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DESIGN OF REDISPERSIBLE DRY EMULSION AS AN ADVANCED DOSAGE FORM OF OILY DRUG (VITAMIN E NICOTINATE) BY SPRAY-DRYING TECHNIQUE

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ABSTRACT

An oily drug, dl-α-tocopherol nicotinate (VEN) was transformed to the newly developed powdered form, termed dry emulsion, by spray-drying the emulsified VEN or oily solutions of VEN with additives. The drug releasing property from the resultant particles was dependent on various factors such as the emulsifying method and the type and amount of the oily carrier and surfactant formulated. The desired releasing property was offered by use of medium chain triglyceride (MCT) as the oily carrier and polyoxyethylene-polyoxypropylene-blockcopolymer (Pluronic F-68) or polyoxyethylenesorbitan monolaulate (Tween 80) as the emulsifying agent. The difference in drug releasing property with various formulations was found to be mainly attributed to the difference in physical state of VEN and

surfactant in the dry emulsion particle, which was detected by differential scanning calorimetry.

INTRODUCTION

There are a lot of oily drugs like lipophilic vitamins used in current therapies. Lipophilic liquids have also been reported to be effective to improve the absorption of poorly water soluble drugs in the gastrointestinal tract when used as carriers (1,2,3) or co-administered (4,5). In formulating the oily materials into oral dosage form, powdered forms are desirable due to easiness in treating and manufacturing. In order to achieve the sufficient bioavailability of drugs the drug releasing property of the preparations is important. Tokumura et al (6) has reported that a hard gelatin capsule filled with an oily solution of drug is superior in bioavailability to the corresponding tablet form. While a soft gelatin capsule filled with oily ingredients, and tablet and hard gelatin capsule forms prepared with powdered oily drugs are available, ideal dosage forms of oily drug have been desired to improve bioavailability and patient compliance.

Dry emulsion system is a novel oral dosage form of oily drugs developed by present authors. The dry emulsion particle is spherical and freely flowing because it is prepared by using a spray-drying technique. The oily ingredients formulated in this system are easily released to form a stable emulsion when rehydrated, which leads to preferable bioavailability of drugs. These properties of

dry emulsion system have been confirmed in our previous studies by using a model oily drug, vitamin E acetate (7,8,9).

The aim of this work is to demonstrate usefulness of the dry emulsion system by applying it to another oily drug, vitamin E nicotinate (VEN). VEN has a melting point of 38°C and shows waxy like characteristics below at the temperature. These properties may lead to the difficulties in manufacturing and to the uncertain bioavailability in administration. It was reported that extent of bioavailability of the commercial VEN preparations filled in hard gelatin capsules was closely related to the difference in water dispersibility including the dissolution property (10). To design the dry emulsion system of VEN, much attention was paid to the physical state of the drug in the particle to achieve the reliable drug releasing property.

EXPERIMENTAL

Materials

VEN was gifted by Eisai Co. and subjected to all experiments as received. Nonporous colloidal silica (Aerosil 200, Nippon Aerosil), medium chain triglyceride (MCT) (Panasate 810, Nippon Oil and Fats Co.), propyleneglycol dicaprylate (PDC)(Sefsol 228, Nikko Chemicals Co.), and polyoxyethylene-polyoxypropylene-blockcopolymer (Pluronic F-68 and L-44, Asahi Denka Co.) were used. Propyleneglycol, oleic acid (OA) and linoleic acid (LA), glycerol, polyethyleneglycol 400 (PEG 400), and

polyoxyethylenesorbitan monolaulate (Tween 20) were reagent grade.

Preparation of VEN dry emulsions

Heating method --- An aqueous solution (972.5ml) of Pluronic F-68 (2g) heated at 60°C was added to VEN (20g) melted on a water bath. The mixture was agitated at 60°C with a homomixer (T.K. auto homomixer, Tokushu Kika Kogyo Co.) at 8,000 rpm for 10 min. After adding Aerosil 200 (7.5g), agitation was continued for more 10 min under the same conditions. The resultant emulsion of VEN kept at 60°C was fed into a spray-dryer (L-12, Okawara Kakoki Co.) by a peristaltic pump at the flow rate of 50 ml/min. The drying conditions were as follows: inlet air temperature, 220°C; outlet air temperature, 120°C, the rotation speed of atomizer (disk type), 16,500 rpm.

Ethanol method --- Aerosil 200 (7.5g) was dispersed in an aqueous phase (920ml) containing Pluronic F-68 (2g) by agitating gently with a spatula. VEN (20g) dissolved in ethanol (150ml) was dispersed into the Aerosil suspension by agitating with a homomixer at 6,000 rpm. After agitating for 10 min, resultant VEN emulsion was fed to the spray-dryer. The inlet and outlet temperatures of the spray-drying process were 125°C and 84°C, respectively.

Oily carrier method --- VEN melted on the water bath was mixed with an oily carrier at the weight ratio of 1:1. In the case of MCT, the ratio was varied from 1:7 to 3:1. The oily mixture (20g) was then emulsified in an aqueous

suspension composed of Aerosil 200 (7.5g), surfactant (Pluronic F-68, L-44 or Tween 20, 2g) and water (970.5ml) with a homomixer at 6,000 rpm for 10 min. The resultant emulsion was spray-dried to the dry emulsion under the same conditions as in the heating method. The oily carriers used in this method were MCT, PDC, OA and LA.

Evaluation of VEN releasing property of dry emulsions

The VEN releasing property of the dry emulsion was evaluated by the amount of VEN released within 1 h after dispersed. The dry emulsion (280-325mg) was dispersed in water (9.5ml) at 20-70°C in a test tube by hand-shaking 10 times. After the suspension was allowed to stand for 1 h, an aliquot (0.5ml) of the VEN emulsion reproduced in the aqueous phase was sampled with a syringe, and the VEN drops in the aliquot were solubilized by adding methanol (9.5ml). After centrifuging at 3,000 rpm for 10 min and subsequently filtrating through a membrane filter (0.22μm), the methanol solution was subjected to a high performance liquid chromatogragh (HPLC) to measure VEN concentration released. The stationary and mobile phases were Nucleosil 5C18 filled in a stainless column (150mm x 4.6mm i.d.) and 100% methanol, respectively. This system was operated at ambient temperature at the flow rate of 2.0 ml/min. The drug separated was detected by a spectrophotometer (UVIDEC 100-V, Japan Spectroscopic Co.) at 264 nm.

To determine VEN content, VEN entrapped in the dry emulsion (280-325mg) was extracted with methanol (9.5ml) by

shaking with a horizontally sliding shaker at 240 strokes per minute for more than 1 h. After removing the insoluble ingredients from the extract by the centrifugation (3,000rpm, 10min) and the filtration (0.22μm), the filtrate (0.5ml) was diluted with methanol (9.5ml). The concentration of VEN in the resultant solution was determined by the HPLC method under the same conditions as for the determination of VEN released from the dry emulsion.

Thermal analysis of dry emulsion

The thermal property of the dry emulsions was analyzed by using a differential scanning calorimeter (DSC, CN8089A1, Rigaku Denki Co.). About 10 mg of the dry emulsion was packed in an aluminum pan and heated at the rate of 5°C/min. To ensure the analysis in the lower temperature, the measurement was set off after cooling the sample to less than 10°C by means of a simple cooling unit attached to the calorimeter. The sensitivity of the calorimeter was ± 2 mcal/s.

RESULTS AND DISCUSSION

Micromeritic and VEN releasing properties of dry emulsion

VEN could be converted into the dry emulsions by the spray-drying technique as well as VEA(8). A scanning electron micrograph (SEM) of the particles prepared with the heating method is shown in Figure 1. This picture illustrates that the particles are spheres with the diameter of 3-30 μm. Due to such shape of the particles, the dry emulsions were

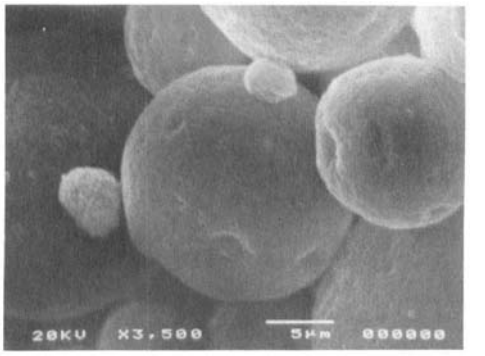

FIGURE 1

Scanning electron micrograph of dry emulsion particles with VEN prepared with heating method

so flowable. Such micromeritic properties were found for other dry emulsion particles prepared with the ethanol and the oily carrier methods.

On the other hand, the different emulsifying methods offered the resultant dry emulsions a different VEN releasing property in an aqueous medium at 20°C. Fig.2 is a photograph of the aqueous dispersion of the dry emulsions after standing for 1 h, indicating that only the dry emulsion prepared with the oily carrier method successfully reproduced a VEN emulsion under such a mild redispersing method as hand-shaking. The percent VEN released in this system was 57.2%. The size of the oily droplets released from the particle was microscopically observed to be comparable to that in the original emulsion.

The VEN releasing property of the dry emulsions was influenced by the temperature of dispersion medium. The

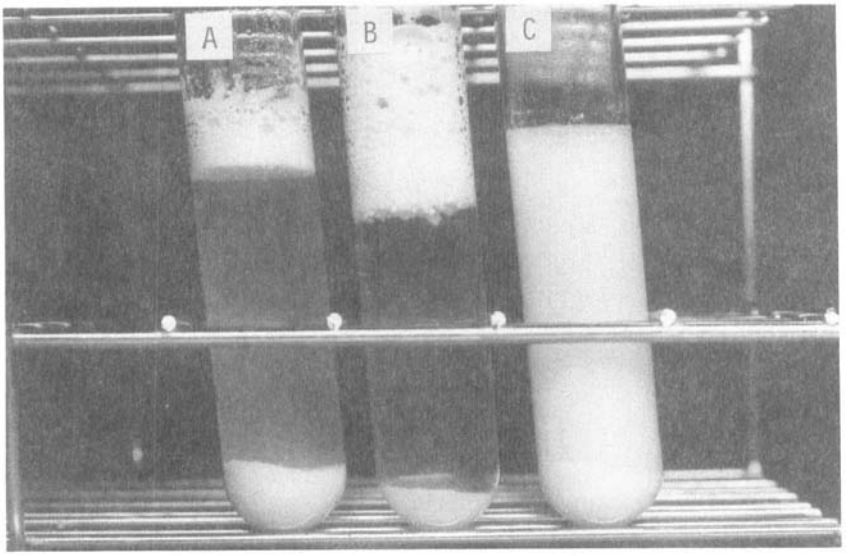

FIGURE 2

Photograph of dry emulsion with VEN 1 h after dispersed in water at 20°C : (A) heating method ; (B) ethanol method ; (C) oily carrier method

amount of VEN released from the dry emulsions prepared by the different three methods was plotted as a function of temperature of the water in Fig.3. The released % of VEN increased with an increase in the temperature for the dry emulsions. Especially for the dry emulsion prepared with the heating method, the value increased so sharply around 40°C and resultantly traced a sigmoidal curve. The dry emulsion prepared with the ethanol method also gave a curve with the similar pattern. The temperature of 40°C was corresponding to the melting point of VEN (38°C), implying that the drug releasing property of dry emulsions reflected

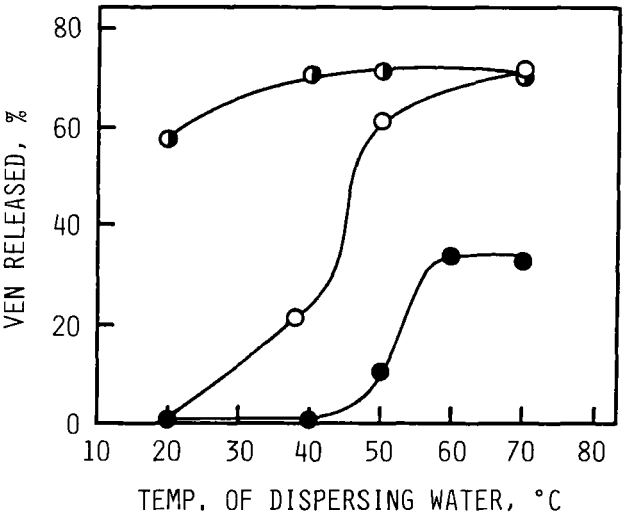

FIGURE 3

Effect of preparation method on VEN releasing property of dry emulsion in water at 20-70°C : ○, heating method ; ●, ethanol method ; ◑, oily carrier method

the state of the drug in the particles. The dry emulsion prepared with the oily carrier method showed a good VEN releasing property even at room temperature. The releasing property was slightly improved at 40°C and unchanged above at the temperature. This observation indicated that the drug was incorporated as the oily solution in the dry emulsion particle.

To confirm the physical state of the drug in the dry emulsion particles, the thermal analysis was carried out for each dry emulsion by means of DSC. The resultant DSC curves are shown in Fig.4. On the curve for the physical mixture of VEN and Pluronic F-68, two endothermic peaks at around

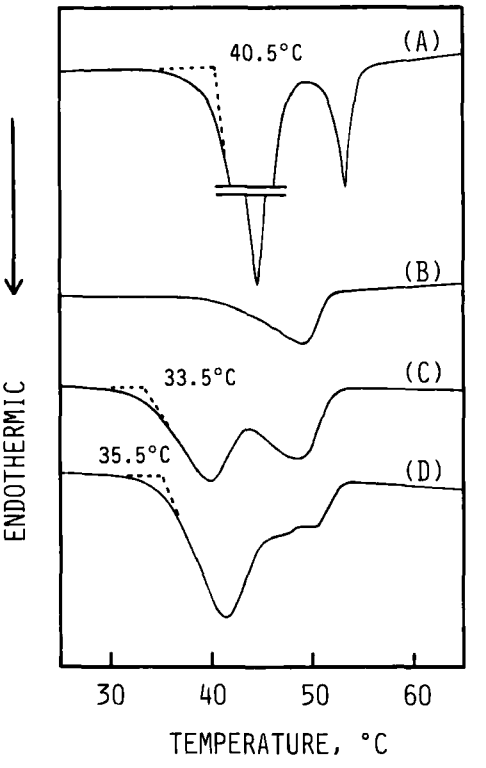

FIGURE 4

DSC thermograms of VEN-surfactant physical mixture and dry emulsions with VEN : (A) VEN-Pluronic F-68 physical mixture ; (B) dry emulsion prepared with oily carrier method ; (C) dry emulsion prepared with heating method ; (D) dry emulsion prepared with ethanol method

40°C and 50°C identified to melting points of the drug and the surfactant, respectively, were observed. For the dry emulsion prepared with the heating or ethanol method, both peaks were observed on the chart, which indicated that the drug and the surfactant exist as crystal form in the particles at room temperature. The lower temperature of the drug melting point (33.5 or 35.5°C) for the dry emulsion

than the original value (38°C) may be attributed to the incomplete recrystallization of the drug in the particles. On the other hand, no drug peak was observed for the dry emulsion prepared with the oily carrier method, confirming that the drug was dissolved in the carrier in the particle.

Effect of oily carriers on VEN releasing property of dry emulsion

The investigation was focused on the dry emulsion with the oily carrier method, which showed a good VEN releasing property. First of all, the miscibility or solubility of the various carriers with the drug was evaluated to select the available carriers for this formulation. The carriers tested were both types of hydrophilic materials (glycerol, propylene glycol, Pluronic F-68 and PEG 400) and lipophilic ones (PDC, MCT, OA and LA). Fig.5 illustrates the appearance of the mixtures of the drug with each carrier before and after storing at 4°C for 8 days. The carriers of the lipophilic group were found to be good solvents for the drug. All of them were miscible with the drug and well restricted its precipitation during storage. In contrast, hydrophilic carriers were immiscible with VEN.

These lipophilic carriers offered the different drug releasing properties to the resultant dry emulsions. Fig.6 represents the drug releasing property of the dry emulsions with these carriers at various temperatures of the medium. The dry emulsion with MCT gave the highest releasing value at any temperature, whereas the value for the others were

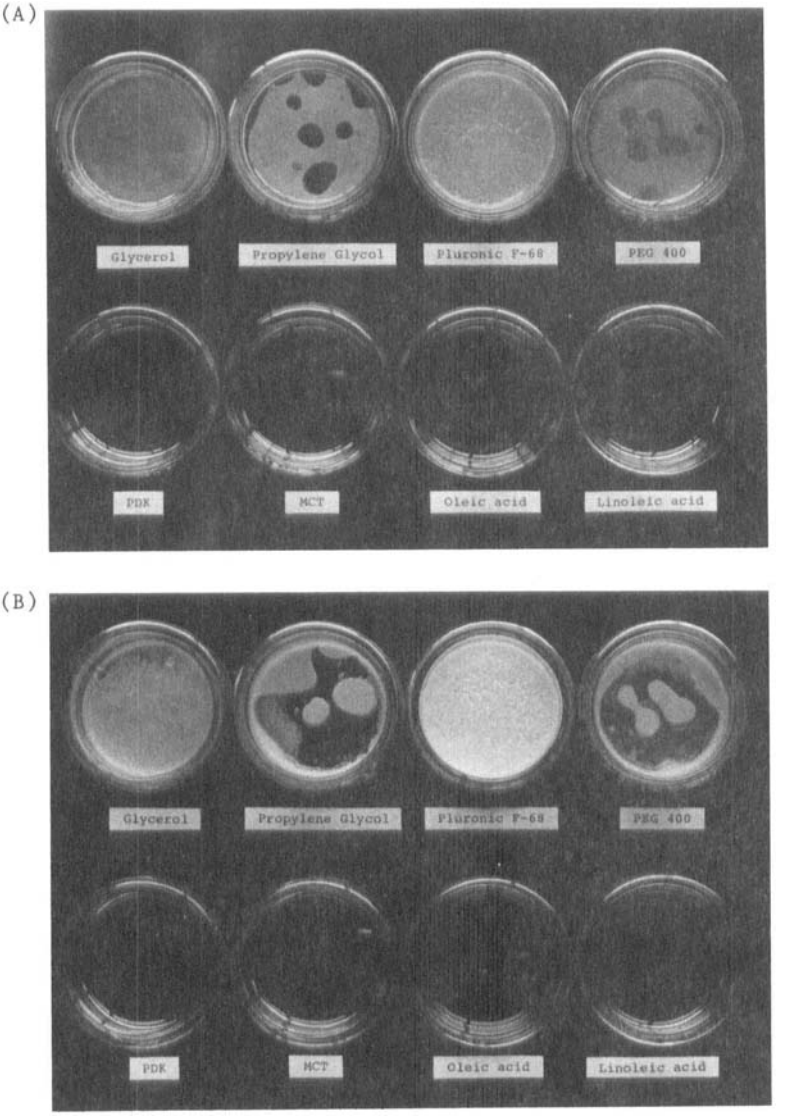

FIGURE 5

Photographs of mixtures of VEN with various carriers (1:1) :
(A) just prepared ; (B) after storing for 8 days
Upper line : glycerol, propyleneglycol, Pluronic F-68 and PEG 400 from left to right
Lower line : PDC, MCT, OA and LA from left to right

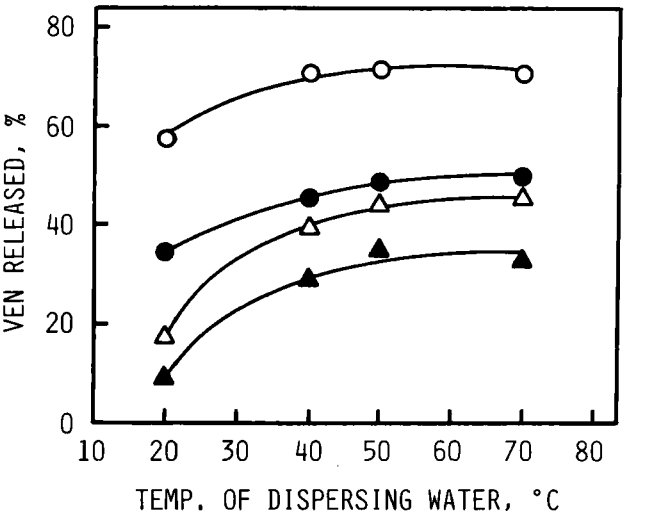

FIGURE 6

Effect of type of oily carrier on VEN releasing property of dry emulsion in water at 20-70°C : ○, MCT ; ●, LA ; △, OA ; ▲, PDC

lower than 50%. In the case of PDC, such a poor releasing property was due to the partial solidification of the drug in the dry emulsion particles. It was confirmed by a very broad drug's peak ranging up to the surfactant's one on a DSC chart (Fig.7). For the fatty acids, the low releasing value was attributed to the instability of the emulsion reproduced.

The drug releasing property of the dry emulsion prepared with the oily carrier method was also influenced by the amount of the carrier in the formulation. The relationship between the mixing ratio of MCT to the drug and the VEN releasing value of the dry emulsion is illustrated in Fig.8. The value increased with an increase in the ratio

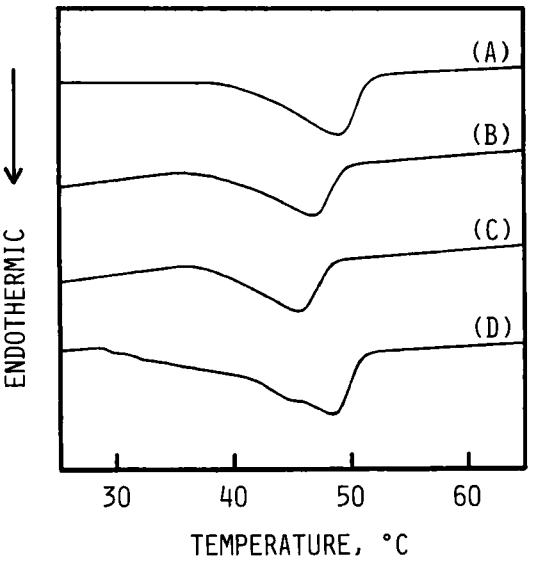

FIGURE 7

DSC thermograms of dry emulsions with VEN dissolved in various oily carriers : (A) MCT ; (B) OA ; (C) LA ; (D) PDC

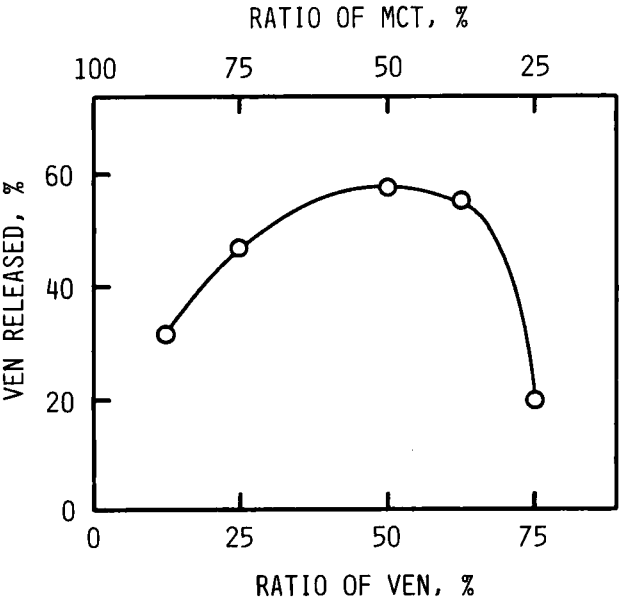

FIGURE 8

Effect of mixing ratio of VEN with MCT on VEN releasing property of dry emulsion in water at 20°C

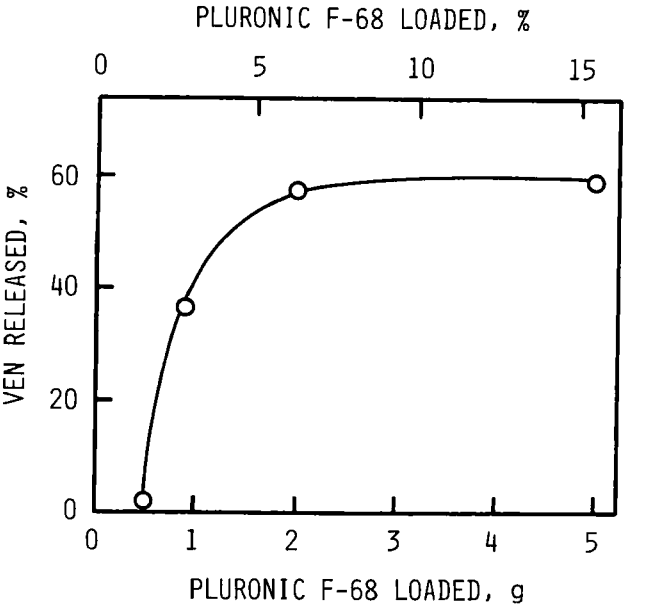

FIGURE 9

Effect of formulating amount of surfactant on VEN releasing property of dry emulsion in water at 20°C

of MCT up to 50%. It was presumed that the change in viscosity of oil drops incorporated in the dry emulsion particles was responsible for this phenomenon. Considerably low releasing value at 75% of VEN content was attributed to crystallization of VEN in the particle.

Effect of surfactant on VEN releasing property of dry emulsion

The drug releasing property also depended on the amount of surfactant formulated. As the weight percent of Pluronic F-68 increased, the releasing value increased drastically and leveled off above at 6.8% of surfactant content (Fig.9).

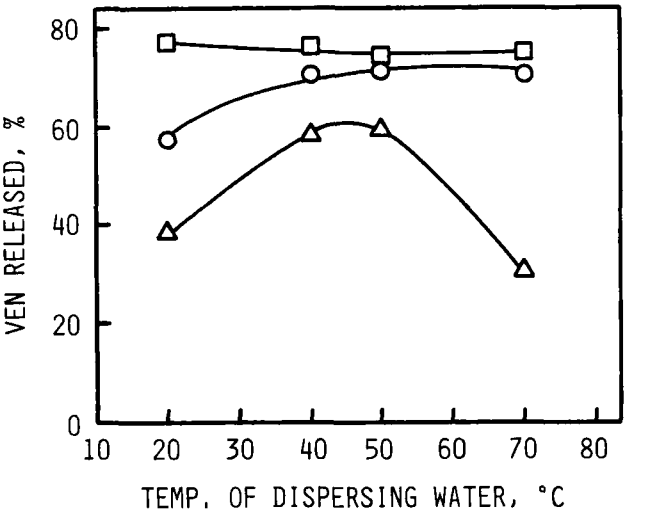

FIGURE 10

Effect of type of surfactant on VEN releasing property of dry emulsion in water at 20-70°C : ○, Pluronic F-68 ; △, Pluronic L-44 ; □, Tween 20

In our previous study (4), it was found that adsorption form of the surfactant on Aerosil 200 in the aqueous suspension is changed from monolayer to bilayer as the amount of surfactant increases, which affects the VEA releasing property of the resultant dry emulsion particle. In the present study, the adsorption form of Pluronic F-68 on Aerosil was presumed to change from monolayer to bilayer as the amount of the surfactant contained increased up to 6.8%. Above at 6.8% of surfactant content the resultant particle is considered to be hydrophilic enough to disperse and release lots of VEN droplets.

The type of surfactant also affected the VEN releasing property of the dry emulsion particle (Fig.10). When Tween

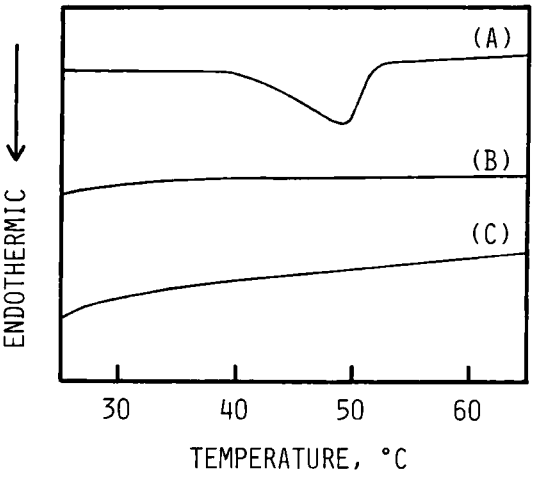

FIGURE 11

DSC thermograms of dry emulsions with VEN and various surfactant : (A) Pluronic F-68 ; (B) Tween 20 ; (C) Pluronic L-44

20 was formulated, the releasing property was much improved compared with Pluronic F-68. DSC analysis indicated that the excess amount of Pluronic F-68 in the dry emulsion particle was solidified (Fig.11). On the other hand, Tween 20 formulated in the particle can be in liquid state as shown in DSC chart (Fig.11). The physical state of these surfactants formulated in the dry emulsion may cause the difference in the VEN releasing property. This assumption was supported by a slight increase in VEN releasing value for the dry emulsion with Pluronic F-68 with increasing temperature from 20 to 40°C (Fig.10).

However, Pluronic L-44, which is also in liquid form at room temperature, offered the poorer drug releasing property to the corresponding dry emulsion than the other

surfactants tested. The low releasing value at room temperature (20°C) was attributed to the relatively lower HLB value of the surfactant. At higher temperature, the oily droplets were released much more probably because the Pluronic L-44 becomes more easily soluble, but the resultant emulsion was unstable at around 70°C. Pluronic L-44 has a cloud point of 65°C, which may be responsible for the instability of the redispersed oily droplets.

CONCLUSION

A waxy drug, VEN, could be transformed into the dry emulsion particle by the spray-drying technique as well as a liquid oily drug, VEA. The drug releasing property of the dry emulsions was closely related to the physical state of the drug. The good releasing property was provided when the dry emulsion was prepared with oily carriers. This dry emulsion released much drug and form a stable emulsion irrespective of temperature of the dispersing medium. When MCT and Tween 20 or Pluronic F-68 were used as an oily carrier and a surfactant, respectively, the best drug releasing property was obtained. Thus the dry emulsion system can provide an advanced dosage form of waxy drug as well as oily drug. This system is also applicable to an oily solution of poorly absorbable drug under investigating by the present authors.

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