Thermochimica Acta, 92 (1985) 333-336
Elsevier Science Publishers B.V., Amsterdam

CALORIMETRIC STUDY AS A TOOL ON PREPARATION OF POLYETHYLENE GLYCOL SUPPOSITORIES

S. Srčič[+ 1], P. Bukovec[2], J. Šmid - Korbar[1]

[1]Department of Pharmacy, [2]Department of Chemistry and Chemical Technology, Edvard Kardelj University, 61000 Ljubljana, Aškerčeva 9, Yugoslavia

ABSTRACT

Through DSC and DDSC approach some findings in molecular pharmaceutics concepts of PEO suppositories were confirmed. It was stated that the cooling rate of solidification, core-crust location in suppository and aging, influence the nature of PEO 4000 structure.

INTRODUCTION

Polyethers of $\left[(CH)_2 - O\right]_n$ type (PEO) find their use also in pharmacy and medicine as a suppository base. Because of their high melting point, far above the body temperature ($\sim 60^{o}C$), their use is bound to the solution of the prepared dosage form and subsequent release and dissolution of active principle-drug.

As the literature shows (1) the differences in physical properties of PEO e.g. their water solubility speed, can be explained through the molecular conformation and the crystal structure (1, 2). Firstly supposed zigzag and meander form of PEO molecules was lately substituted through the 7_2 Helix conformation with oxygene atoms located in the interior. This location results in higher dipol moment and chemical reactivity of PEO molecules (3, 4).

It has already been stated that the different technology, i.e. fast and slow cooling rate of PEO 4000 used as a suppository base, results in different physical properties (1, 5): density, hardness, dissolution time and x - ray difraction, which anticipate the suppository bioavailability.

The fast cooling rate favours the more amorphous structure compared to the slow cooling approach (1). The x - ray measurement showed, that the result of this two different cooling rates were the two different monoclinic modifications, I and II. Fast cooling rate favours the modification II (5). Nevertheless, the fast cooloing rate favours faster dissolution of PEO molecules

Proceedings of ICTA 85, Bratislava

and faster pharmacological action. The dissolution time difference amounts ~10 % (1). The calorimetric approach in this report, has the ambition to throw some light on the thermic properties of PEO suppository base, which are the result of:

1. different cooling rate
2. different core - crust location in the suppository and
3. shelf time .

EXPERIMENTAL

PEO 4000 was melted on a steam bath and heated to 70°C. The melted mass was poured into the suppository forms of the room and ice - salt bath (-10°C) temperature, respectively. The DSC analysis was performed within some days after preparation.

The DSC Mettler TA 2000 C System (Mettler Instruments AG, CH) was used. Samples (of 20-50 mg) and references (α-Al_2O_3 of about 20 mg and PEO 4000) in Pt - crucibles with lid - hole were heated with 4° and 5° K/min., respectively, in air atmosphere of 30 ml/min. flow. The DSC range was 100 and 50 μV , respectively, and the chart speed 60 cm/h. Also the DDSC approach was used to confirm the differences among the investigated suppositories. The viscosity of melted mass was determined with rotational viscometer Rheotest 2 (WEB Medingen, GDR) and the density of suppository base with Mohr - Westphal balance.

RESULTS AND DISCUSSION

Thermogram of PEO 4000 (crust of the suppository), Fig. 1, shows three endothermic changes, among which the second, the greatest, represents the melting process. The first coincides with the onset of density decreasing (6) of solid PEO and the third with viscosity change of the melted PEO (6). We can hardly speak about the precise ground of this density and enthalpic change respectively, but the reason could be the change in specific molecular volume because of helices denaturation - intramolecular melting process (7). The melting peak as a measure of the phase transition solid/liquid is comprehensive and

its quantitative value was taken as the measure of the crystalinity degree and the presence of the corresponding monoclinic modification, respectively. Also the third enthalpic change, which reflecting in viscosity change should have the ground in the helix - coil form equilibrium of PEO molecules (7). Comparing the melting peak of suppositories crust at slow and fast cooling rate solidification it was found, through DSC and DDSC (Fig. 2) approach, that the difference of 2,2 and 6,3 %, respectively, exists.

The next step in our molecular pharmaceutics was to confirm the difference between core and crust. It was expected, because of the nature of cooling the suppository in mould, that the slow cooling in the core would prefer the higher crystalinity and the modification I, respectively. The DDSC (Fig. 3) of core and crust in suppository proved our expectations. The use of PEO suppositories has shown, that their hardness increases with the shelf time. According to literature (1) it was possible to conclude, that this increase reflects in the greater crystalinity of the aged suppository. The DDSC thermogram (Fig. 4) of a fresh and a 4 month aged crust (slow cooling approach) confirmed that, and the quantification brings a difference of 1,4 %.

CONCLUSION

The selected thermal (DSC and DDSC) approach was found as appropriate for the evaluation of technology (fast and slow cooling rate) and moulding of suppositories and their structure changes through aging. The method anticipates also its value in the research of drug inclusion influence on the base and vice versa.

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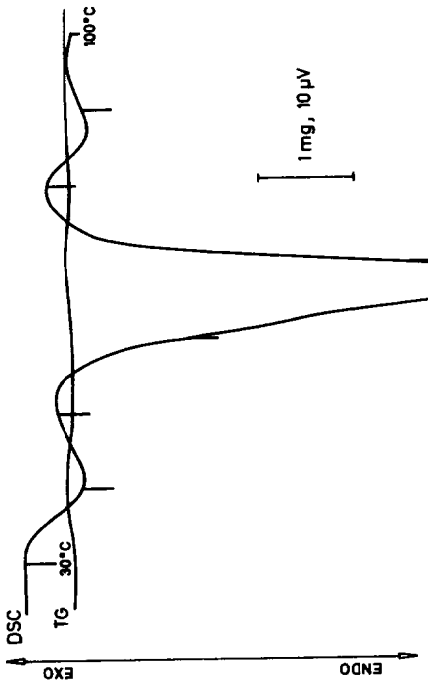

Fig. 1: DSC of PEO 4000 suppository crust.

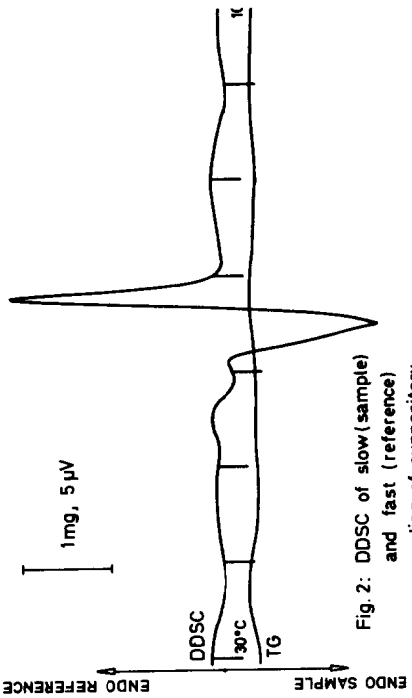

Fig. 2: DDSC of slow (sample) and fast (reference) cooling of suppository.

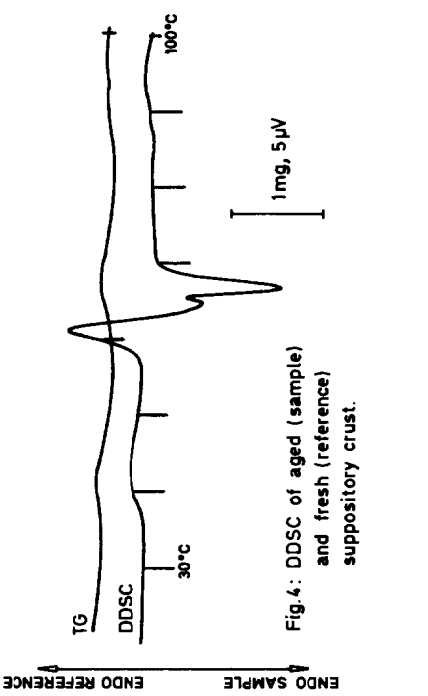

Fig. 4: DDSC of aged (sample) and fresh (reference) suppository crust.

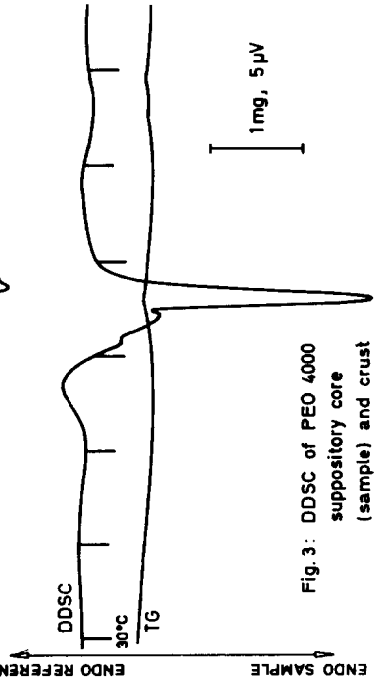

Fig. 3: DDSC of PEO 4000 suppository core (sample) and crust (reference).