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DIFFERENTIAL THERMAL ANALYSIS OF POLYETHYLENE GLYCOL AND GLYCEROL MONOSTEARATE SUPPOSITORY BASES CONTAINING THEOPHYLLINE

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ABSTRACT

Water soluble polyethylene glycol 4000 (PEG4) suppositories were prepared containing 4% (w/w) theophylline. Various concentrations of polyethylene glycol 1000 (PEG1) and glycerol monostearate (GMS) were also added. Differential thermal analysis (DTA) of the PEG4 and PEG1 combination suppositories showed no melting endotherm for theophylline. But when theophylline concentration in the base was 12% (w/w) and above, sharp endothermic peak of theophylline was obtained. In contrast, when GMS was added as a base material above 50% (w/w) with PEG4, the melting endotherm of theophylline (4%, w/w) appeared at 273-274°C. The melting endotherm of the suppository bases increased upto 2 to 4°C due to storage at 4°C for six months.

INTRODUCTION

Fatty bases are commonly used for suppository preparation. The major disadvantage of fatty suppository base is that the base is immiscible with the aqueous rectal fluid and the drug release is totally dependent on melting of the base at body temperature, 37°C. This creates a serious stability problem during storage, because in many countries temperature goes beyond 37°C in summer. Therefore attention has been paid towards the development of water miscible suppository bases of higher melting temperature. Polyethylene glycol 4000 (PEG4), a wax type water miscible polymer is being investigated by the researchers to make different solid dispersions (1). Nakajima *et al* (2) and Onishi *et al* (3) reported sustained release suppository formulations containing PEG4 as a base material. Drug release characteristics of the polyethylene glycol suppositories have also been reported (4). Although PEG's have already demonstrated its usefulness in suppository and solid dispersions of drugs, each formulation needs careful evaluation. Because the thermal history of the PEG containing formulations may affect the dissolution rates of both the drug and the base itself (5,6). In the present study the thermal characteristics of theophylline supppsitories prepared from PEGs and GMS have been reported. Changes in thermal properties due to storage are also reported.

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MATERIALS

Polyethylene glycol 1000 (BDH), polyethylene glycol 4000 (BDH), glycerol monsotearte (E. Merck), theophylline, anhydrous (E. Merck); other chemicals were of reagent grade.

METHODS

Preparation of Suppositories : A series of six suppository bases were prepared by mixing PEG4 and PEG1 (total weight 14 g) in 250 ml glass beaker. Concentration of PEG1 in the PEG4 was 0, 10, 20, 30, 50 and 70% w/w. They were melted at 90°C in a hot plate magnetic stirrer. To each beaker 0.56 g theophylline (4% w/w of the base) was added and stirred for 5 minutes at 90°C. The molten bases were then made into torpedo shaped suppositories using stainless steel mold and they were cooled slowly to room temperature. Similarly, another series of PEG4 suppositories were prepared using glycerol monostearte (GMS) instead of PEG1 as a combination. Another series of six suppositories were prepared with concentrations of theophylline 2,4,8,12, 16 and 20% w/w in PEG4 base. All suppositories were kept in a dessicator at room temperature until used. A set of suppositories were stored at 4°C in a refrigerator for six months.

Differential Thermal Analysis : The differential thermal analysis of the suppositories was studied using a Differential Thermal Analyzer (DTA 30, Shimadzu, Japan). The instrument was calibrated using Indium.

RESULTS AND DISCUSSION

Differential thermal analysis is a valuable tool for characterizing solid dispersions containing drugs. The physical state of drug, whether crystalline or molecular dispersion can be assessed especially after prepared by melt cooling method. Moreover, any changes in the thermal characteristics of the base can also be detected by this method. In this experiment, theophylline (4% w/w) suppositories were prepared using PEG4 and PEG1 combination bases. When theophylline was added to the molten PEG bases at 90°C, it dissolved and formed a clear solution. But when cooled, theophylline could recrystallize again or may form homogenous molecular dispersion. The DTA experiment showed no melting endotherm of theophylline in PEG4 and PEG1 combination suppositories (Fig. 1) indicating that a molecular dispersion of theophylline was formed during cooling of the PEG bases. The melting endotherm of the PEG4 was found at 60°C (Fig. 1) which gradually reduced to 47°C with the increase in concentration of PEG1 (Table 1). This lowering of melting endotherm with the addition of PEG1 was due to low molecular weight of PEG1 polymer.

The increase in concentration of theophylline upto 8% w/w in the PEG4 base did not show appreciable endothermic peak for the theophylline. However the PEG4 suppositories containing 12, 16 and 20% w/w theophylline showed sharp endothermic peaks at 273 to 247°C which is characteristic for theophylline (Fig. 2). Although theophylline was dissolved in hot PEG4 melt, even at high concentration of 20% w/w, it is clear from the DTA analysis that a portion recrystallized during slow cooling process in the suppository dies.

The DTA analysis showed that the physical state of theophylline in PEG4 and GMS mixed base is entirely different than that of PEG4-PEG1 base. Even at low concentration of theophylline (4% w/w), the endothermic peaks at 273-274°C appeared when PEG4:GMS ratio was 7:3. Sharp endothermic peaks of theophylline was obtained when PEG:GMS ratio was 3:7 and 1:9 (Fig. 3). This is certainly due to low solubility of theophylline in PEG4 and GMS mixed base. Unlike PEG4 and PEG1 mixed bases, the melting endotherm of PEG4 and GMS base did not vary significantly due to changes in the proportion (Fig. 3). At all proportions of PEG4 and GMS the melting endotherm remains within 56° to 60°C (Table 1). This is due to close melting points of PEG4 and GMS.

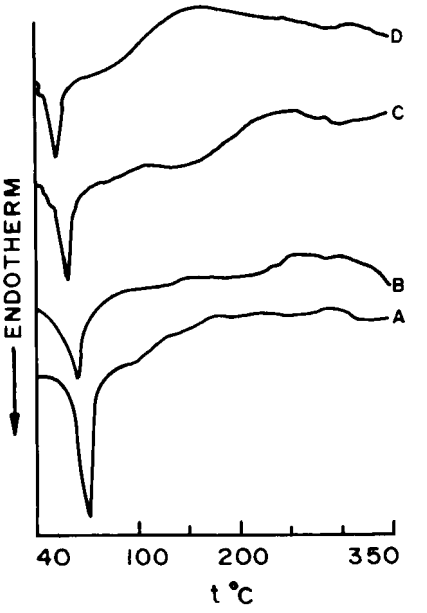

Figure 1. DTA thermograms of PEG4 and PEG1 based suppositories containing 4% w/w theophylline. PEG4 and PEG1 ratio: A, 10 : 0; B, 7 : 3; C, 5 : 5; D, 3 : 7.

Table 1. Melting points of the base materials and theophylline obtained from differential thermal analysis of suppositories.

Base composition	Ratio	Base melting endotherm (° C)	Theophylline melting endotherm* (° C)
PEG4 and PEG1	10 : 0	60	No peak
	8 : 2	59	No peak
	7 : 3	53	No peak
	5 : 5	50	No peak
	3 : 7	47	No peak
PEG4 and GMS	10 : 1	60	No peak
	8 : 2	58	No peak
	7 : 3	56	No peak
	5 : 5	57	273
	3 : 7	55	274
	1 : 9	56	274
PEG4 and PEG1**	3 : 7	51	No peak
PEG4 and GMS**	3 : 7	57	273

* = Theophylline content 4% (w/w) of the base. ** = Stored at 4°C for six months.

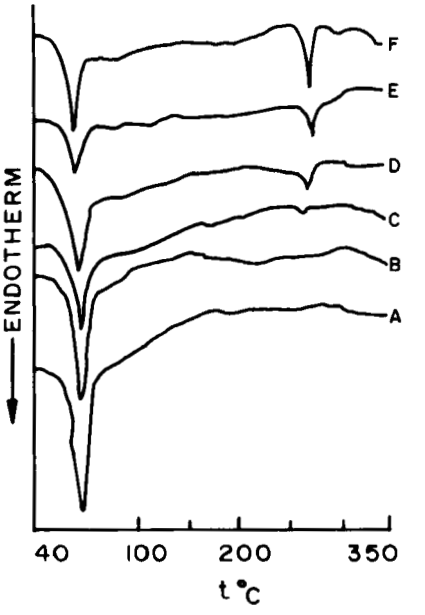

Figure 2. DTA thermograms of PEG4 suppositories. Theophylline content (% w/w) in the PEG4 base : A, 2%; B, 4% ; C, 8% ; D, 12% E, 16% ; F, 20%.

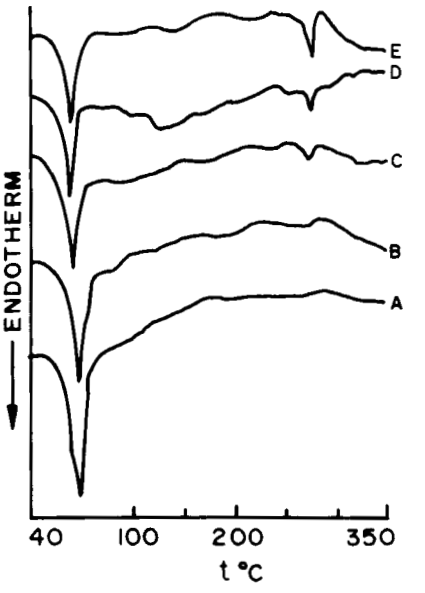

Figure 3. DTA thermograms of PEG4 and GMS based suppositories containing 4% w/w theophylline. PEG4 : GMS ratio: A, 10:1; B, 7:3; C, 5:5; D, 3:7; E, 1:9.

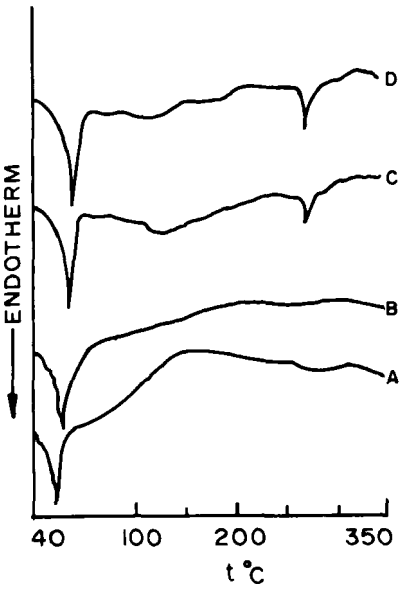

Figure 4. DTA thermograms of freshly prepared and cold stored suppositories. A, freshly prepared PEG4 : PEG1 (3:7) suppository; B, same product stored at 4°C for six months; C, freshly prepared PEG4 : GMS (3:7) suppository; D, same product stored at 4°C for six months.

Storage of the suppositories at 4°C for six months showed an increase in melting endotherm of PEG4 : PEG1 (3 : 7) base to 51°C compared to 47°C obtained from the freshly prepared sample. Similarly PEG4 : GMS (3:7) base showed melting endotherm at 57°C after cold storage whilst it was 55°C for freshly prepared samples (Fig. 4). There was no change in the melting endotherm of the theophylline in the PEG4 : GMS suppositoriy base due to cold storage. The increase in melting endotherm of the bases after cold storage was due to semicrystalline nature of the PEG polymer. During cold storage, a portion of the amorphors region of the PEG molecules may have formed crystalline lamellae which required higher temperature for melting compared to that of freshly prepared samples. Mandelkern (7) reported that thermal history of a polymer may determine the solid structure which has also been reported for PEGs (5). PEG4 and PEG1 (3:7) mixture showed an increase of 4°C due to storage, whilst the PEG4 and GMS mixture showed only an increase in 2°C after six months of storage (Fig.4). Little increase in melting endotherm in the PEG4-GMS mixture (3:7) was due to lower proportion of the PEG4 polymer and also because of the fact that GMS is not a semicrystalline material.

It is worth mentioning here that the DTA thermograms of the suppositories did not show either exothermic or endothermic peaks other than those for the base material and theophylline. This indicates that neither a metastable nor a permanent complex was formed between theophylline and the base material. It has been reported earlier that the PEG4 forms a metastable complex with phenobarbitone, which was characterized by a sharp endothermic peak in the DTA thermograms (8). No such extra characteristic peaks were observed in these experiments.

CONCLUSION

Mixtures of polyethylene glycols of different molecular weights or in combination with glycerol monostearate can be used as an excellent suppository bases. It is also possible to manipulate the melting point by mixing various grades of PEGs. However, the state of the drug in the suppository base, i.e. whether crystalline or molecular dispersion should be carefully evaluated, where DTA can be an useful tool. The nature of drug dispersion will affect the dissolution rate. Any change in the physicochemical properties of the material due to storage, incompatibility or complex formation may also be detected by DTA. Therefore it can be concluded that the thermal analysis of the suppository formulations should be an essential part of the product developmental process. The theophylline release kinetics from these suppositories will be reported later.

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