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DSC AS SUPPORT FOR THE DEVELOPMENT OF SUPPOSITORIES

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ABSTRACT

The use of DSC, which allows to study modifications in the suppository bases and behaviour of the drug substance and excipients, is proposed for the development of suppository: choice of the suppository base or adjuvants, manufacture and storage conditions.

INTRODUCTION

Fatty suppository bases are complex mixtures of triglycerides which are known to exhibit three different crystalline modifications α, β', β and a vitrous state. The metastable forms α and β' undergo transition to the higher melting stable β form. In addition, the triglycerides, the excipients and the active ingredient may give rise to solid solutions, complexes or eutectics, which then makes prediction of the behaviour difficult.

The melting point of suppositories increases on storage (1-10). The bioavailability of the suppositories must be guaranteed and the melting process of the suppository base is the first point to be carefully controlled.

EXPERIMENTAL AND DISCUSSION

Suppositories prepared using various drug substances, excipients and suppository masses were investigated with DSC (DSC-2 Perkin-Elmer, weight 5-6 mg, 2.5 °C. min^{-1} heating rate, nitrogene) and their behaviour studied after storage.

Three main peaks - low, medium and high melting - were observed. DSC curves of fresh suppositories show a mixture of medium and high melting parts. On storage, at temperatures of 20 - 25 °C they undergo transitions to the high melting form. After storage at 27.5 - 30 °C, due to partial melting, the lower melting range appears, but the end of the melting increases.

A typical DSC behaviour is shown in fig. 1. The plot of % solid versus temperature (fig. 1b) is very often prefered for ease of interpretation of the dissolution rate curves.

Suppositories manufactured by compression, for example with Witepsol H15 may contain more stable form than fused suppositories, but on storage the changes are very similar to those seen with fused suppositories (example fig. 2 for an experimental suppository and fig. 3 for paracetamol suppository).

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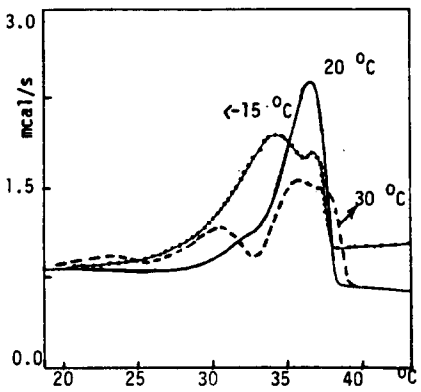


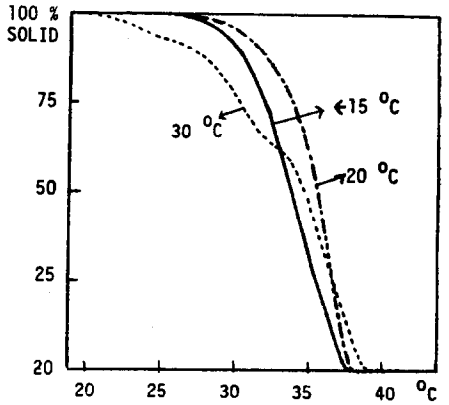


Fig. 1: DSC curves of suppositories stored 2 years at <-15, 20 and 30 °C.

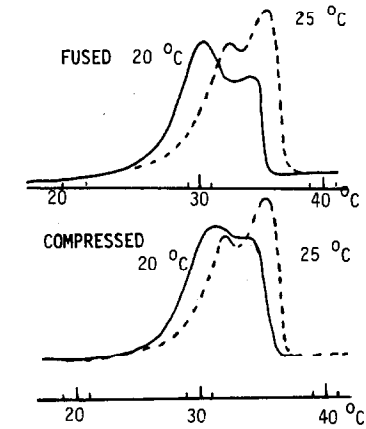


Fig. 2

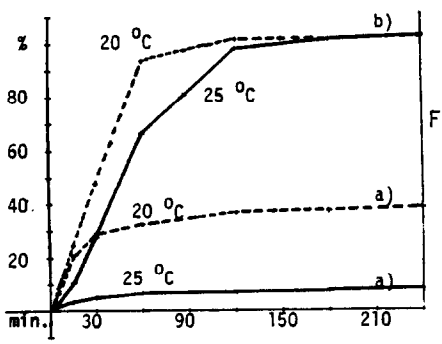


Fig. 4

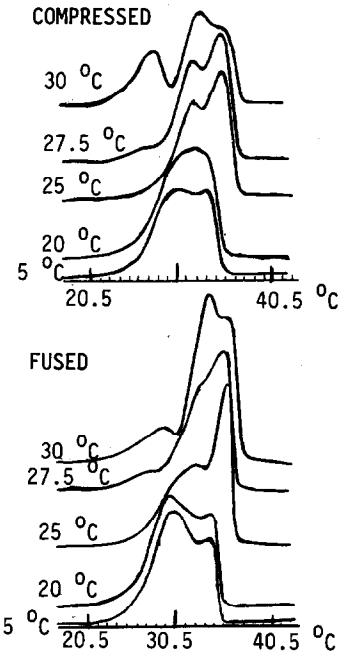


Fig. 3

Fig. 2. DSC behaviour of experimental suppositories after 6 months storage.

Fig. 3. Fused and compressed paracetamol suppositories stored 8 months.

Fig. 4. Dissolution rate curves at a) 36.5 °C and b) 37 °C of fused paracetamol suppositories stored 8 months at 20 ° and 25 °C.

The hardning effect observed by DSC is confirmed by the dissolution rate curves (fig. 4) and other physical parameters (table 1).

Table 1: Physical parameters of stored suppositories after 6 months storage

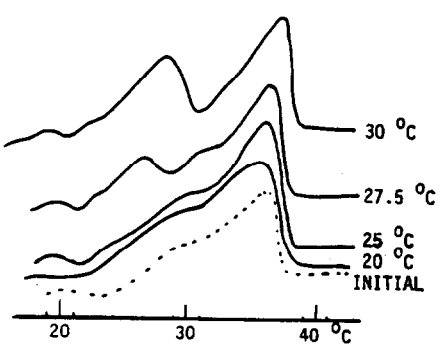
	Experimental suppository fused			Experimental suppository compressed			Paracetamol fused suppositories				
	Initial value	20 °C	25°C	Initial value	20 °C	25°C	Initial value	20 °C	25 °C	27.5 °C	30 °C
drop point °C	37.4	37.8	40.2	37.2	38.4	39.9	39.5	39.2	40.8	42.6	39.4
penetration (37 °C)	9.5'	10'	16'	7.5'	10'	13'	11'	12'	18'	15'	13'
desintegration (37 °C)	9'	10'	17'	7'	10'	13'	10'	11'	19'	17'	14'

The suppositories masses were investigated. Themselves they undergo such transitions. This fact has a consequence if the suppositories are manufactured by compression and must be carefully controlled.

It has been assumed that low melting glycerides of short chain length accelarate the transition to the high melting form due to quicker attainment of the stable form (3,5). This may explain the behaviour of suppocire AM, whose hardning effect on storage was found lower as it is for Witepsol, but the melting range is quite uncomfortable (fig. 5).

DSC allows to study the melting behaviour of the components of the suppository. For example for the suppositories of paracetamol, in both manufacturing processes "fused" or "compressed" after melting of the triglycerides, the DSC melting peak of paracetamol is observed. Some drug substances which we analysed melt with the suppository mass. In dissolution rate experiments the equilibrium process is not the same if the drug substance is melted in the mass, or if it remains in a crystalline state.

Fig. 6 shows DSC curves of experimental compressed suppositories containing mannitol and a tenside with the same composition, changing the suppository base. The DSC curve is valuable for the choice of the mass.



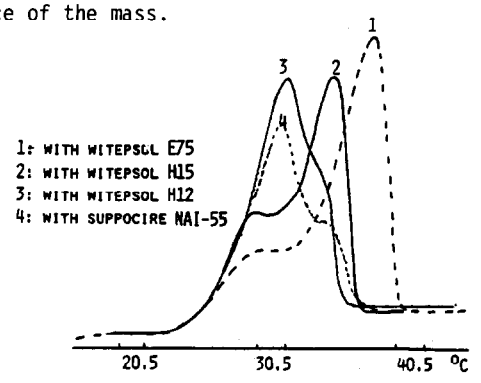


Fig.5. DSC curves of suppositories made with suppocire AM after 6 months storage

Fig.6. Influence of the suppository mass on the DSC melting curves of mannitol compressed suppositories of the same composition.

Fig. 7 gives the DSC and the dissolution rate curves of 2 batches of a mannitol suppository made with the same raw materials. Both methods show a big difference in the batches, due to an unreliable manufacturing process. DSC is useful for checking the manufacturing reproducibility.

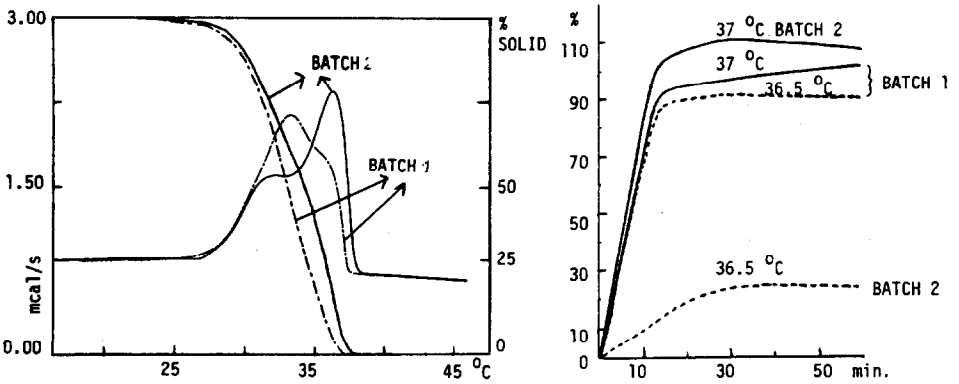


Fig. 7a). DSC curves of 2 batches of compressed suppositories with Witepsol H15 of the same composition, b) Dissolution rate curves of the 2 batches.

CONCLUSION

In comparison to melting point or drop point determinations the DSC has the advantage of analysing the whole melting range which shows the polymorphic state. The DSC is useful:

- For the formulation: choice of the suppository mass and the excipients in order to attain the stronger depressing effect of the melting point and knowledge of the thermodynamic behaviour of the drug substance with the triglycerides.
- To study the polymorphic transitions in order to control them:
  a) manufacturing of metastable forms and prevention of transitions by means of adjuvants or storage conditions (low temperatures).
  b) manufacturing of the stable form and use of excipients which depress the melting point by means of thermodynamic effects.
- To check the manufacturing process.

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