

Characterization and Compatibility Studies between Policosanol, a New Hypocholesterolemic Drug, and Tablet Excipients Using Differential Scanning Calorimetry (DSC)

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Summary

Characterisation of policosanol, a new active principle composed of 8 high molecular weight fatty alcohols, viz. 1-tetracosanol, 1-hexacosanol, 1-heptacosanol, 1-octacosanol, 1-nonacosanol, 1-triacontanol, 1-dotriacontanol, and 1-tetratriacontanol, shows it have a very stable, well defined composition which is reproducible from batch to batch. Compatibility studies by differential scanning calorimetry (DSC) and thermogravimetry (TG) gave very useful physicochemical information and reveal the characteristic transitions, as well as the thermal stability of this drug. DSC facilitated compatibility studies between policosanol and several tablet excipients generally used for the manufacture of this pharmaceutical dosage form. It is seen that the combination of policosanol with each excipient in every one of the ratios used did not produce any changes in the melting point of policosanol or those of the excipients mixed with it. Also, no new peaks were observed in the policosanol/excipient mixtures. It can be concluded from these results that no dissolution of policosanol in the excipients occurs, and also that no physicochemical interactions take place between them.

Introduction

In developing the formulation of a pharmaceutical solid dosage form, it is very important to select the excipients to be used in order to increase the administration and bioavailability of the drug and, also, to avoid changes in the physical, chemical, microbiological, or therapeutic properties. In order to diminish the toxicity and guarantee a good pharmacological effect it is necessary to know the possible interactions between policosanol and the excipients that may be used. Policosanol is a mixture of eight primary fatty alcohols of high molecular weight comprising mainly 1-octacosanol ($\approx 65\%$); the other alcohols in the mixture are 1-tetracosanol ($\approx 0.7\%$), 1-hexacosanol ($\approx 6.7\%$), 1-heptacosanol ($\approx 3.3\%$), 1-nonacosanol ($\approx 0.8\%$), 1-triacontanol ($\approx 13.1\%$), 1-dotriacontanol ($\approx 5.4\%$), and 1-tetratriacontanol ($\approx 0.9\%$)^[1,2]. Also, the excipients should be suitable for the proposed manufacturing process. The chemical, physical, and mechanical properties of policosanol were previously studied^[3] in order to determine its behavior for the development of this pharma-

ceutical formulation. The compatibility between the different tablet excipients to be considered in the formulation, such as diluents, disintegrants, lubricants, and others^[4], and policosanol were studied using DSC because thermal analysis permits investigation and prediction of any physicochemical interaction between them^[5].

The development of a tablet formulation usually requires the presence of different excipients and their compatibility with policosanol was therefore studied. The advantage of DSC over more traditional compatibility screening methods is that no long-term storage of the mixture is required prior to evaluation and differential thermal analysis can aid immensely in the evaluation of new compounds and their screening for compatibility with various solid dosage form excipients^[6–10].

Changes in the thermogram of a mixture, such as unexpected shifts, depressions, and addition or loss of peaks are considered to be significant. Prior to the compatibility study, the objective of the present work, thermal characterization of policosanol and each one of the excipients was undertaken. This was done in order to discover the characteristic thermal transitions of each one of the substances, which is very important for corroborating the presence or absence of chemical incompatibilities.

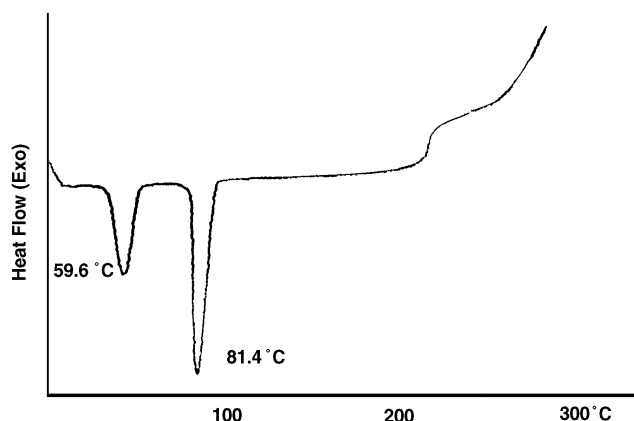


Figure 1. DSC thermogram of policosanol.

Results and Discussion

Figure 1 shows the DSC thermogram of batch 30821197 of policosanol. Two endothermic transitions were observed, one at 59.6 °C and other at 81.0 °C, and a third one of exothermic type was seen at a temperature near 200 °C, which is due to the thermal decomposition of policosanol. These endothermic transitions were not expected, because while the mixture of eight components may produce 8 peaks only two were to be seen. To determine the origin of these transitions, the same thermal analytical technique was used to study five of the main alcohols present in policosanol that were used as reference substances. The result of each melting transition is reported in Table 1.

Table 1. Melting temperature of five alcohol's present in policosanol

Alcohol	Melting temperature (°C)
1-tetracosanol	75.9
1-hexacosanol	81.3
1-heptacosanol	82.1
1-octacosanol	83.0
1-triacontanol	85.7

Figure 2 shows the DSC thermograms of each one of the excipients considered in this study and the thermogram of policosanol analyzed by thermogravimetry. The latter was determined in order to recognise whether a loss of mass occurs in the temperature range where the transitions take place, and to determine whether these transitions are related to a melting process or not.

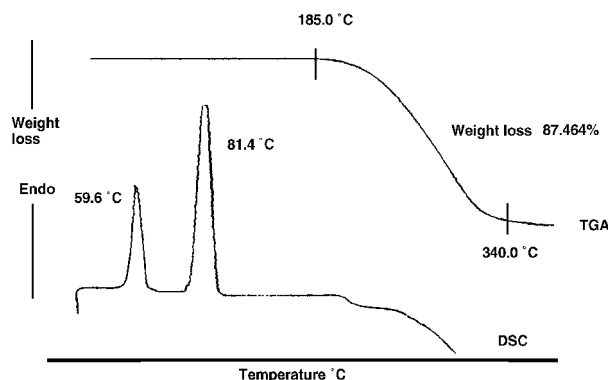


Figure 2. TG and DSC thermograms of policosanol.

No loss of mass was detected in the temperature range between 35 to 185 °C, demonstrating that these transitions were related to melting processes, but do not correspond to any melting temperatures of the individual alcohols. This is deduced from information about eutectic mixtures between the alcohols that are present in the active principle. Between 185 and 340 °C a loss of mass of 87.5 % is detected which

corresponds to thermal decomposition of policosanol. At the same time, this result provides useful information about the thermal stability of policosanol, because the loss of mass starts at 185 °C, meaning that it is stable up to that temperature. Also, the calculated high energy of activation of 288.12 kJ/mol confirms the high thermal stability of policosanol.

Analysis of the DSC thermograms of the mixtures of policosanol with each one of the excipients, in the different ratios previously established, demonstrates that policosanol does not undergo any chemical or physical interaction with the excipients that were evaluated. Figure 3 shows the thermal curves of some of the binary mixtures formed between policosanol and some of the excipients used in the ratio 1:1. In these thermograms it is seen that the characteristic transitions of policosanol as well as those of the excipients do not undergo any changes in relation to the transitions detected in the individual study of each substance. The two endothermic transitions of policosanol appear near 60 and 81.0 °C; however, the appearance of new peaks in each one of the mixtures confirms the absence of chemical incompatibility between policosanol and the studied excipients.

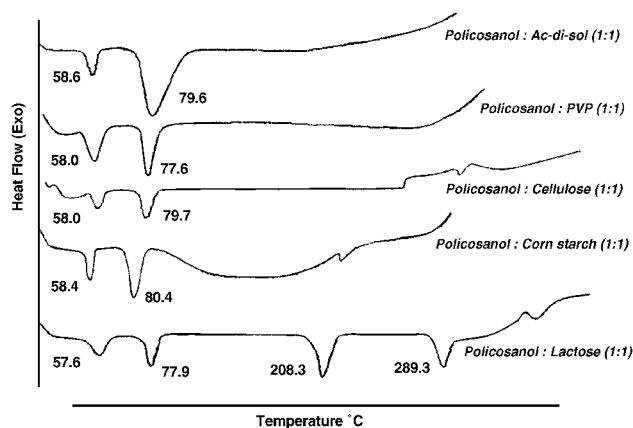


Figure 3. DSC thermograms of policosanol and excipients.

Conclusions

It was corroborated that the appearance of two endothermic transitions in policosanol corresponds to characteristic transitions in the formation of eutectic mixtures between the primary alcohols that are present, which melt at temperatures that are close to one another. With the DSC study of the compatibility between policosanol and excipients most commonly used in the development of oral solid forms, it is possible to determine the absence of chemical interactions in the binary mixtures studied. This means that all the studied excipients could be used in the formulation studies of policosanol tablets. On the other hand, it was demonstrated that thermal analysis is a powerful tool for these studies, having the advantages of speed, precision, and use of small quantities of samples.

Experimental

Policosanol (batches 250493 and 30821197) was supplied by Laboratories DALMER S.A., Havana City, Cuba. 1-Tetracosanol, 1-hexacosanol, 1-heptacosanol, 1-octacosanol and 1-triacontanol (Sigma USA).

The excipients used in this study were of pharmaceutical quality and were used in the same condition as supplied by the suppliers, after being submitted to the corresponding quality control. The following excipients were studied: lactose, corn starch, gelatin, polyvinylpyrrolidone (PVP), magnesium stearate, talc special for tablets, microcrystalline cellulose (Avi-Cel), sodium croscarmellose (Explocel, Ac-Di-Sol), sucrose, cellulose acetophthalate, dicalcium phosphate dihydrate (Encompress), sodium carboxymethyl starch or sodium starch glycolate (Explotab), polyethylene glycol 20 000 (Carbowax 20 000) and dyes such as indigotine FDC lake, tartrazine FDC lake, titanium dioxide and white polycoat No.2.

Equipment

Differential scanning calorimeter, Mettler TA 3000 coupled with a thermal cell DSC 20 (Greifensee Switzerland). Analytical balance, Mettler TG50 (Greifensee, Switzerland). Vacuum oven (Web, Germany).

Procedure for Analysis

The following experimental conditions were used:

Sample size = 5–7 mg

Temperature range = 35–350 °C

Scan rate = 10 °/min

Determination of the base line = Type 8

Aluminum crucible of 40 µL

The calorimeter was calibrated with an indium standard

Preparation of the Samples

In order to know if some kind of interactions were produced between policosanol and the excipients, which are also crystalline substance in most cases, it was necessary to prepare mixtures of policosanol with each one of the excipients in mass/mass ratios of 3:1, 1:1, and 1:3.

In all cases, 30 mg of policosanol were accurately mixed with 10, 30, and 90 mg of each one of the excipients previously related. These mixtures were sieved at 300 µm and mixed for 10 min at the different weight ratio. In order

to obtain the thermograms of policosanol, of the individual excipients, as well as those of their mixtures, all the samples were processed in the following way: they were warmed to 85 °C for 1 hour and dried in a vacuum oven for several hours. Later on, they were cooled slowly down up to room temperature (25 °C), prior to the analysis.

These analyses are performed under nitrogen flux in order to avoid oxidative or pyrolytic effects related to standard heating in the temperature range of the DSC apparatus, which will encompass any thermal changes due to both the drug and the excipient.

References

- [1] A. Laguna, J. Magraner, D. Carbajal, M. L. Arruzazabala, R. Más, M. García, (Laboratorios DALMER S.A), USA Patent 5.663.156, **1997**.
- [2] A. Laguna, J. Magraner, R. Ramos, E. Uribarri, U. G. Perdomo, D. Carbajal M. L. Arruzazabala, J. Martínez, M. Lorenzo, L. Montejo, R. Más (C.N.I.C.), CU patent 22.225, **1995**.
- [31] E. Uribarri, A. Laguna, Y. Ricardo, *Drug Develop. Ind. Pharmacy*, **1999**, in press
- [4] G. E. Peck, G. J. Baley, V. E. McCurdy, G. S. Banker in *Tablet Formulation and Design of Pharmaceutical Dosage Forms: Tablets*; Vol. 1 (Ed. by H.A. Lieberman, L. Lachman, J.B. Schwartz); Marcel Dekker Inc., New York; **1989**, Chapter 2, p. 78.
- [5] J.I. Wells, *Pharmaceutical Formulation in: The Physicochemical Properties of Drug Substances*, Ellis Horwood Ltd., Chichester, England, **1988**, p. 216.
- [6] B.W. Muller, *Acta Pharm. Technol.* **1977**, 23, 257
- [7] B.W. Botha, A. P. Lotter, *Drug Develop. Ind. Pharmacy* **1990** 16, 673–683
- [8] S.A. Botha, A. P. Lotter, *Drug Develop. Ind. Pharmacy* **1990** 15, 415–426.
- [9] S.A. Botha, A. P. Lotter, *Drug Develop. Ind. Pharmacy* **1990**, 16, 1945–1954.
- [10] E. Ciranni *et al.*, *Drug Develop. Ind. Pharmacy* **1986**, 12, 603–620.

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