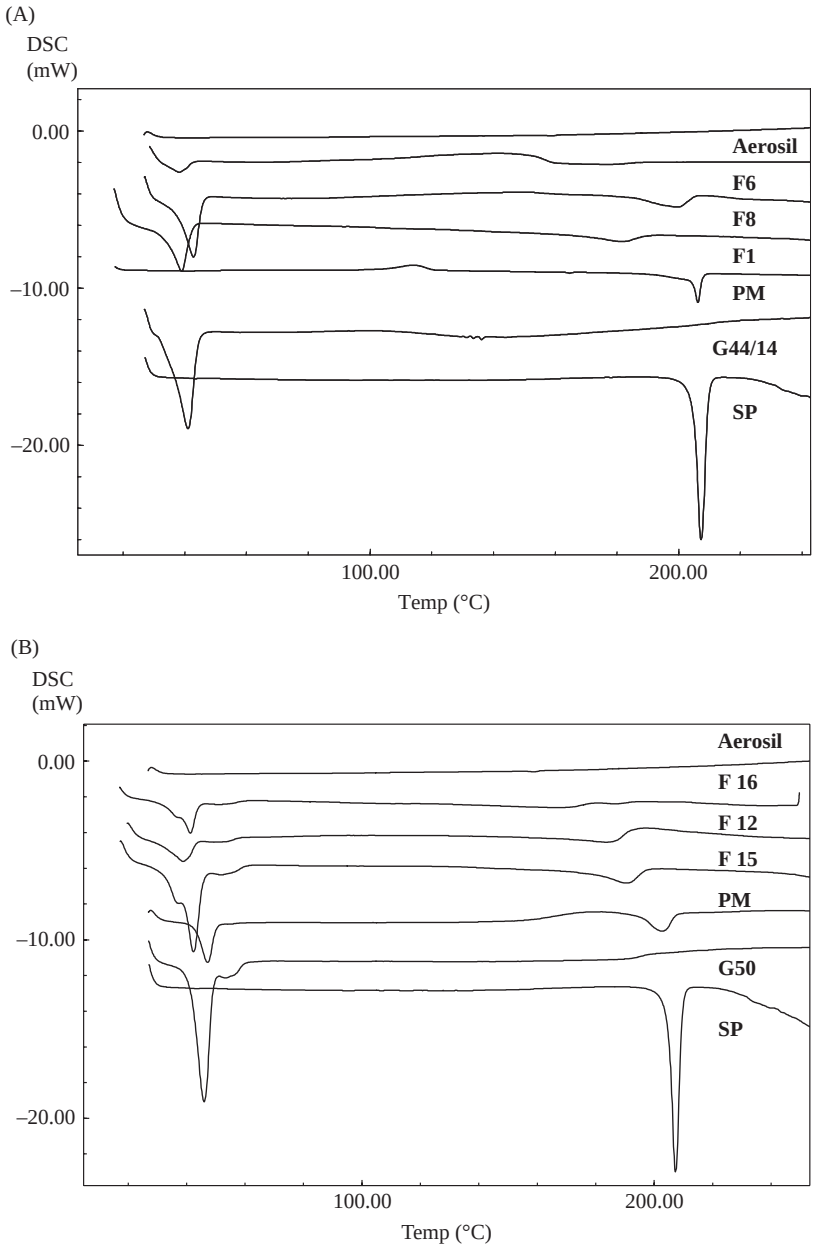

FIGURE 2. (A–C) Differential scanning calorimeter thermograms of spironolactone and various spray-dried particulate formulations. PM, physical mixture.

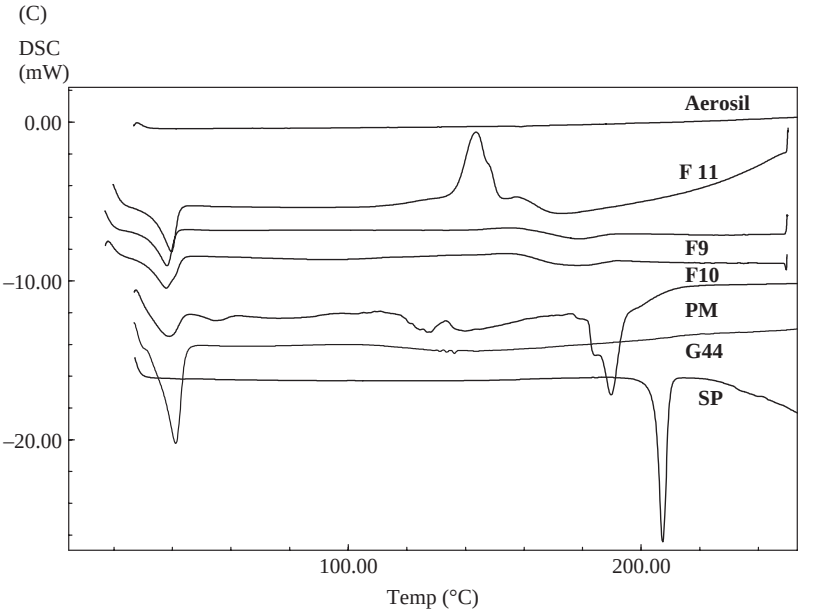

FIGURE 2. *(Continued).*

TABLE 2
Saturation Solubility of Different Formulations of Spironolactone Tested in Distilled Water at 25 ± 0.5°C

Type of Formulations	Saturation Solubility (μg /mL)[a]
Pure SP	28.64 ± 0.86
F8	42.90 ± 0.34
PM F8	31.38 ± 0.73
F4	31.95 ± 0.25
F16	52.21 ± 0.65
F10	39.51 ± 0.70
PM F16	30.61 ± 0.63
F3	32.62 ± 1.76
F14	34.76 ± 0.98

[a]Mean ± *SD*; *n* = 3.

dissolution behavior over F9, F10, and F11, having the same composition ratios as F7 and containing different ratios of PG (Figure 4). However, a direct proportion was found between the increase in the PG ratio and the enhancement of the dissolution behavior among the three formulae.

Figure 5 represents the dissolution behavior of F12–F16 containing different SP:G50:Aerosil ratios compared with the pure SP powder. It is clear that all the formulae showed significant increase in the cumulative percent amount dissolved in 60 min (92–100%) compared with pure SP (45%). The cumulative percent dissolved after 20 min were 37, 71, 81, 96, 92, and 100 for SP, F12, F13, F14, F15, and F16, respectively.

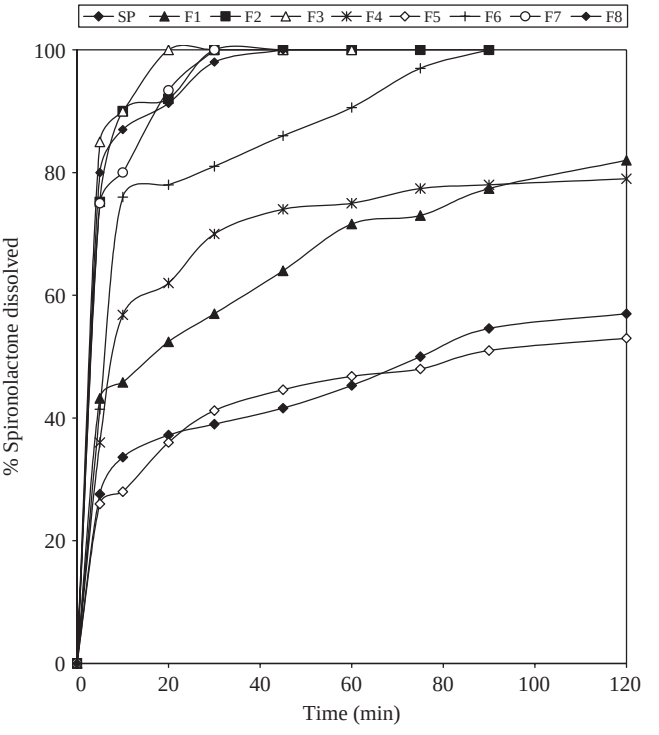

FIGURE 3. Spironolactone dissolved in 0.1 N HCl from spray-dried G44: Aerosil particles.

The major factor affecting the dissolution enhancement is the magnitude of G50 in the formula. The increase in the ratio of G50 in the formulae is accompanied by increase in the rate of dissolution.

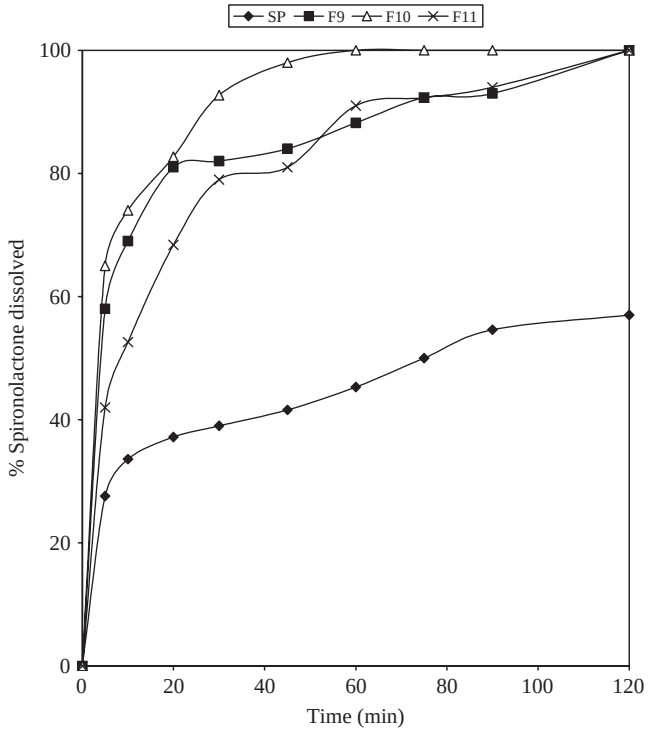

FIGURE 4. Spironolactone dissolved in 0.1 N HCl from spray-dried G44: Aerosil: PG particles.

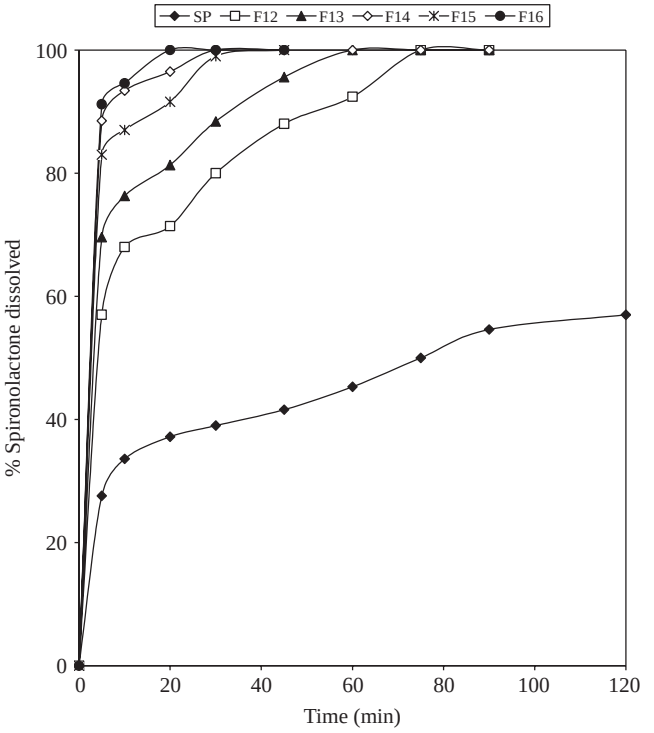

FIGURE 5. Spironolactone dissolved in 0.1 N HCl from spray-dried G50: Aerosil particles.

Generally, SD particulate systems showed differences in the extent of drug release at the 5-min time point (25–90%). All of the SD particulate systems exhibited a higher burst release of SP.

The increase in dissolution of drug was probably attributed to an improvement of wettability of the drug particles (Broman, Khoo, & Taylor, 2001; Leuner & Dressman, 2000), emulsifying effect of carriers, local solubilization by the excipients in the diffusion layer (Vippagunta et al., 2002), presence of amorphous form of drug (Hancock & Parks, 2000), or the inherently higher rate of dissolution of the soluble component of spray-drying particulate formulations, which would pull along the more insoluble but finely mixed drug into the dissolution medium (Dordunoo et al., 1991; Passerini et al., 2002). Also due to the presence of –OH groups on the microparticle surface, Aerosil can form a great number of hydrogen bonds with the dissolution medium, absorbing water on the particle surface. The gelation ability will probably be greater as the specific surface area and the amount of Aerosil increase. It could be assumed that SP dissolves in this gel layer rather than in the dissolution medium; then the drug can easily diffuse out of the swelled gel causing the improvement of the release rate (Albertini, Passerini, González-Rodríguez, Perissutti, & Rodriguez, 2004). It was reported that the mechanism for G44 to improve the bioavailability of a poorly water-soluble drug is related to its ability to act as a dispersing or emulsifying agent for the liberated drug (Serajuddin, 2002).

This enhancement in the dissolution profile might lead to improvement in the bioavailability of SP and any poorly water-soluble drugs because it forms a very fine emulsion, improves the wettability of the drug, and increases the solubility of the drug when it contacts with GI fluid at 37°C (Aungst, Nguyen, & Rogers, 1997; Barakat, 2006b; Hauss, Fogal, & Ficorilli, 1998; Pozzi, Longo, Lazzarini, & Carenzi, 1991; Sheen, Kim, Petillo, & Serajuddin, 1991).

CONCLUSION

Microparticles containing sparingly soluble SP with combination of safe excipients G44, G50, and Aerosil® 200 were formulated successfully by spray-drying technique. The effect of different formulation variabilities on the particle morphology, thermal behavior, and drug-entrapped capability, as well as the drug release was investigated. SD particulate formulations exhibited dramatical improvement in initial rate as well as the extent of in vitro drug dissolution.

ACKNOWLEDGMENTS

The authors thank the Research Center at College of Pharmacy, King Saud University, for providing facilities to carry out the study (Grant C.P.R.C.214).

REFERENCES

Alanazi, F. K. (2007). Evaluation of spray and freeze dried excipient bases containing disintegration accelerators for the formulation of metoclopramide orally disintegrating tablets. *Saudi Pharm. J., 15*, 105–119.

Albertini, B., Passerini, N., González-Rodríguez, M. L., Perissutti, B., & Rodriguez, L. (2004). Effect of Aerosil® on the properties of lipid controlled release microparticles. *J. Control. Release, 100*, 233–246.

Asada, M., Takahashi, H., Okamoto, H., Tanino, H., & Danjo, K. (2004). Theophylline particle design using chitosan by the spray drying. *Int. J. Pharm., 270*, 167–174.

Aungst, B. J., Nguyen, N., & Rogers, N. J. (1997). Amphiphilic vehicles improve the oral bioavailability of a poorly soluble HIV protease inhibitor at high dose. *Int. J. Pharm., 156*, 79–88.

Barakat, N. S. (2006a). Etodolac-liquid filled dispersion into hard gelatin capsules: An approach to improve dissolution and stability of etodolac formulation. *Drug Dev. Ind. Pharm., 32*, 865–876.

Barakat, N. S. (2006b). Etodolac-liquid filled dispersion into hard gelatin capsules II: Enhancement of bioavailability and the anti-inflammatory effect. *Bull. Fac. Pharm. Cairo Univ., 44*, 259–269.

Billon, A., Bataile, B., Cassanas, G., & Jacob, M. (2000). Development of spray-dried acetaminophen microparticles using experimental designs. *Int. J. Pharm., 203*, 159–168.

Broadhead, J., Rouan, S. K., & Rhodes, C. T. (1992). The spray drying of pharmaceuticals. *Drug Dev. Ind. Pharm., 8*, 1169–1206.

Broman, E., Khoo, C., & Taylor, L. S. (2001). A comparison of alternative polymer excipients and processing methods for making solid dispersions of a poorly water-soluble drug. *Int. J. Pharm., 222*, 139–151.

Chauhan, B., Shimpi, S., & Paradkar, A. (2005a). Preparation and evaluation of glibenclamide-polyglycolized glycerides solid dispersions with silicone dioxide by spray drying technique. *Eur. J. Pharm. Sci., 26*, 219–230.

Chauhan, B., Shimpi, S., & Paradkar, A. (2005b). Preparation and characterization of etoricoxib solid dispersions using lipid carriers by spray drying technique. *AAPS PharmSciTech, 6*, E405–E412.

Chaumeil, J. C. (1998). Micronization: A method of improving the bioavailability of poorly soluble drugs. *Methods Find. Exp. Clin. Pharmacol., 20*, 211–215.

Chiou, W. L., & Riegelman, S. (1971). Pharmaceutical application of solid dispersion systems. *J. Pharm. Sci., 60*, 1281–1302.

Corrigan, D. O. (1995). Thermal analysis of spray dried products. *Thermochin. Acta, 248*, 245–258.

Dollo, G., Le Corre, P., Guerin, A., Chevanne, F., Burgot, J. L., & leverge, R. (2004). Spray-dried redispersible oil-in-water emulsion to improve oral bioavailability of poorly soluble drugs. *Eur. J. Pharm. Biopharm., 19*, 273–280.

Dordunoo, S. K., Ford, J. L., & Rubinstein, M. H. (1991). Preformulation studies on solid dispersions containing triamterene or temazepam in polyethylene glycols or gelucire 44/14 for liquid filling of hard gelatin capsules. *Drug Dev. Ind. Pharm., 17*, 1685–1713.

Ford, J. L. (1986). The current status of solid dispersions. *Pharm. Acta Helv., 61*, 69–88.

Giunchedi, P., & Conte, U. (1995). Spray drying as a preparation method of microparticulate drug delivery systems: An overview. *STP Pharm. Sci., 5*, 276–290.

Hancock, B. C., & Parks, M. (2000). What is the true solubility advantages for amorphous pharmaceuticals? *Pham. Res., 17*, 397–404.

Hauss, D. J., Fogal, S. E., & Ficorilli, J. V. (1998). Lipid-based delivery systems for improving the bioavailability and lymphatic transport of a poorly water-soluble LTB4 inhibitor. *J. Pharm. Sci., 87*, 164–169.

He, P., Davis, S. S., & Illim, L. (1999). Chitosan microspheres prepared by spray drying. *Int. J. Pharm., 187*, 53–65.

Kaukonen, A. M., Kilpeläinen, I., & Mannermaa, J. P. (1997). Water-soluble β-cyclodextrins in pediatric oral solutions of spironolactone: Solubilization and stability of spironolactone in solutions of β-cyclodextrin derivatives. *Int. J. Pharm., 159*, 159–170.

Lee, S. W., Kim, M. H., & Kim, C. K. (1999). Encapsulation of ethanol by spray drying technique: Effect of sodium lauryl sulfate. *Int. J. Pharm., 187*, 193–198.

Leuner, C., & Dressman, J. (2000). Improving drug solubility for oral delivery using solid dispersions. *Eur. J. Pharm. Biopharm., 50*, 47–60.

Masters, K. (1991). *Spray-drying handbook*. New York: Longman Scientific and Technical.

Moretti, M. D. L., Gavini, E., Juliano, C., Pirisino, G., & Giunchedi, P. (2001). Spray-dried microspheres containing ketoprofen formulated into capsules and tablets. *J. Microencapsul., 18*, 111–121.

Muller, C. R., Bassani, V. L., Pohlman, A. R., Michalowski, C. B., Petrovick, P. R., & Guterres, S. S. (2000). Preparation and characterization of spray-dried polymeric nanocapsiles. *Drug Dev. Ind. Pharm., 26*, 343–347.

Mura, P., Manerioli, A., Bramanti, G., & Ceccarelli, L. (1996). Properties of solid dispersions of naproxen in various polyethylene glycols. *Drug Dev. Ind. Pharm., 22*, 909–916.

Paradkar, A. R., Chauhan, B., Yamamura, S., & Pawar, A. P. (2003). Preparation and characterization of glassy celecoxib. *Drug Dev. Ind. Pharm, 29*, 739–744.

Passerini, N., Perissutti, B., Moneghini, M., Voinovich, D., Albertini, B., Cavallari, C., & Rodriguez, L. (2002). Characterization of carbamazepine-Gelucire 50/13 microparticles prepared by a spray-congealing process using ultrasounds. *J. Pharm. Sci., 91*, 699–707.

Pozzi, F., Longo, A., Lazzarini, C., & Carenzi, A. (1991). Formulations of Ubidearenone with improved bioavailability. *Eur. J. Pharm. Biopharm., 37*(4), 243–246.

Serajuddin, A. T. M. (1999). Solid dispersion of poorly water-soluble drugs: Early promise, subsequent problems, and recent breakthroughs. *J. Pharm. Sci., 88*, 1058–1066.

Serajuddin, A. T. M. (2002). Poorly aqueous soluble drugs and surface-active solid dispersion carriers. *Gattefosse Newsletter: Formulink, 7*, 1–4.

Sheen, P. C., Kim, E. I., Petillo, J. J., & Serajuddin, A. T. M. (1991). Bioavailability of a poorly water-soluble drug from tablet and solid dispersion in humans. *J. Pharm. Sci., 80*, 712–714.

Soliman, O., Kimura, K., Hirayama, F., Uekama, K., El-Sabbagh, H., Abd El-Gawad, A., & Hashim, F. (1997). Amorphous spironolactone-hydroxypropylated cyclodextrine complexes with superior dissolution and oral bioavailability. *Int. J. Pharm., 149*, 73–83.

Torchilin, V. P., Lukyanov, A. N., Gao, Z., & Papahadjopoulos-Sternberg, B. (2003). Immunomicelles: Targeted pharmaceutical carriers for poorly soluble drugs. *Proc. Natl. Acad. Sci. USA, 100*(10), 6093–6044.

Vippagunta, S. R., Maul, K. A., Tallavajhala, S., & Grant, D. J. W. (2002). Solid-state characterization of nifedipine solid dispersions. *Int. J. Pharm., 236*, 111–123.