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# IMPROVEMENT OF AQUEOUS SOLUBILITY AND DISSOLUTION KINETICS OF CANRENONE BY SOLID DISPERSION IN SUCROESTER

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## ABSTRACT

Sucroester 7 (sucrose di-stearate), by melting and rapid cooling, gives a product with a glassy appearance that corresponds to a low physical stability state or a high solubility power. This property, added to its surfactive characteristics, enables considerable improvement not only in aqueous solubility, but, to a greater degree, in the dissolution kinetics of canrenone. This result should lead to a reduction in the long lag time observed after oral administration before the diuretic effect of the product.

## INTRODUCTION

Solid dispersions are systems prepared for the purpose of improving dissolution, and thereby the bioavailability of active ingredients slightly soluble or insoluble in water.

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In the work presented here, the active ingredient is canrenone. It is a diuretic steroid, an antagonist of aldosterone. After oral administration, canrenone is rapidly resorbed but, due to its low aqueous solubility, a lag time is observed before activity begins, and the optimal effect is not seen until 18 to 24 hours following administration. An improvement in canrenone solubility and dissolution kinetics should normally shorten this delay.

The carrier employed is sucroester 7 (sucrose di-stearate). After melting and cooling, this product has a glassy appearance. This state is interesting in solid dispersions <1 to 10>, because it corresponds to a low structured state, between a crystallized and an amorphous state, with a low internal energy, normally leading to greater solubility.

## MATERIALS AND METHODS

### Raw materials

The main physical properties of canrenone (Rhône-Poulenc, Paris) (Figure 1) are molecular weight 340.44, melting point 165 to 166 °C, the aqueous solubility at 20 °C is 21 mg/ℓ, and UV absorption 292 nm.

Sucroester 7 (Gattefossé, Saint Priest, France) has a melting point between 44 and 45 °C.

### Systems investigated

#### Physical mixtures

Physical mixtures of canrenone/sucroester are prepared in a Turbula blender (Prolabo, Paris). They contain 0 to 100% of canrenone, varying in steps of 10%.

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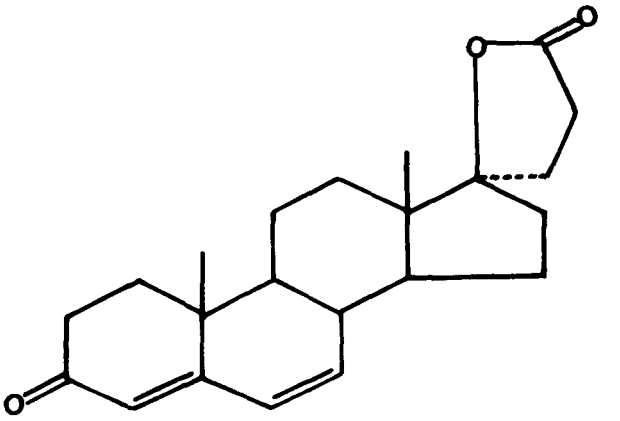

Figure 1 Canrenone

Solid dispersions

Solid dispersions are prepared using 10 g of the above-mentioned physical mixtures, by melting in a silicone oil bath, with manual stirring. When the liquid is homogeneous and transparent, it is cooled suddenly by steeping in a 2:1 mixture of ice and NaCl.

After solidification, the product takes on a brownish glassy appearance. Its hardness enables easy recovery and grinding (mortar). As will be seen later, the brownish appearance is due to slight 'caramelization' of the sucroester, and not to the degradation of the active ingredient.

Physical studies

The main objectives of these studies are (1) to determine if there is degradation or a chemical interaction between the ingredients of the solid dispersion, and (2) to evaluate the change in physical state between the physical mixtures and solid dispersions.

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The methods employed are the following.

- Thin layer chromatography (precoated TLC plates, silica gel 60F-254, Merck), the mobile phase being ethyl acetate or acetone/water (90:10). The products are previously dissolved in acetone/ethanol (50:50). The reading is taken in UV light at 254 nm.

- IR spectrometry (Perkin Elmer 257). The spectra are obtained on KBr tablets.

- Differential scanning calorimetry (Perkin Elmer DSC-II). The heating speed is 8 °C/min (slope 20, sensitivity 16).

During the experiments, the physical mixtures undergo two increases in temperature, the second one corresponding to the study of the melts. As well as noting the temperature of the peaks corresponding to the melting of each product, the areas under the curve are also measured. These values should normally evolve regularly, according to the concentration of each ingredient in the product. This study enables the detection of possible interactions between various ingredients.

## Solubility and dissolution studies

Solubility is measured by the saturation method at room temperature and at 37 °C on samples corresponding to 5 mg of canrenone. The sample is placed in 25 mℓ of deionized water (pH 5.47) and stirred for 48 h in darkness. The amount of dissolved canrenone is measured by UV absorption at 292 nm (Beckman 25 spectrophotometer). The absence of 'interference' with the sucroester had been previously checked. Results are the mean of six determinations. The heterogeneity of results can be explained by the difficulty in obtaining a sharply homogeneous sample of the solid dispersion, due to the manual stirring.

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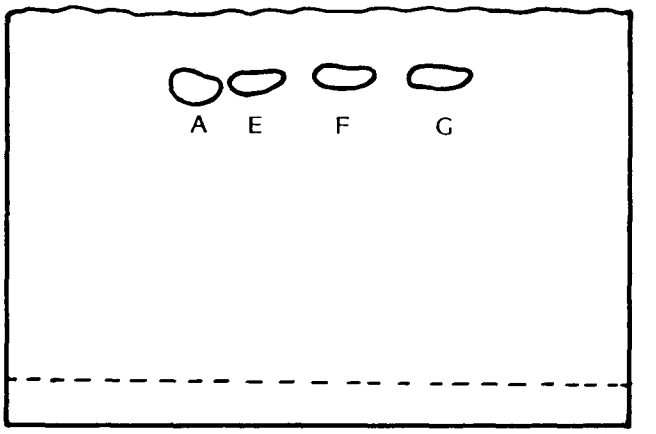


A pure canrenone, RF 0.79
E 10% canrenone physical mixture, RF 0.70
F 10% canrenone solid dispersion melt at 110 °C, RF 0.79
G 10% canrenone solid dispersion melt at 166 °C, RF 0.79

Figure 2 Thin layer chromatography

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Dissolution kinetics are carried out with a USP apparatus (Dissolutest, Prolabo, Paris) at 37 °C on samples containing 10 mg of canrenone. A pump (Minipuls 2 Gilson) continuously conveys the dissolution medium to a UV spectrophotometry measurement unit (Safas 210). The variability of the results can be explained as above.

## RESULTS AND DISCUSSION

### Stability of ingredients

As can be seen from Figures 2 and 3, neither the melting of canrenone alone (m.p. 165 to 166 °C) nor its melting with sucroester, whatever the temperature employed, modifies the product.

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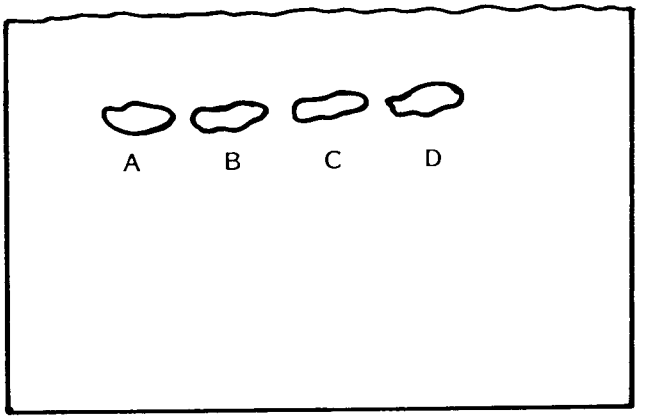


A pure canrenone, RF 0.73
B canrenone melt, RF 0.74
C 40% canrenone physical mixture, RF 0.76
D 40% canrenone solid dispersion, RF 0.76

Figure 3 Thin layer chromatography

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Furthermore, with respect to the IR spectra (Figure 4), it appears that, as in the case of the physical mixtures, the spectra of the solid dispersions are merely the addition of the spectrum of each ingredient individually (canrenone and sucroester).

These two experiments prove that the preparation of solid dispersions of canrenone and sucroester 7 by a melting process does not lead to degradation of the active ingredient, neither to a chemical interaction between the two products.

## Difference between physical mixtures and solid dispersions

The melting temperatures of canrenone and sucroester are reported in Table 1 for the physical mixtures and in Table 2 for the solid dispersions.

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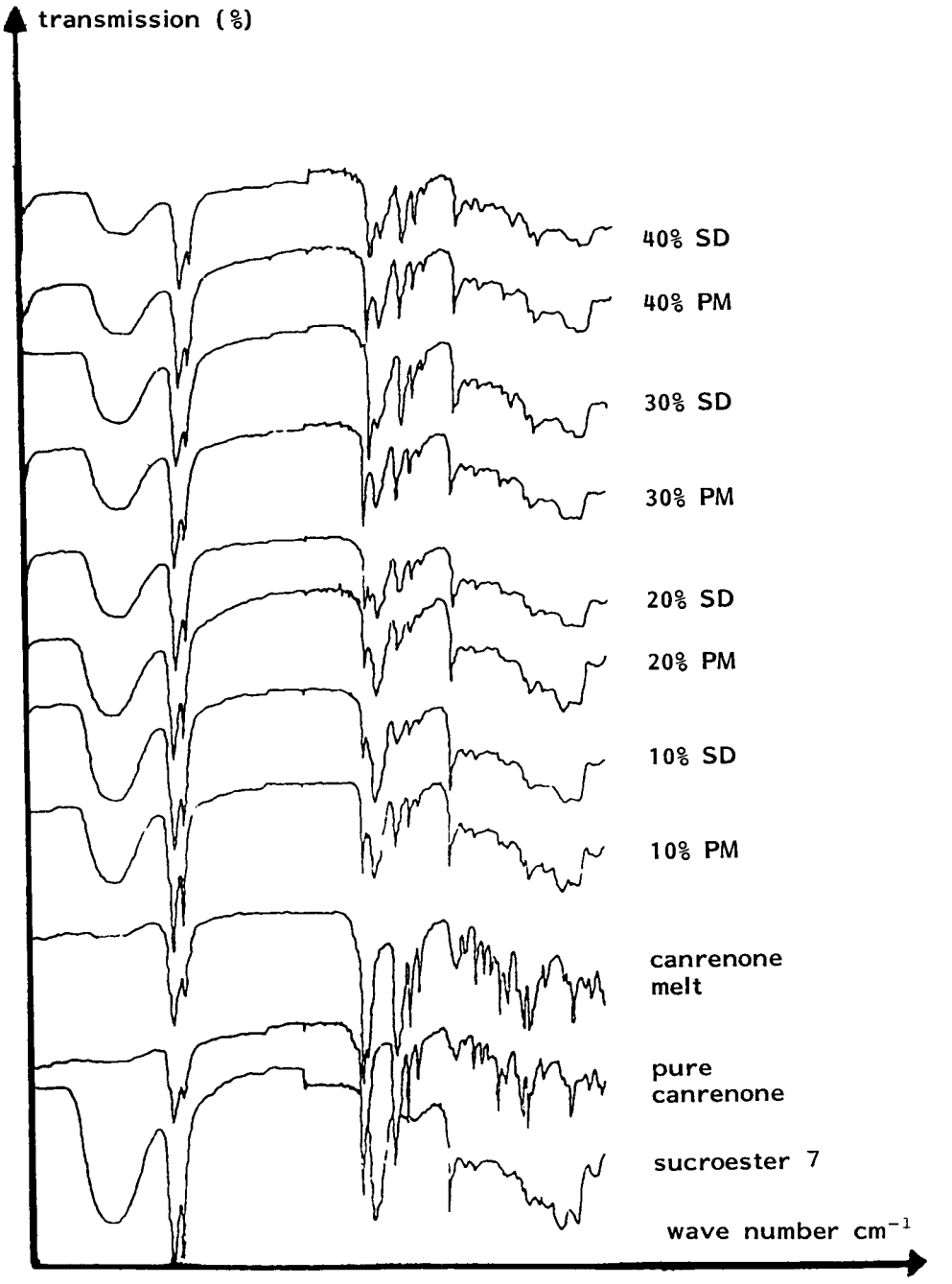


Figure 4 IR spectra of different proportions of physical mixtures (PM) and solid dispersions (SD)

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Table 1

Temperatures observed during the first pass

(Physical mixtures)

| canrenone (%) | sucroester 7 (%) | melting temperature of sucroester 7 | melting temperature of canrenone |
|---|---|---|---|
| 0 | 100 | 41 | - |
| 10 | 90 | 40 | 142 |
| 20 | 80 | 38 | 145 |
| 30 | 70 | 38 | 145 |
| 40 | 60 | 40 | 150 |
| 50 | 50 | 41 | 153 |
| 60 | 40 | 40 | 154 |
| 70 | 30 | 40 | 158 |
| 80 | 20 | 42 | 159 |
| 90 | 10 | - | 163 |
| 100 | 0 | - | 165 to 166 |

Table 2

Temperatures observed during the second pass

(Solid dispersions)

| canrenone (%) | sucroester 7 (%) | melting temperature of sucroester 7 | melting temperature of canrenone |
|---|---|---|---|
| 0 | 100 | 44 | - |
| 10 | 90 | 43 | - |
| 20 | 80 | 41 | - |
| 30 | 70 | 40 | - |
| 40 | 60 | 41 | - |
| 50 | 50 | 42 | - |
| 60 | 40 | - | - |
| 70 | 30 | - | - |
| 80 | 20 | - | 157 |
| 90 | 10 | - | 160 |
| 100 | 0 | - | - |

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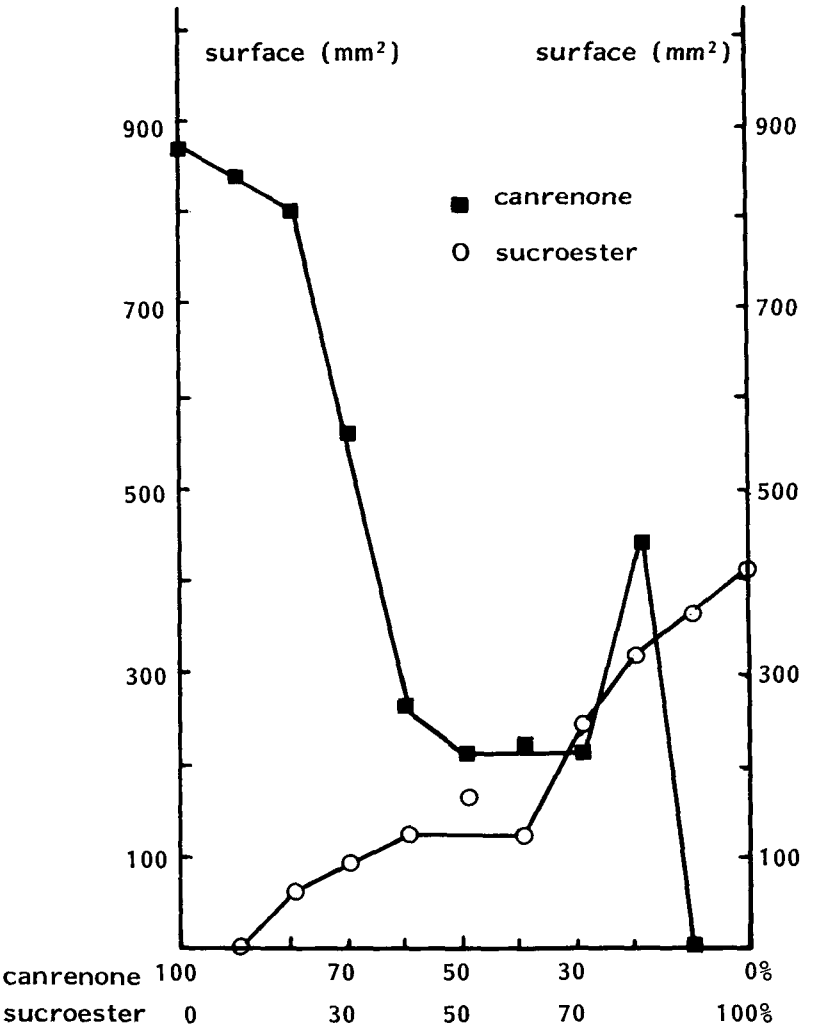


Figure 5 Analysis of area under curve of canrenone and sucroester

The melting temperatures obtained during the second rise in temperature indicate that there is a strong interaction between canrenone and sucroester, since there is no separate melting peak for these products when they are only in a small proportion in the melt.

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Table 3

Solubility study

| composition | solubility in $mg \cdot 10^3 cm^{-3}$ at ambient temperature | | at 37 °C | |
|---|---|---|---|---|
| pure canrenone | 21.7 ±0.9 | | 30.5 ±2.8 | |
| | physical mixture | solid dispersion | physical mixture | solid dispersion |
| canrenone/sucroester 7: | | | | |
| 10:90 | 49.6 ±12.1 | 48.5 ±7.4 | 54.6 ±14.0 | 51.0 ±2.2 |
| 20:80 | 54.2 ±7.3 | 59.6 ±10.7 | 53.0 ±2.8 | 54.0 ±2.9 |
| 30:70 | 38.0 ±5.5 | 42.5 ±7.5 | 49.0 ±8.8 | 47.3 ±4.7 |
| 40:60 | 38.8 ±4.2 | 40.8 ±6.6 | 49.6 ±3.8 | 50.6 ±6.3 |
| 50:50 | 36.3 ±1.2 | 36.0 ±3.7 | - | - |

The study of the area under the curve (Figure 5) of each type of peak confirms this fact, especially between 30 and 70% of canrenone. It was not possible to determine the kind of interaction, which is of a physical type only, but it is probably a solid solution.

## Water availability

The solubility study (Table 3) indicates that, whatever the temperature of the experiment, sucroester is beneficial for canrenone solubility, especially for the proportion canrenone/sucroester 20:80. However, it seems that there is no value in preparing solid dispersions compared with physical mixtures.

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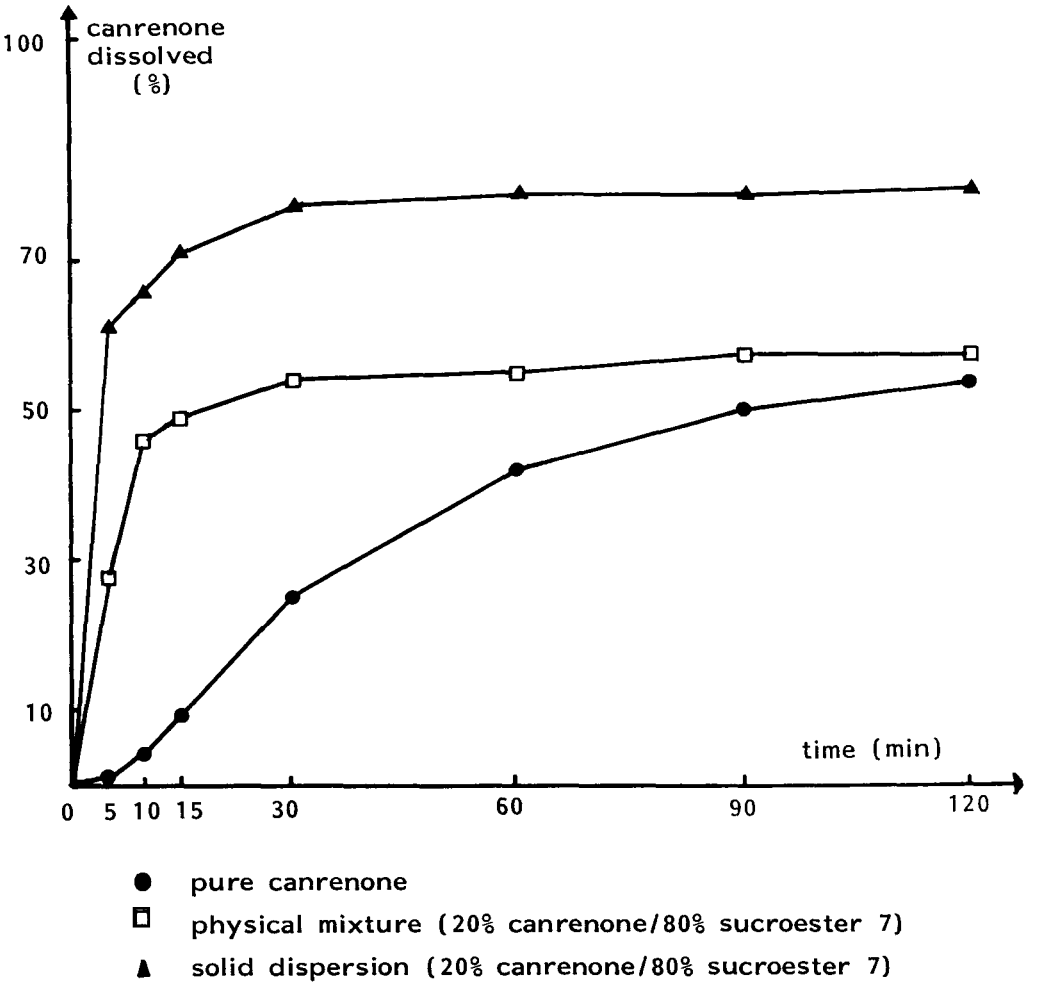


Figure 6 Dissolution rate of canrenone

The dissolution kinetics are more interesting.

The comparison of the physical mixture and solid dispersion (Figure 6) (canrenone/sucroester 20:80) reveals that the dissolution is more than twice as fast for the solid dispersion than for the physical mixture in the first five minutes of the experiment, and about 60% of the canrenone is dissolved (1% for pure canrenone).

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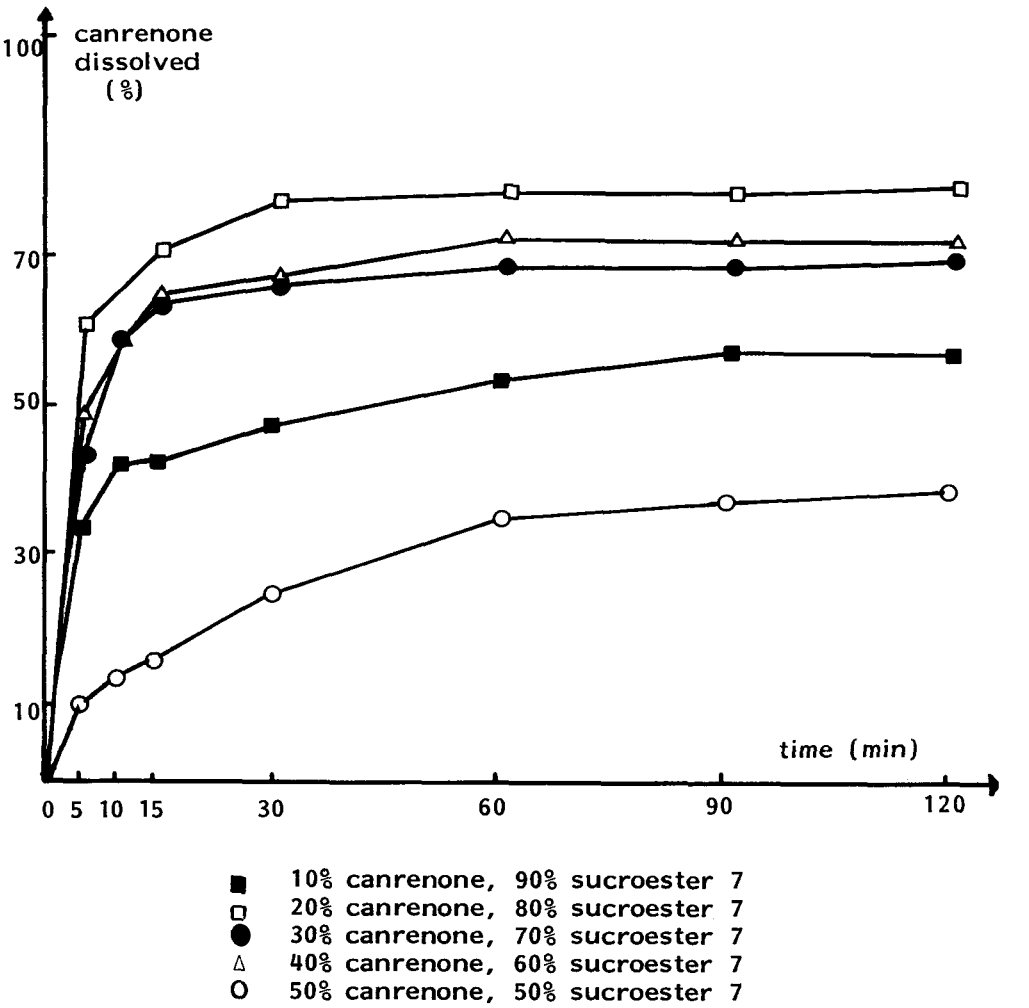


Figure 7 Canrenone dissolution rate from freshly-prepared solid dispersions

A comparison of the various solid dispersions (Figure 7) confirms the special dissolution power of the system with 20% of canrenone followed by systems with 30 and 40% of canrenone. It is interesting to note that the system with only 10% of canrenone does not have a good dissolution power.

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## CONCLUSION

In conclusion, it appears that the use of sucroester 7 is a very interesting method to improve the aqueous solubility and dissolution kinetics of canrenone, especially in the form of a solid dispersion. This can be attributed to the glassy state of the product obtained by melting, and probably also to the wetting and solubilizing effect of the sucroester, which can be considered as a surfactive product because of its 'amphiphilic' nature.

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