Optimization of Spray-Dried and -Congealed Lipid Micropellets and Characterization of Their Surface Morphology by Scanning Electron Microscopy

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Lipid micropellets prepared from glycerides and phospholipids may be a physiological drug carrier system for improving the intestinal absorption of lipophilic drugs. They can be prepared by spray-drying and spray-congealing processes. In this study, formulation and optimization parameters of spray-dried and -congealed lipid pellets in the micro- and nanometer size were investigated. The rapid evaporation of solvents from the droplets, which in turn causes a rapid solidification, influenced the crystalline structures of spray-dried glycerides. Moreover, solvents, the chain length, and the type of lipids and drugs used in the formulations of spray-dried micropellets affected the surface morphology of the micropellets. In contrast to the variations of the surface structure of spray-dried micropellets, formulated spray-congealed micropellets possessed smooth surface properties. The surface morphology and microstructure of both types of micropellets were characterized by SEM.

KEY WORDS: lipid micropellets; spray-drying; spray-congealing; steroid carriers; scanning electron microscopy; triglyceride.

INTRODUCTION

Since lipid (fats) play an important role in the cotransport and absorption of lipophilic substances from the gastrointestinal tract, their use in oral drug delivery has an extended application. Lipid drug delivery systems based on different types of fats such as lipid micropellets, microemulsions, liposomes, and Pharmacosomes are widely studied in order to enhance oral drug absorption (1).

Lipid micropellets possess some advantages as a solid dosage form by containing well-defined physiological lipids such as mono-, di-, and triglycerides and phospholipids.

The first stage of lipid absorption is their degradation by lipolytic enzymes (1). Due to their ultrafine particle size, lipid micropellets provide a large surface area to these enzymes in the gastrointestinal tract, thereby avoiding incomplete enzymatic degradation of lipids and enhancing absorption of drugs in the hydrolyzed lipid phases via the lymphatic pathway (1).

Lipid micropellets can be prepared by conventional spraying processes, i.e., spray-drying and spray-congealing. By using these techniques micropellets having spherical shapes with smooth surfaces and good flow properties can be prepared. These properties are advantageous when sprayed micropellets are filled into hard gelatin capsules.

Spray-drying (2) is the transformation of a feed from a fluid state into a dried solid particulate form by spraying the feed into a hot drying medium. It is also a single-stage, rapid, batch or continuous particle-processing operation involving drying (3,4).

Spray-congealing (cooling) relies on the same principle and can be applied to heat-stable substances. Without using the solvent, the feed is melted and the molten feed is sprayed into an ambient temperature (3). By using this technology lipids that have a sufficiently high melting point can be spray-congealed to yield fine powdered fat pellets. However, a melt (liquid form of a fat) can crystallize in different polymorphic forms when different cooling rates are applied. Especially rapid cooling rates crystallize many of the triglycerides in their unstable α-form (5,6). In this form trans-oriented chains eventually predominate and an α-form crystal nucleus having vertically disordered chains is obtained (7). Consequently, because of the rapid cooling rate in spray-congealing, such lipids may be transformed into their unstable polymorphic structures.

Spray-drying has been widely used for drying heat-sensitive drugs and foods because exposure to elevated temperatures is short, normally ranging from 5 to 30 sec. As a result, solvents are evaporated rapidly from the sprayed droplets (2–4,8). However, rapid solvent evaporation may influence and modify the crystalline structure of some substances.

In an usual crystallization process, the crystal habit and morphological appearance of triglycerides such as tristearin and tripalmitin are affected differently by various solvents. Only their stable β-form is independent of the solvent (9). Apart from the influence of solvents, temperature and the chain-length variations complicate the phase transition of lipids (7). Therefore, the appearance of various crystal forms of triglycerides and their surface morphology are technologically important, while variations in crystal forms determine the texture of final products.

Thermal analysis microscopy (TAM)[4] enables the simultaneous microscopic observation of samples on a hot stage during heating and cooling and recording of differential calorimetric data. According to the TAM results, the α-form of triglycerides (tristearin and tripalmitin) reveals a round spherulitic pattern. The β′-form shows a loosely packed spherulite and the β-form illustrates large coagulated platelets (10).

On the basis of these observations, we addressed the question of whether spraying processes influence the microstructure of lipid micropellets. Although there is extensive information on the polymorphic and crystallization proper-

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[4] Abbreviations used: SEM(s), scanning electron micrograph(s); bp, boiling point; temp, temperature; Dyn 116, Dynasan 116; Dyn 118, Dynasan 118; Trip, Tripalmitin; Trist, Tristearin; Comp 888, Compritol 888; Lec, Sojalecithin; ECY, estradiol cypionate; MPA, medroxyprogesterone acetate; TAM, thermal analysis microscopy.

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ties of fats, little is known about their micro- and/or infrastructure when they are used as drug carriers.

In this study we prepared lipid micropellets containing steroids by spray-drying and spray-congealing techniques and examined by SEM the effect of formulation parameters, i.e., spraying techniques, type and concentration of lipids and solvents used, on the surface morphology of sprayed micropellets.

MATERIALS AND METHODS

In the formulations of lipid micropellets the following substances and solvents were used: Dynasan 116 (glycerol tripalmitate >95%, mp 60–64°C) and Dynasan 118 (glycerol tristearate >95%, mp 69–71°C) from Dynamit-Nobel Chemie (Troisdorf, West Germany); Precirol WL 2155 ATO (glycerol mono-di-tristearate, mp 62–66°C), Precirol ATO-5 (glycerol mono-di-tri-palmitostearate, mp 52–55°C), and Compritol-888 (glycerol behenate, mp 70–73°C) from Gattefossé (Saint Priest, France); GTS-33 (glycerol tristearate, mp 59–60°C) from Hefti AG (Zürich, Switzerland); tristearin (65%, mp 58–63°C) and tripalmitin (95%, mp 58–64°C) from Fluka AG (Buchs-Switzerland); Sojaphosphatid NC 95H (Sojalecithin) from Nattermann Chemie GmbH (Köln, West Germany); estradiol 17-β cypionate from Upjohn Inc. (Michigan) and Hoechst AG (Frankfurst, West Germany); medroxyprogesteron acetate from Upjohn Inc. (Michigan); and chloroform and methylene chloride (p.a) from E. Merck (Darmstadt, West Germany).

In the spray-drying process a Büchi 190 Mini-Spray Dryer (Büchi Laboratoriums, Technik AG, Flawil, Switzerland) with a 0.5-mm nozzle cap was used. As a modification from the standard form, in order to collect ultrafine particles, one additional cyclone, product collector and an outlet filter were used.

Solvents and their mixtures used in the solubilization of lipids are given in Table I. By using these solvents 1, 5, 10, 15, 20, and 25% solutions of lipids were prepared and sprayed. In order to prevent the aggregation and to improve the flow properties of sprayed product, lecithin was added to the formulations. While the concentration and the viscosity of the sprayed solutions may influence the surface properties of the micropellets, the amounts of lecithin (3.5%) and steroids (10%) added to the formulations were determined over the solid triglyceride amount. The operating conditions of the spray-dryer such as inlet/outlet temperature, sucking rate of aspiration, pump performance of the feed solution, and spray flow rate were optimized first by spraying the solutions of above mentioned glycerides alone and then by spraying their mixtures with lecithin and with drugs. Under these conditions an inlet temperature which was below the melting point of lipids and above the boiling point of solvent was maintained. Some of the optimized formulations dealing with spray-drying are shown in Table II.

Table I. Solvents Used in Spray-Drying Process

Solvent	Ratio (v/v)	bp (°C)
A. Chloroform/methylene chloride	(1:1)	47
B. Chloroform/methylene chloride	(1:2)	44
C. Methylene chloride		40

In the spray-congealing process the same spray equipment with a prototype spray nozzle (0.5-mm nozzle cap) (Büchi Laboratoriums, Technik AG, Flawil, Switzerland) was used. The identical amount of lipids (or lipid-drug mixture) as in spray drying were melted 10°C above their melting points in the specially thermostated container of spray nozzle. The molten feed was spray-congealed by using microfiltered pressure air into the spray cylinder, which was at room temperature. In order to compare both of the spraying processes, the similar types and mixtures of lipids with the same concentrations were used. The formulations dealing with spray-congealing are illustrated in Table III.

SEMs were taken one day after the preparation of the formulations (called "fresh samples") with a Hitachi S-700 scanning electron microscope. During this time samples were stored at -15 ± 1°C in well-closed containers. Prior to the microscopy, the samples were mounted on aluminum stubs and covered with gold/palladium (200 Å) by using a Diode sputtering device (Balzers, Lichtenstein).

RESULTS AND DISCUSSION

The most favorable triglyceride concentrations for spray-drying are found to be 20 and 25% for the formulations containing Dynasan 116, Dynasan 118, Tristearin, Tripalmitin, and GTS-33. Above these concentrations it is not possible to spray triglyceride solutions because of their high viscosity. The maximum Compritol 888 concentration which can be spray-dried is 1.5% because of its poor solubility in solvents. Attempts for preparing spray-dried micropellets with both types of Precirol are unsuccessful in all concentrations and solvents examined. SEMs of spray-dried lipid micropellets dealing with the formulations are illustrated in Figs. 1 to 10.

Formulations 1 to 3, which are spray-dried from solvent A and B, show mainly amorphous structures. In spite of added lecithin, most of the micropellets are aggregated. The same results are obtained with formulations 4 and 5 without any detectable change in the surface morphology.

Formulations 6 (Fig. 1) to 8 display the same surface properties as in formulations 1 to 5. A noticeable difference in the spray-dried end product is that they are less electrostatically charged than the formulations 1 to 5. The use of different solvents (formulations 6 and 7) and the use of the same solvents with the spray concentration of 20 to 25% (formulations 6 and 8) do not show any significant improvements in the surface morphology of micropellets with tripalmitin.

The spherical structure of micropellets can only be observed to some extent in formulations 9 to 14. This is shown in Figs. 2 and 3, dealing with formulations 9 and 12, which are composed of 20 to 25% Tristearin with equal amounts of lecithin, respectively. Their surfaces are smoother than the formulations containing Dynasan 116 and Tripalmitin (Fig. 1).

A drastic change in the surface morphology of the spray-dried micropellets with GTS-33 can be observed in Fig. 4 (formulation 15). The influence of solvent on the surface structure of GTS-33 is also very clear in Figs. 5 and 6

Table II. Formulation Parameters of Spray-Dried Lipid Micropellets

FN[a]	Spray concentration (%)	Composition and ratio (%)	Solvent (ad 100 ml)	Inlet temp (°C)	Outlet temp (°C)
1	20	Dyn 116:Lec (100:3.5)	A	52–53	35–36
2	20	Dyn 116:Lec (100:3.5)	B	51–52	35–36
3	25	Dyn 116:Lec (100:3.5)	A	53–54	36–37
4	20	Dyn 118:Lec (100:3.5)	A	53–54	36–37
5	20	Dyn 118:Lec (100:3.5)	B	52–53	35–36
6	20	Trip:Lec (100:3.5)	A	52–53	36–37
7	20	Trip:Lec (100:3.5)	B	52–53	36–37
8	25	Trip:Lec (100:3.5)	A	52–53	36–37
9	20	Trist:Lec (100:3.5)	A	51–52	35–36
10	20	Trist:Lec (100:3.5)	B	51–52	36–37
11	20	Trist:Lec (100:3.5)	C	49–50	34–35
12	25	Trist:Lec (100:3.5)	A	50–51	36–37
13	25	Trist:Lec (100:3.5)	B	50–51	36–37
14	25	Trist:Lec (100:3.5)	C	48–49	34–35
15	20	GTS-33:Lec (100:3.5)	A	51–52	36–37
16	20	GTS-33:Lec (100:3.5)	B	48–49	34–35
17	20	GTS-33:Lec (100:3.5)	C	48–49	34–35
18	20	GTS-33:Lec:ECY (100:3.5:10)	A	51–52	36–37
19	20	GTS-33:Lec:MPA (100:3.5:10)	A	52–53	36–37
20	1.5	Comp 888 (100)	A	58–59	39–40
21	1.5	Comp 888:Lec (100:3.5)	A	58–59	39–40
22	1.5	Comp 888:Lec:ECY (100:3.5:10)	A	59–60	40–41
23	1.5	Comp 888:Lec:MPA (100:3.5:10)	A	59–60	40–41

[a] Formulation number.

(formulations 16 and 17). Even though formulations 9 and 15, 10 and 16, and 11 and 17 contain the same triglyceride (mainly tristearin) and the concentrations of lipids and solvents used are the same, similar surface structures are not obtained.

The spray-dried micropellets from solvent A containing GTS-33 show the best results with almost spherical shape and smooth surface also with good flow properties (Fig. 4). Subsequently GTS-33 was selected for drug incorporation. As presented in Figs. 7 and 8 (formulations 18 and 19), among added steroids, estradiol cypionate does not alter the surface structure as much as medroxyprogestrone acetate.

Compritol 888 (glycerol behenate) and its mixture with lecithin (formulations 21 and 22) also give amorphous structures as shown in Fig. 9 (formulation 21). In spite of that, estradiol cypionate (Fig. 10) and medroxyprogestrone acetate were incorporated in this glyceride in order to compare the results with spray-congealed micropellets (formulations 22 and 23). With both of them amorphous structures are obtained.

Table III. Formulation Parameters of Spray-Congealed Lipid Micropellets

Formulation No.	Composition and ratio (%)
24	GTS-33 (100)
25	GTS-33:Lec (100:3.5)
26	GTS-33:Lec:ECY (100:3.5:10)
27	Comp 888 (100)
28	Comp 888:Lec (100:3.5)
29	Comp 888:Lec:ECY (100:3.5:10)
30	Trist (100)

According to the spray-drying results and in order to compare both of the processes, spray-congealed lipid micropellets are prepared with the following substances: GTS-33, Tristearin, Compritol 888, and their combination with leci-

Fig. 1. SEM of freshly spray-dried micropellets dealing with formulation 6.

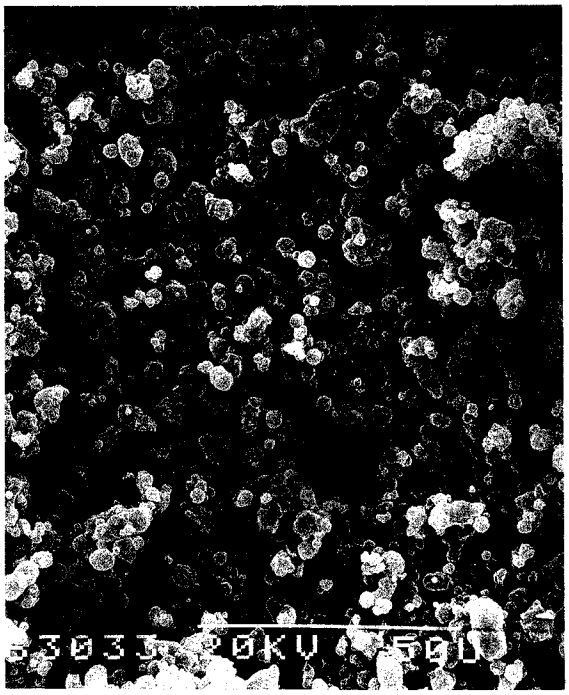

Fig. 2. SEM of freshly spray-dried micropellets dealing with formulation 9.

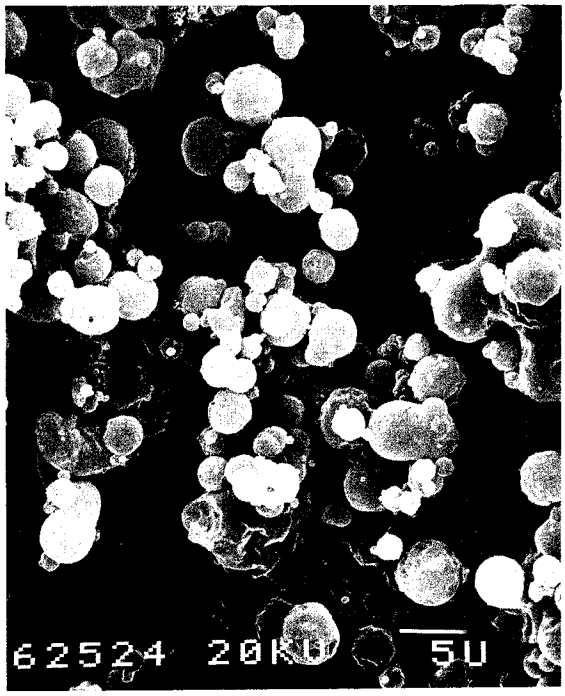

Fig. 4. SEM of freshly spray-dried micropellets dealing with formulation 15.

thin and estradiol cypionate (Table III). SEMs of spray-congealed lipid micropellets between formulation 24 and formulation 29 are illustrated in Figs. 11 to 16.

Spray-congealed micropellets containing GTS-33 (Fig. 11), Tristearin, and Compritol 888 (Fig. 14) acquire the same surface conformation. Spherical micropellets having smooth surfaces are obtained, although they have large particle size distributions. As illustrated in Figs. 12 and 15 (formulations 25 and 28), the addition of lecithin improves the surface morphology. As shown in Figs. 13 and 16 (formulations 26 and 29), the addition of estradiol cypionate does not alter their surface structure.

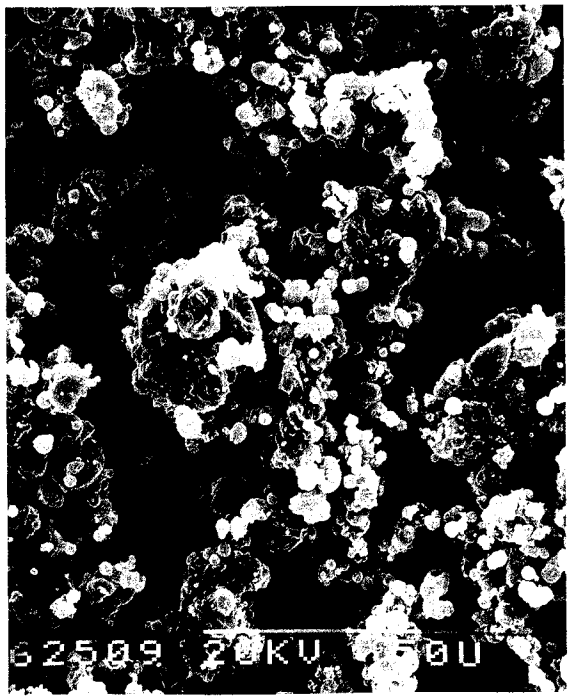

Fig. 3. SEM of freshly spray-dried micropellets dealing with formulation 12.

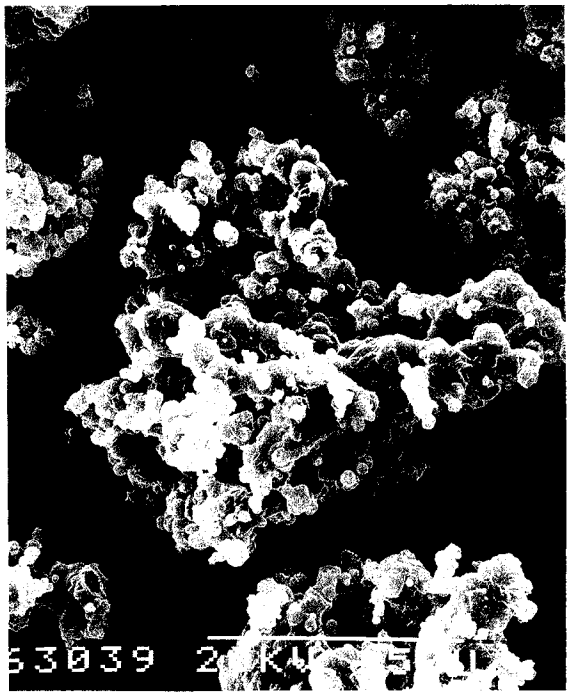

Fig. 5. SEM of freshly spray-dried micropellets dealing with formulation 16.

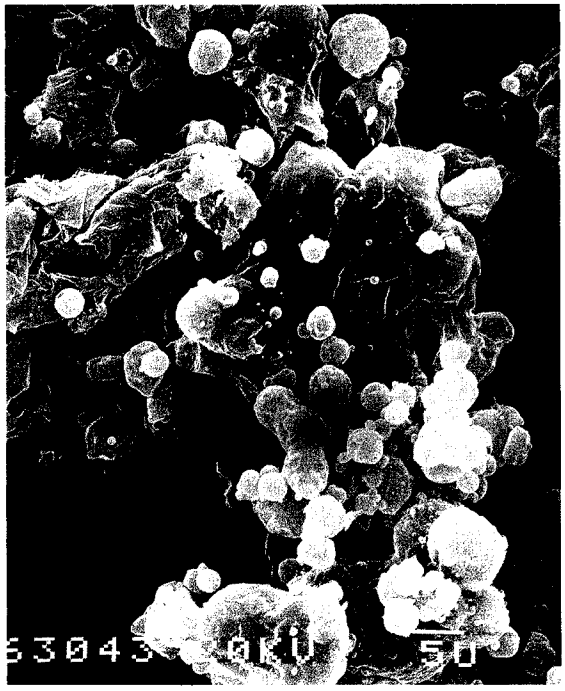

Fig. 6. SEM of freshly spray-dried micropellets dealing with formulation 17.

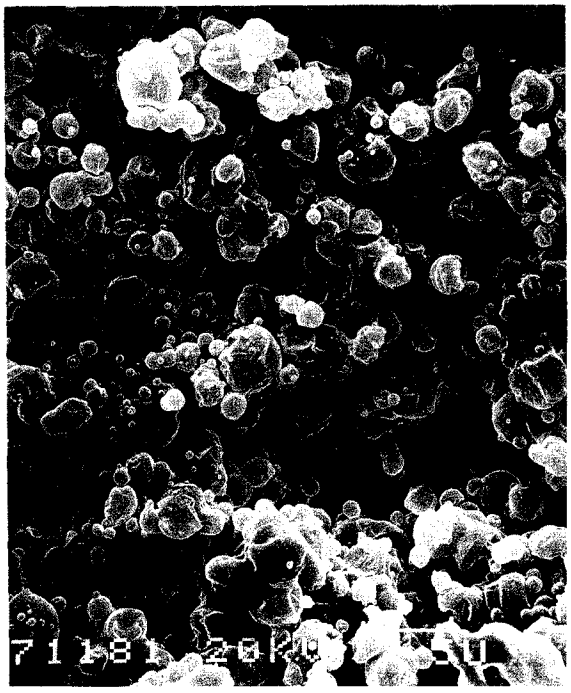

Fig. 8. SEM of freshly spray-dried micropellets dealing with formulation 19.

According to further investigations on the polymorphic phase transitions of sprayed micropellets, unstable polymorphic structures of triglycerides are found in both types of sprayed micropellets with the aid of differential scanning calorimetry and scanning electron microscopy, which will be discussed in detail subsequently (11).

In conclusion, depending on the above-mentioned results, the surface morphology of spray micropellets observed can be explained as follows.

(i) In spray-drying the rapid solvent evaporation as a consequence of heating and the type of solvent influence the crystalline structure of lipid micropellets adversely. As pre-

Fig. 7. SEM of freshly spray-dried micropellets dealing with formulation 18.

Fig. 9. SEM of freshly spray-dried micropellets dealing with formulation 21.

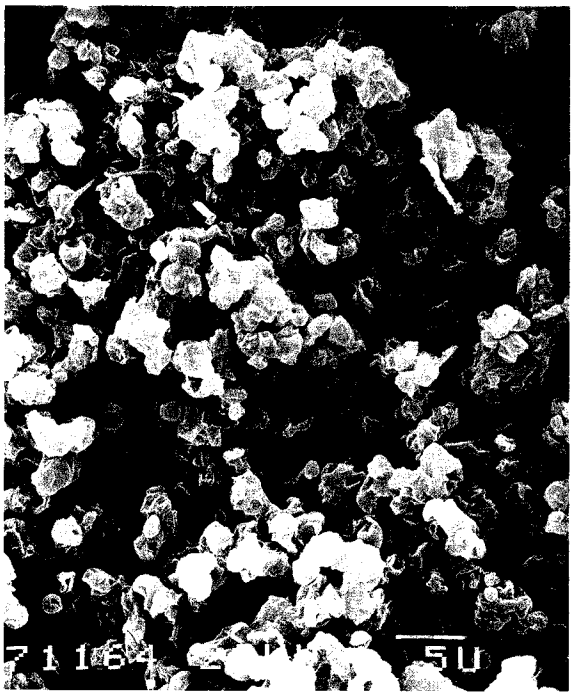

Fig. 10. SEM of freshly spray-dried micropellets dealing with formulation 22.

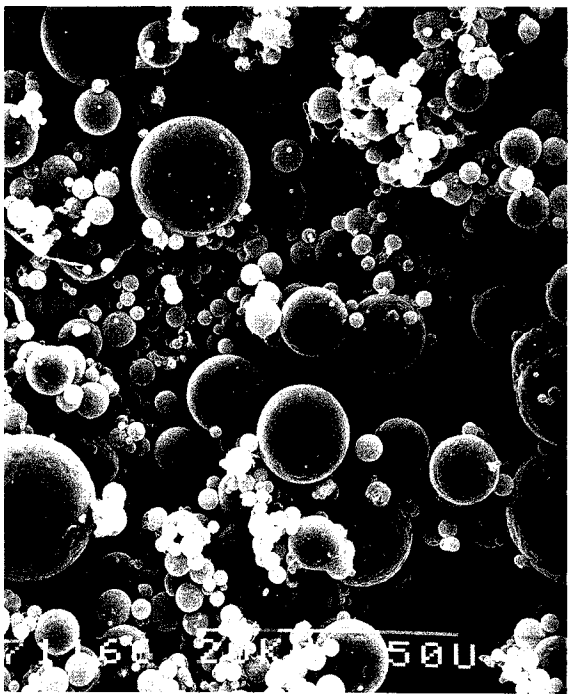

Fig. 12. SEM of freshly spray-congealed micropellets dealing with formulation 25.

sented in Figs. 4 to 6 (formulations 15 to 17) spray-dried micropellets containing mainly GTS-33 have different surface properties with solvents A, B, and C. Even though all of them possess an unstable form, this variation is due to the different solubility behavior of GTS-33 in the solvent mixtures tested. Its solubility in solvent A is higher than in solvent B. It is probable that the chain disorder of GTS-33 in solvent A is similar and/or close to the chain disorder of it in its melted form. Therefore in its completely solubilized form, it behaves like a melt. When this completely solubilized lipid solution is spray-dried, as a result of the rapid crystallization, unstable polymorphic forms are obtained. Since GTS-

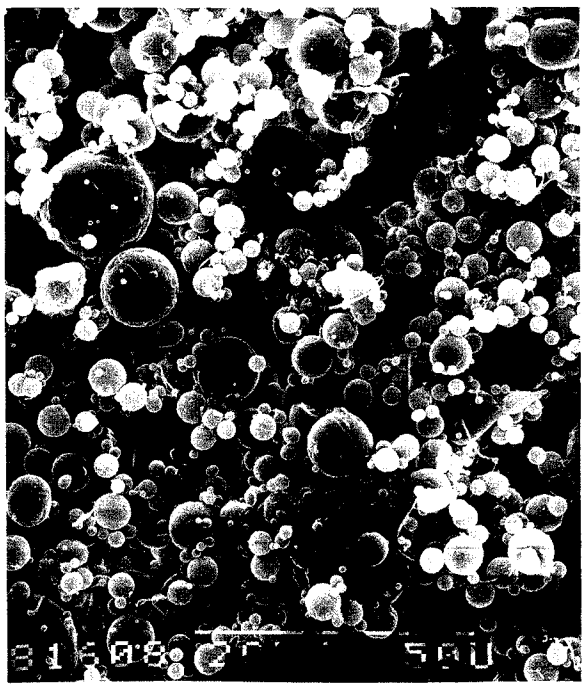

Fig. 11. SEM of freshly spray-congealed micropellets dealing with formulation 24.

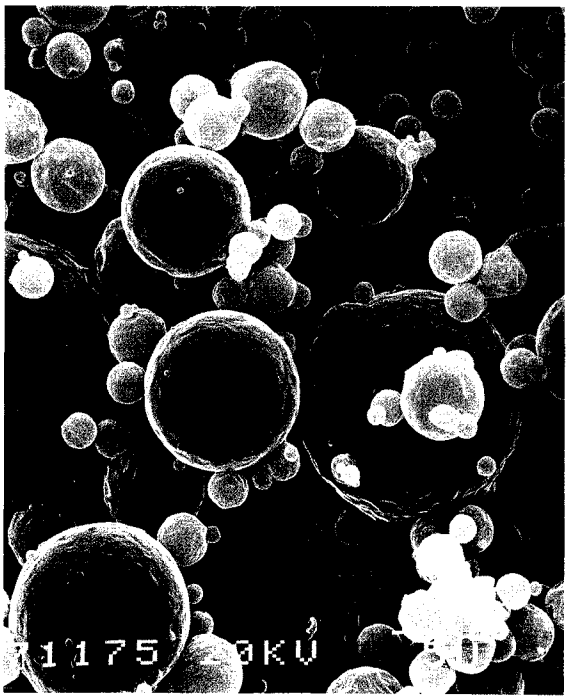

Fig. 13. SEM of freshly spray-congealed micropellets dealing with formulation 26.

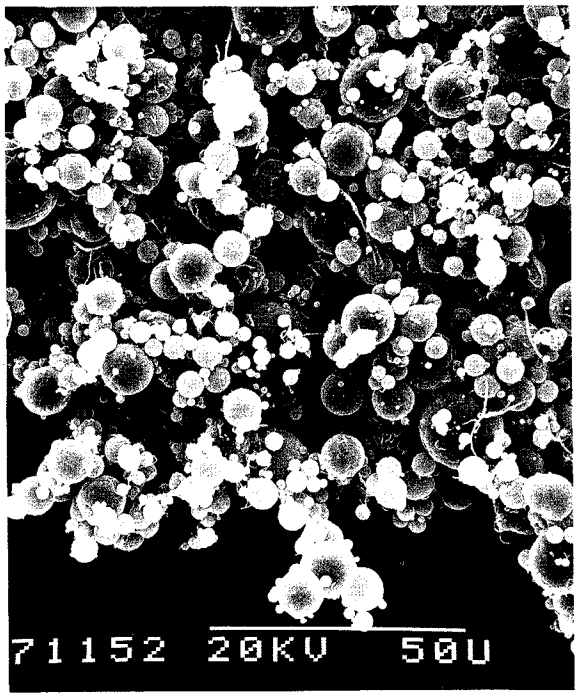

Fig. 14. SEM of freshly spray-congealed micropellets dealing with formulation 27.

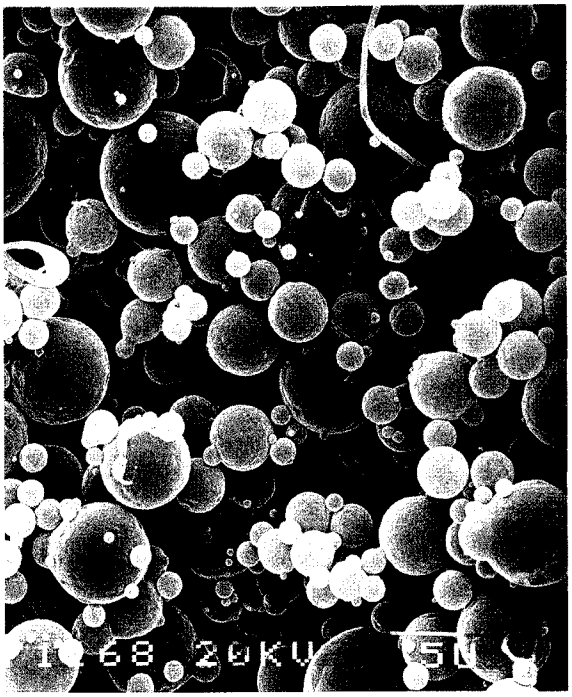

Fig. 16. SEM of freshly spray-congealed micropellets dealing with formulation 29.

33 has mainly tristearin (65%) in its composition, the almost-spherical shape of spray-dried micropellets represents and corresponds to its unstable form. The same spherical structure is also observed with the spray-congealed lipid micropellets containing GTS-33. Consequently, these results are in agreement with the TAM results in which the round spherulitic appearance of the unstable α-form of tristearin is illustrated (10).

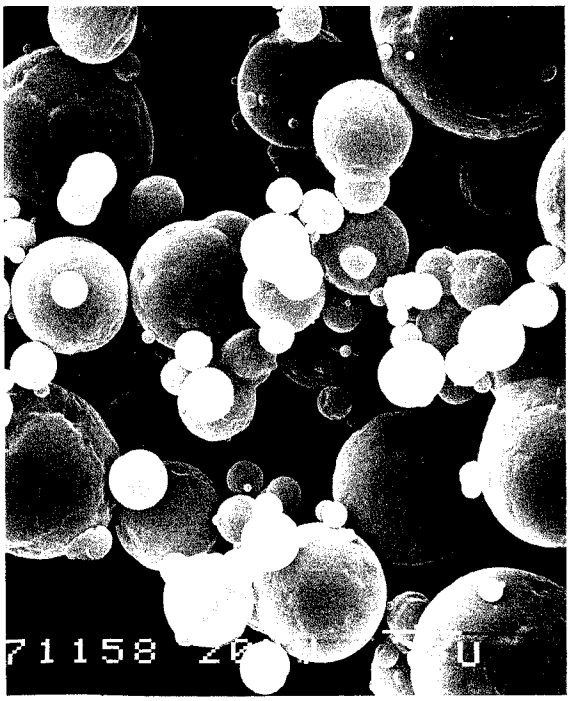

Fig. 15. SEM of freshly spray-congealed micropellets dealing with formulation 28.

(ii) The reason the spray-dried lipid micropellets containing tristearin (formulations 4, 9, and 15, formulations 5, 10, and 16, and formulations 11 and 17) do not possess the same morphology may be due to the variations in their glyceride content. It is well known that the commercially available, technical fats consist of many different triglycerides, and their crystallization and polymorphic behaviors are determined by one of the dominant fraction in them. Therefore when a technical fat crystallizes, this fraction dictates the overall crystallization process (5,12). Although the main constituent of GTS-33, Tristearin, and Dynasan 118 is tristearin, its amount and the presence of other glycerides may lead to the different surface structures of spray-dried lipid micropellets. These results show the dissimilarities in technical fats with relation to their glyceride composition, which also cause various surface and crystallization properties.

Apart from the solvent effect, the chain length of the glycerides also play an important role in the surface morphology of spray-dried micropellets. This influence can be seen with the formulations containing Dynasan 116 and Tripalmitin (Fig. 1) in which their main constituent is tripalmitin.

(iii) Attempts at spray-drying with Precirol WL 2155 and ATO-5 were unsuccessful. These fats consist of mixtures of mono-, di-, and tristearin and mono-, di-, and tripalmitostearin and vary in their content. While they are mixtures of mono-, di-, and triglycerides and mixtures of mixed glycerides, their behavior is assumed to be complex and remains to be solved.

(iv) Spray-dried micropellets containing Compritol 888 also show amorphous structures, because of their poor solubility in the solvent tested. With a better solubilizing agent the same results as in GTS-33 could eventually be obtained. Even though Compritol 888 is a mixture of mono-, di-, and tribehenate, in their spray-congealed form they show a similar smooth surface morphology as the other spray-congealed lipids. Without having any solvent effect, their surface microstructure can be observed much better.

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