Polymorphic Behavior of Sprayed Lipid Micropellets and Its Evaluation by Differential Scanning Calorimetry and Scanning Electron Microscopy

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Received July 13, 1989; accepted June 21, 1990

Considering the importance of polymorphism occurring in solid dosage forms causing instability, the polymorphic behavior of spray-dried and -congealed lipid micropellets was examined by differential scanning calorimetry and scanning electron microscopy. The results showed that both of the spraying processes exert an important effect on their polymorphic and crystallization properties. In spray-drying, due to the rapid solvent evaporation, the obtained lipid micropellets possess an unstable polymorphic form. This unstable form transforms gradually toward a stable form by storage at elevated temperatures. The same modifications were observed with spray-congealed lipid micropellets. The type of glyceride (composition, chain length), solvent and drugs (estradiol cypionate, medroxyprogesterone acetate) and, further, the presence of a stabilizing agent such as lecithin affect the polymorphic transition and its rate.

KEY WORDS: polymorphism and crystallization of fats; triglyceride; spray-drying; spray-congealing; differential scanning calorimetry; scanning electron microscopy.

INTRODUCTION

Polymorphism is defined as the ability to reveal different unit cell structures in crystal, originating from a variety of molecular conformations and molecular packings (1). This phenomenon may cause significant differences in solubility and melting point of active and auxillary substances, and the conversion of one polymorph to another may change the physical properties of the substances. Consequently, polymorphism is one of the important physical degradative routes which affects the stability of solid dosage forms (2).

In fat polymorphism, the triglyceride molecules can be packed in the solid state in alternative ways so that each crystal form has a different melting point (3). The main polymorphic forms in glycerides are the α, β′, and β forms (4). These different crystal forms of simple triglycerides are structurally similar. The hydrocarbon chains in all forms are arranged as "chairs," with the chains in the 1 and 3 position opposite to the chain in the 2 position. Their molecular dimer form can have the same structure in all three forms. However, the main difference lies in the arrangement of the dimers with relation to each other and the way of the hydrocarbon chain packing (4).

The hydrocarbon chains in the least stable α form have a loosely packed hexagonal subcell structure (4,5). This form can be obtained on cooling from the melt (6). As a result of the irregular methyl end-group region in its hydrocarbon chains and the hydrocarbon-chain oscillation, this form reveals some freedom of molecular motion (4,5). The α form therefore has the tendency to be quickly transformed to a form with a better chain packing such as the β′ form (4). The change from the vertical α form to the tilted β′ form is suggested to occur via a collapse of hydrocarbon chains or a bending of each molecule in the glycerol region (6).

In the β′ form, the hydrocarbon chains are arranged according to the orthorhombic subcell structure. Its transition to the most stable β form is economically very important because this transition is associated with the swelling or blooming of triglylcerides. This phenomenon is believed to occur with the rapid formation of the β form. It is also proposed that synchronous movements of layers can allow this phase transition (6). As a result of such a β′ transition, the obtained β form has an extended chain conformation with a triclinic subcell structure (5). Therefore the transition of liquid (melt) $\rightarrow\alpha\rightarrow\beta'\rightarrow\beta$ is the pathway for triglycerides to the optimum packing form of the molecules (4).

When lipids are used as drug carriers, i.e., lipid micropellets, such polymorphic transformation may also occur during the preparation of the dosage forms which influence the quality and texture of the end product during shelf storage. Some kinds of formulation processes such as spraying may especially trigger problems dealing with the crystallization properties of fats.

In order to examine the roles of spraying processes on the surface morphology and on the crystallization properties of lipids, spray-dried and -congealed lipid pellets in the micro- and nanometer size were prepared. Their surface morphology was studied by means of scanning electron microscopy to optimize sprayed micropellets and their surface microstructure (7). Rapid solvent evaporation, as a result of thermal energy, was found to affect the surface and crystalline structures of spray-dried lipid micropellets. The chain length of the triglycerides used in the formulations, their composition, and the presence of drugs are further impacting parameters on the surface morphology of the sprayed pellets (7). While crystallization of fats is closely related to their polymorphism (5), the results and the variations on the surface structures of lipid micropellets are attributed mainly to their polymorphic structures from the melt and solvents tested (7).

The aim of this study was to verify the polymorphic phase transition of spray-dried and -congealed lipid micropellets during and after spraying processes and, furthermore, to establish how crystalline modifications take place and relate to the formulation parameters.

MATERIALS AND METHODS

Substances, solvents, and their sources were as follows: Compritol 888 (glycerol behenate, mp 70–73°C), Gattefossé (Saint Priest, France); GTS-33 (glycerol tristearate, mp 59–60°C), Hefti AG (Zürich, Switzerland); tristearin (>99%, mp 72–73°C), Fluka AG (Buchs, Switzerland); Sojaphosphatid NC 95H (Sojalecithin), Natermann Chemie GmbH

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0724-8741/91/0200-0178$06.50/0

Table I. Spray-Dried Lipid Micropellets

GTS-33[a]
GTS-33:Lec (Formulation 15)[a]
GTS-33:Lec (Formulation 16)[b]
GTS-33:Lec:ECY (Formulation 18)[a]
GTS-33:Lec:MPA (Formulation 19)[a]
Comp 888 (Formulation 20)[a]
Comp 888:Lec (Formulation 21)[a]
Comp 888:Lec:ECY (Formulation 22)[a]
Comp 888:Lec:MPA (Formulation 23)[a]

[a] Solvent A, chloroform/methylene chloride (1:1).
[b] Solvent B, chloroform/methylene chloride (1:2).

Table II. Spray-Congealed Lipid Micropellets

GTS-33 (Formulation 24)
GTS-33:Lec (Formulation 25)
GTS-33:Lec:ECY (Formulation 26)
Comp 888 (Formulation 27)
Comp 888:Lec (Formulation 28)
Comp 888:Lec:ECY (Formulation 29)

(Köln, West Germany); estradiol 17-β cypionate, Upjohn Inc. (Kalamazoo, Mich.) and Hoechst AG (Frankfurt, West Germany); medroxyprogesteron acetate, Upjohn Inc. (Kalamazoo, Mich.); and chloroform and methylene chloride (p.a.) E. Merck (Darmstadt, West Germany).

Spray-dried and -congealed lipid micropellets containing glycerides, lecithin, and drugs were prepared as described previously (7). Some of the formulations are given in Tables I and II with the same formulation numbers as in the other study (7). After preparation all samples were stored in well-closed containers for 6 months at four different temperatures such as *T*1 (−18 ± 1°C), *T*2 (4 ± 1°C), *T*3 (25 ± 1°C), and *T*4 (37 ± 1°C).

Calorimetric analysis were performed with a Perkin–Elmer DSC-2 differential scanning calorimeter (Norwalk, Conn.). Thermograms were evaluated and recorded by a Perkin–Elmer DSC-2 Data Station 3600 (Norwalk, Conn.). Samples were weighted (2.5 ± 0.1 mg) in tight-covered aluminum pans and were analyzed against an empty, covered blank pan. The test runs were carried at a heating rate of 10°C/min starting from 20°C up to some degree above the melting point of the substances. All samples were examined initially upon spraying process and called fresh samples. Samples which were aged at four different temperatures were analyzed in the same way. Further, in order to facilitate a more direct comparison of the results the thermal behavior of tristearin (>99%), GTS-33, Compritol 888, and their mixtures with lecithin was also examined by DSC.[3] In this case samples were heated at a rate of 10°C/min above their melting points and heating thermograms were recorded. In order to simulate the spraying processes (especially spray-congealing) the melted samples were cooled down very rapidly (320°C/min) and reheated at a scan rate of 10°C/min. In the meantime surface microstructure of fresh and aged samples was characterized by scanning electron microscopy. Samples for scanning electron microscopy were prepared in a similar way as described previously (7).

RESULTS AND DISCUSSION

The thermal behavior of the pure tristearin and GTS-33 without applying any of the spraying processes is illustrated in Fig. 1. The first DSC thermogram (Fig. 1A) belongs to the first heating scan of pure tristearin at a rate of 10°C/min. Here the stable crystalline form (β) of tristearin is melted directly to the liquid form at its transition temperature by giving only a single endothermic peak. When this melted form is cooled rapidly and reheated (second heating scan), a typical thermal behavior from a melt is obtained which corresponds to a DSC α-form thermogram (Fig. 1B). As shown in Fig. 1B the thermogram is composed of two endothermic and one exothermic peaks. The first endothermic peak describes the melting behavior of the α form. This is followed by an exotherm which indicates the recrystallization of the α form. This exotherm also shows the arrangement of the α form to the crystalline β form. By further heating the second endothermic peak is obtained, which displays the melting of the β form from crystalline to its liquid state. Although for tristearin in most cases three polymorphs are reported, here no additional intermediate polymorphs are observed. This result is in agreement with the results of some other studies (6,8). An explanation for this behavior may be the overlapping of recrystallization and melting endotherms. As reported, because of the high scan speed, time does not allow

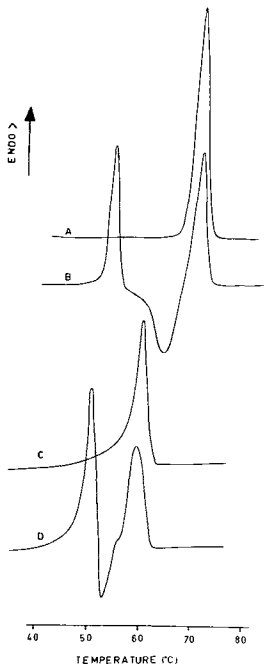

Fig. 1. DSC thermogram of pure tristearin (A and B) and GTS-33 (C and D). (A, C) First heating scan; (B, D) second heating scan after cooling down the melt.

[3] Abbreviations used: SEM(s), scanning electron micrograph(s); Trist, tristearin; Comp 888, Compritol 888; Lec, Sojalecithin; ECY, estradiol cypionate; MPA, medroxyprogesterone acetate; DSC, differential scanning calorimetry; TAM, thermal analysis microscopy.

the complete transformation pattern and all of the polymorphs cannot be seen (6).

The same observation is found with GTS-33 (Fig. 1), which is a mixture of 65% tristearin and 35% tripalmitin. In Fig. 1C the first endothermic peak represents the melting of its stable form to the liquid state. After cooling rapidly and reheating, two melting endotherms and one exotherm are obtained (Fig. 1D), similarly as in tristearin (Fig. 1B).

The mixture of GTS-33 with lecithin shows similar thermal behavior to GTS-33 alone (Fig. 1).

Analyzing the thermal behavior of spray-dried micropellets containing GTS-33 (Fig. 2), the thermogram obtained (Fig. 2A) in the first heating has similar peaks as the second heating thermogram of GTS-33 (Fig. 1D) and the DSC α-form thermogram of tristearin (Fig. 1B). Therefore in Fig. 2A the first melting endotherm belongs to the unstable (α) form and the second endotherm shows the melting of the stable form. This thermogram shows that during spray-drying a crystalline modification takes place as a result of rapid solvent evaporation. The lipid micropellets obtained have an unstable polymorphic structure. By storing these micropellets—with their unstable structure—at different temperatures, some modifications in their crystalline structure occur. This is verified by analyzing the thermal behavior of micropellets which are stored at *T*1, *T*2, *T*3, and *T*4. As shown in thermogram B (Fig. 2B) lipid micropellets keep their unstable structure at *T*1. At *T*2 some minor rearrangements occur, which are shown in Fig. 2C, with diffuse endothermic peaks. At *T*3 most of the α form is transformed to its stable form, which is shown in Fig. 2D. Further, this thermogram (Fig. 2D) also indicates the presence of the mixture of both polymorphic forms at *T*3. As illustrated in Fig. 2E, micropellets stored at *T*4 show only one endotherm. This endotherm represents the melting transition of the stable form to its liquid state. These results show that all of the unstable polymorphic forms in the spray-dried micropellets containing GTS-33 are transformed almost completely to the stable form after storing at *T*4.

The thermal behavior of spray-dried micropellets containing GTS-33 and lecithin (Formulation 15) (Table I) shows the same polymorphic modification as GTS-33 alone. A SEM of micropellets aged at *T*4 (Formulation 15) is given in Fig. 3, which shows the surface modifications with relation to the polymorphic phase transition.

Dealing with the influence of surfactants on the polymorphic phase transition of fats, it is mentioned that some kinds of emulsifiers, i.e., lecithin and monoglycerides, can be used as viscosity controllers and antibloom agents in order to prevent or delay transformation to the β form (6,9–11). Some surfactants possess the ability to be incorporated into the crystal lattice. They behave as a crystal structure modifier and conserve the α-form modification. According to Garti (9) they can interfere in the solidification and melting process of fat without any detectable alterations in the crystal packing of the fat. This alludes to the ability of the surfactant to vary the kinetics of phase transformation, which is related to the mobility of the molecules rather than to the thermodynamic processes involved in the arrangement of molecules (9).

The stabilizing effects of lecithin are observed with spray-dried micropellets stored at *T*2 to a great extent. At *T*2, micropellets keep their unstable structure more with lecithin than without it. However, with storing at higher temperatures the added lecithin (3.5%) has no effect. The complete transformation to the stable form at *T*4 (Formulation

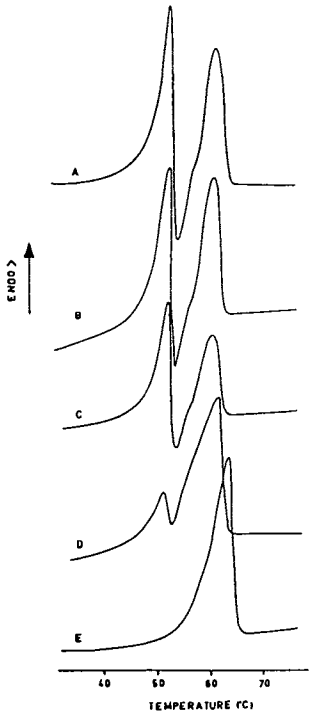

Fig. 2. DSC thermograms of spray-dried lipid micropellets containing GTS-33: (A) fresh; (B) stored at *T*1; (C) stored at *T*2; (D) stored at *T*3; (E) stored at *T*4.

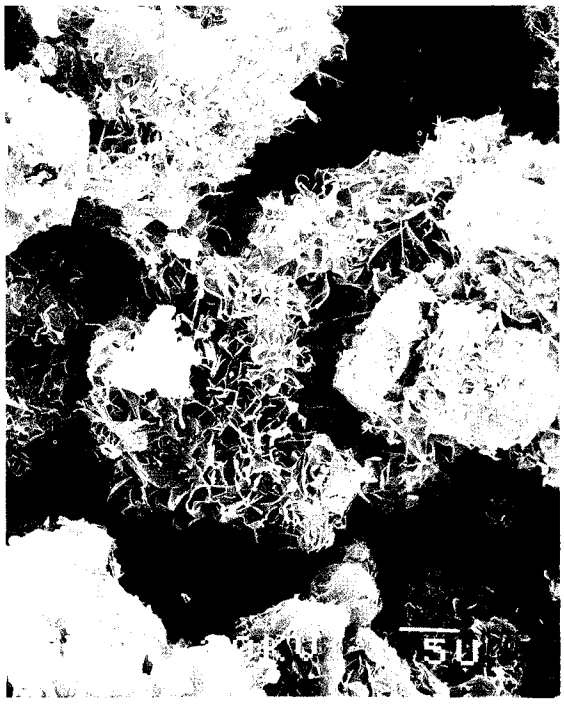

Fig. 3. SEM of spray-dried micropellets containing GTS-33 and Lec (at T3).

15), despite the presence of lecithin, is illustrated in Fig. 3. As mentioned above this may indicate that its effect does not deal with the thermodynamic processes involved in the arrangement of molecules.

The influence of the type of solvent on the crystal modification of spray-dried micropellets can be seen in Fig. 4. In this figure thermograms A and B belong to the spray-dried micropellets from solvent A (Formulation 15) and solvent B (Formulation 16), respectively. In solvent A the content of the formulation (GTS-33 and lecithin) is more soluble than in solvent B. For this reason the same substances solubilized in different solvent mixtures give significantly different thermograms. Thermograms 4A and B illustrate also the presence of a mixture of polymorphs after spray-drying. The micropellets prepared from solvent B retain less unstable α-form content than the other due to its poor solubility in solvent B. Furthermore, thermograms A and B explain the variations on the surface morphlogy of spray-dried lipid pellets because of the solvent effect as discussed previously (see Figs. 4 and 5 in Ref. 7).

In order to investigate the influence of drug incorporation on the polymorphic phase transition rate of spray-dried lipid micropellets, the thermal behavior of fresh and *T*1-, *T*3-, and *T*4-aged spray-dried micropellets containing estradiol cypionate (Formulation 18) and medroxyprogesterone acetate (Formulation 19) is examined. Although the thermograms obtained with the above-mentioned formulations are similar to the others, the main difference is observed with micropellets aged at *T*2. Lipid micropellets containing estradiol cypionate largely conserve their structure, with only some minor rearrangements. However, with micropellets containing medroxyprogesterone acetate, a considerable modification occurs from the unstable to the stable form by storing at *T*2. A possible explanation for this difference may be due to the ability of estradiol cypionate to incorporate into and stabilize the crystal lattice of the GTS-33 better than medroxyprogesterone acetate. Thus the transformation of the α-form occurs less readily than with medroxyprogesterone acetate.

Fresh and aged spray-congealed lipid micropellets containing GTS-33 and GTS-33 with lecithin show thermal behavior similar to that of spray-dried pellets. The polymorphic phase transition of formulation 25 (at *T*3) with relation to its surface morphology is given in Fig. 5. The surface microstructue of fresh and *T*1-, *T*2-, and *T*3-aged spray-congealed micropellets containing estradiol cypionate (Formulation 26) and their thermal behavior were explained previously (12). Almost-complete polymorphic transformation

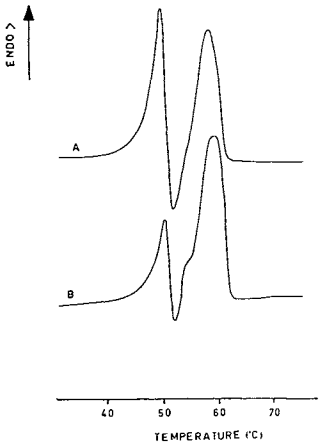

Fig. 4. DSC thermograms of fresh spray-dried micropellets. (A) Formulation 15; (B) Formulation 16.

Fig. 5. SEM of spray-congealed lipid micropellets containing GTS-33 and Lec (at *T*3).

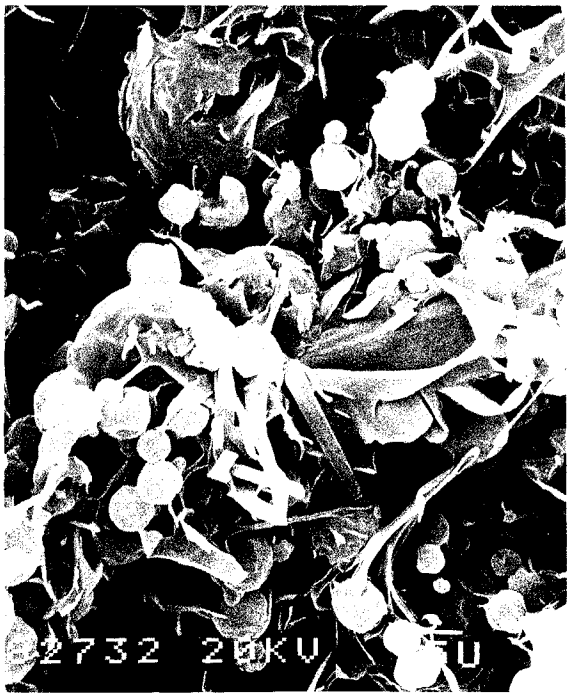

Fig. 6. SEM of spray-congealed lipid micropellets containing GTS-33, Lec, and ECY (at *T*4).

of formulation 26 (at *T*4) is presented in Fig. 6. In Figs. 5 and 6 the reformed chain-segregated stable form can be seen from the surface microstructure as a result of molecular rearrangements in the lipid micropellets.

The thermal behavior of the behenates (Compritol 888) independent of any of the spraying processes is shown in Figs. 7A and B. Thermogram A shows the first heating scan, where the stable crystalline form is melted directly to its liquid form. After rapid cooling and reheating (second heating scan) the second thermogram with some modifications is illustrated in Fig. 7B. As shown in Fig. 7B the thermal behavior of Compritol 888 is considerably different from the thermal behavior of pure tristearin and GTS-33 (Fig. 1).

According to Hernqvist (3,4) if pure tribehenin is cooled down, the unstable polymorph sub-α form is developed. The hydrocarbon chains of the sub-α form are packed according to the orthorhombic subcell formation. Therefore this form can be referred to as the β′ form. The α form to the sub-α form transition is reversible and the expression sub-α is generally used. While the unstable form of pure tribehenin does not have a hexagonal chain packing like the unstable α-form of tristearin, the dissimilarity between thermograms obtained for Compritol 888 and tristearin or GTS-33 is quite clear.

Mono- and diglycerides can also be used for stabilizing and delaying the polymorphic phase transiton of fats (9). Compritol 888 contains mono-, di-, and tribehenates. Consequently, the presence of mono- and dibehenate in this mixture restricts the molecular motion of the chains. Furthermore, the mixture of glycerides, as a result of the interlayer chain penetration, is stabilized in most cases in the β′ form (13). Therefore, upon rapid cooling and reheating, the thermogram obtained (Fig. 7B) does not correspond to a typical DSC α-form thermogram as in tristearin. This form also does not represent a stable form thermogram. Consequently, upon rapid cooling and reheating some modifications can be seen in the thermogram (Fig. 7B) regardless of the presence of mono- and dibehenate.

The diminished stabilizing effect of mono- and dibehenate as the result of spray-drying can be seen more clearly in Fig. 7C, which represents the thermal behavior of fresh and *T*1-stored spray-dried micropellets containing behenates (Formulation 20). This thermogram also shows the presence of two kinds of polymorphs as a result of the poor solubility of behenates in the solvent used. This affects, further, the surface structure of micropellets toward an amorphous structure. Consequently, with Compritol 888 the spray-dried micropellets obtained also have an unstable structure. After storing at *T*2, *T*3, and *T*4 the polymorphic transition are shown in thermograms D, E, and F (Fig. 7), respectively.

Similar thermal behavior is obtained with spray-congealed lipid micropellets containing Compritol 888 (Formulation 27). A SEM of micropellets stored at *T*4 (Formulation 27) is given in Fig. 8.

When the mixture of Compritol 888 with lecithin (without applying any spraying processes) is analyzed by DSC in the same way, a retardation in its polymorphic transition rate is determined. This effect is illustrated in Figs. 9A and B. Here thermograms A and B present the first and the second heating scans of this mixture, respectively. These thermograms are almost identical, thus the influence exerted by the lecithin is obvious. This is also a possible explanation for the effective incorporation of the stabilizing surfactant (lecithin) into the crystal lattice of Compritol 888.

The same effect should be expected when Compritol 888 is spray-congealed in the presence of lecithin. This is shown by examining the thermal behavior of formulation 28 (Fig. 9). Figures 9C, D, E, and F show the thermal behavior of fresh and *T*1, *T*2, *T*3, and *T*4 micropellets, respectively. The ther-

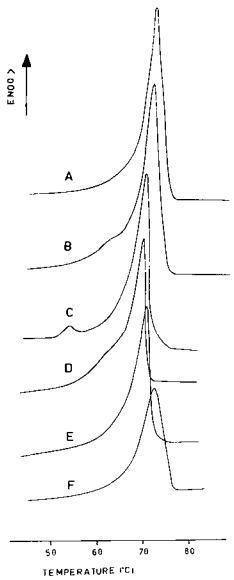

Fig. 7. DSC thermograms of Comp 888 [(A) first heating scan; (B) second heating scan after cooling down the melt] and spray-dried Comp 888 [(C) fresh and stored at *T*1; (D) stored at *T*2; (E) stored at *T*3; (F) stored at *T*4].

Fig. 8. SEM of spray-congealed lipid micropellets containing Comp 888 (at *T*4).

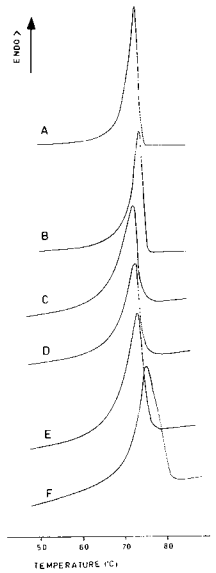

Fig. 9. DSC thermograms of mixture of Comp 888 with Lec: (A) first heating scan; (B) second heating scan after cooling down the melt. DSC thermogram of spray-congealed lipid micropellets containing Comp 888 and Lec: (C) fresh and stored at *T*1; (D) stored at *T*2; (E) stored at *T*3; (F) stored at *T*4.

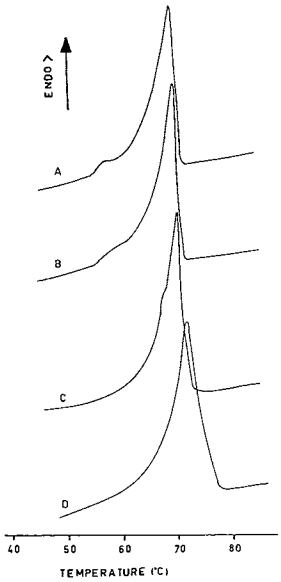

Fig. 11. DSC thermogram of spray-congealed lipid micropellets containing Comp 888, Lec, and ECY. (A) fresh and stored at *T*1; (B) stored at *T*2; (C) stored at *T*3; (D) stored at *T*4.

mograms obtained have only single similar endothermic peaks, which means that micropellets conserve their crystalline structures by storing at *T*1, *T*2, and *T*3 due to the presence of the lecithin. However, the polymorphic transformation is observed only with micropellets stored at *T*4. This is observed as a shift in the melting endotherm (Fig. 9F). The surface microstructure of these micropellets at *T*4 is illustrated in Fig. 10 and the stabilizing effect of lecithin is quite obvious. As seen from the SEMs (Figs. 8 and 10), there is a significant difference in the polymorphic transition rate in the presence of lecithin. With spray-dried micropellets containing the above-mentioned lipids, similar results are obtained.

Incorporation of estradiol cypionate shows an adverse affect on the crystalline structure of lipid micropellets. The new component added to the lipid micropellets suppresses the stabilizing effect of lecithin dramatically by acting as a

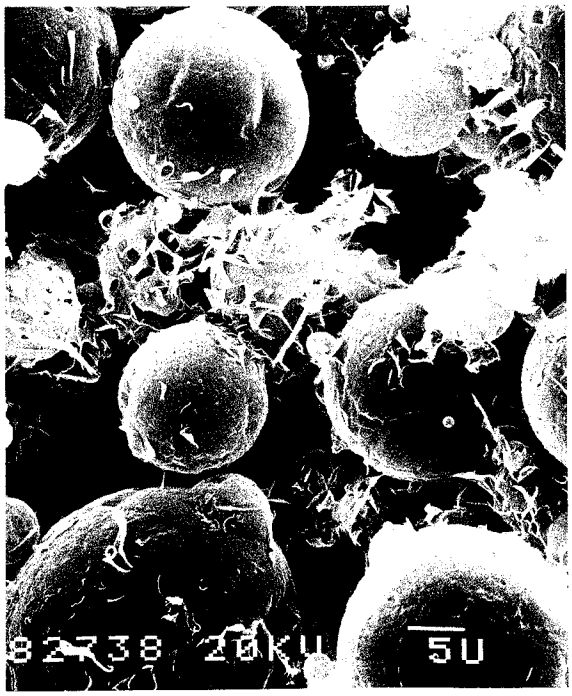

Fig. 10. SEM of spray-congealed lipid micropellets containing Comp 888 and Lec (at *T*4).

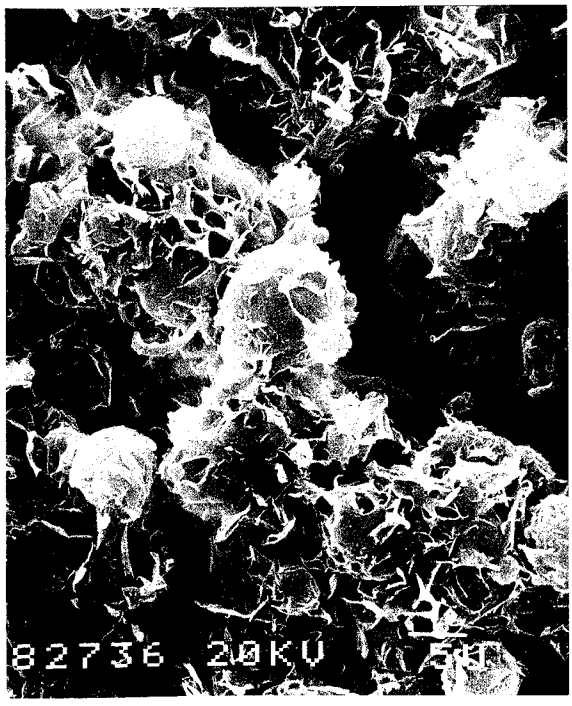

Fig. 12. SEM of spray-congealed lipid micropellets containing Comp 888, Lec, and ECY (at *T*4).

destabilizing agent, probably by disturbing the cystal packing and molecular arrangements. Although incorporation of this steroid into the micropellets containing GTS-33 and lecithin exerts a synergistic effect to lecithin, its molecular interaction with Comp 888 is probable just the opposite. The thermal behaviors of their spray-dried and -congealed lipid micropellets are almost identical. Here the thermal behavior of fresh and *T*1-, *T*2-, *T*3-, and *T*4-aged spray-congealed lipid micropellets (Formulation 29) is shown in Fig. 11. The corresponding surface morphology of *T*4-aged micropellets is presented in Fig. 12. By comparing the thermal data, the endothermic peaks obtained, especially in thermograms 11A and B, reflect the same properties as in thermograms 7C and D. Consequently, the polymorphic and crystallization properties are more severe with drug incorporation than without it, at least in this case (Figs. 10 and 12).

Incorporation of medroxyprogesterone acetate shows the same effect as estradiol cypionate on the thermal behavior of fresh and *T*1-, *T*2-, *T*3-, and *T*4-stored spray-dried lipid micropellets (Formulation 23).

Depending on the basis of the presented data and regarding the polymorphic and crystallization properties of lipid micropellets the following can be concluded:

(i) Spray-drying processes influence the crystallization properties of lipid micropellets with all glycerides, their mixtures with lecithin, and drugs examined. All sprayed micropellets possess an unstable polymorphic structure. During aging at elevated temperatures the unstable form of micropellets is transformed to a stable form while losing their almost spherical surface structures. The main effect of receiving these unstable crystalline structures is rapid solvent evaporation, causing rapid crystallization.

(ii) Without having the solvent effect, the spray-congealed lipid micropellets obtained with all substances tested also have unstable polymorphic structures possessing a smooth surface morphology. These structures are the result of rapid crystalization from melts.

(iii) Therefore spherical smooth surfaces of sprayed lipid micropellets correspond to a less stable form. These results are in agreement with the typical morphology of crystalline aggregates grown from the melt as reported by Sato (5) and with the TAM observations of deMan *et al.* (14).

(iv) According to Sato (5) the α form has a very thin crystal size (smaller than several micrometers) showing the smooth surface of a crystallized sample. The crystal shape of the β′ form looks like long needles (less than 5 μm). The β-form has a large crystal, ranging from 20 to 100 μm, and often growing in clumps that cause grainy microstructures of fats (5). Consequently, all these structures can be seen clearly from the given SEMs of sprayed lipid micropellets.

ACKNOWLEDGMENTS

The Swiss Federal Board of Scholarships for Foreign Students is gratefully acknowledged for their financial support in this study. We are grateful to Dr. E. Wehrli (ETH, Cell Biology, Zürich, Switzerland) for the SEMs. We thank Upjohn Inc. (Kalamazoo, Mich), Hoechst AG (Frankfurt, West Germany), Hefti AG (Zürich, Switzerland), Gattefossé (Saint Priest, France), and Natterman Chemie GmbH (Köln, West Germany) for supplying steroids and lipids. We also thank Büchi Laboratoriums-Technik AG (Flawil, Switzerland) for the prototype spray nozzle.

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