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DESIGN FOR DRUG-EXCIPIENT INTERACTION STUDIES

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ABSTRACT

For routine drug-excipient interaction studies, 2 methods are available, Differential Scanning Calorimetry (DSC) and quantitative assay after an isothermal stress test. Although DSC is generally regarded as one of the methods of first choice in assessing drug-excipient incompatibilities, the evaluation of the curves is often difficult and 'hard' conclusions are rarely obtained. Better results can be achieved if the curves are compared with those of samples stored at 55°C for 3 weeks. Quantitative assays after isothermal stress, however, are still needed. A stress temperature of 55°C and a storage time of 511 hours was found acceptable. To evaluate the degradation, a procedure is used in which the reaction rate and the degradation limits are derived from a requirement of maximum degradation at room temperature. When using this procedure, it is essential to realize the assumptions (both kinetic and analytical) which are implicitly made. However, together with the DSC technique this method forms a rational basis of drug-excipient interaction studies.

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INTRODUCTION

Assessment of possible incompatibilities between an active drug substance and different excipients is an important part of the development of the dosage form of a drug.
The essence of compatibility tests is to mix samples of the active substance with the most common excipients and to study the mixtures in accelerated stability tests. Acceleration is reached by high temperatures, addition of water and (sometimes) irradiation.
It must be kept in mind that the results of such tests may have no or hardly any connection with results under "normal" conditions. Predictions are difficult, an incompatibility as shown in accelerated tests may not appear at all at room temperature.
The contact of two substances in a dry mixture may be very different from the contact in a wet granulation. In solids, the following degradation patterns can occur (1):

1. Degradation via the gas phase by means of nucleation; Prout and Tompkins relationships (2).
2. Degradation according to contracting cube or contracting sphere mechanisms, where nucleation occurs so fast that the complete surface of the particle is soon covered with a layer of degradation product.
3. Degradation via a surface film phase (liquid layer theory of Guillory and Higuchi (3)), for example in a eutectic melt between two substances.
4. Degradation via an aqueous phase (capillary or vapour phase water); (models of Kornblum (4) and Leeson and Mattocks (5)).
5. Degradation involving gases, for example oxygen.
6. Photolysis.

If we limit ourselves to reactions between 2 substances, only the patterns 3 and 4 come into consideration (nucleation is very improbable and oxidation or photolysis can be excluded by the choice of the stress conditions). This means that a perfectly homogeneous mixture is not required, because the reaction can only occur via the liquid phase as eutectic melt and water-capillaries will extend throughout the whole mixture. According to the literature Differential Thermal Analysis (DTA) or Differential Scanning Calorimetry (DSC) is one of the methods of first choice to study drug-excipient interactions (6-9). However, there are a lot of problems associated with the interpretation of the curves, which do not make this technique applicable in its own. It is therefore also necessary to quantitatively assay mixtures of the active ingredient and the excipients after isothermal stress tests. This means, however, that the amount of work in this stage of development is increased considerably and the problem is encountered which stress conditions have to be applied and which criteria of acceptability of degradation are to be chosen.

In this paper, both the use of DSC and of quantitative assays after isothermal stress are discussed. For clarification, an investigational compound was used as an example. It should be mentioned that there are still other methods available, like evaluation of discoloration after lightstress and Diffuse Reflectance Spectroscopy (10, 11). Assessment of multi-component mixtures was also described (12). Inclusion of such techniques in a general compatibility study, with many different excipients to be investigated, would further increase the amount of work and in our opinion it is better to postpone them to the phase of formulation development of the dosage form where only a limited number of excipients play a role.

For similar reasons, we feel that compatibility in the liquid state should be investigated with accelerated stress tests in the stage of formulation development.

MATERIALS AND METHODS

Materials

We used as the active ingredient an investigational compound with a melting point of 212°C.
Excipients for solid dosage forms can be divided into different classes, like diluents, binders, lubricants, disintigrants, colourants, coating aids etc. Important criteria for the choice of excipients are their world-wide applicability and their presence in pharmacopoeias etc. Excipients with similar chemical structure but different physical properties need not always be included both.

Methods

Differential Scanning Calorimetry (DSC)

In a DSC sample holder 1.0 mg of active ingredient was weighed. The suitable amount of excipient was weighed directly on top of it. This amount depends upon the concentration wanted in the mixture. Normal ratios of active ingredient to excipient are 1:5 for diluents, 3:1 for binders or disintegrants, 5:1 for lubricants and 10:1 for colourants etc. The sample pans were closed and the contents homogenized by carefully shaking the pans.
The samples were then subjected to heat-flux DSC (Mettler TA 2000 system) in the temperature region 40-300°C, with a heating rate of 6 K/min. and in an atmosphere of flowing nitrogen. The following determinations were carried out:

1. The active drug substance and the excipients individually.
2. Mixtures of active drug substance and excipients immediately after mixing.

3. The active drug substance and the excipients individually after 3 weeks at 55°C.
4. Mixtures of active drug substance and excipients after 3 weeks at 55°C.
5. Single components and mixtures after 3 weeks at 5°C only if the curves of the mixtures before and after storage at 55°C differ from each other.

Isothermal Stress in Test Tubes

The components were triturated or comminuted separately. Then, 125 mg of the active drug substance was accurately weighed into a test tube and an equal amount of excipient was added.

The mixture was shaken well on a whirlmixer. Water (10 or 20 percent of the total weight of mixture) was sprayed carefully over the sample and the tube was again shaken and closed well. For excipients which can also be used in dry granulations, the mixtures were prepared both with and without added water. With each excipient, two duplicate mixtures were prepared and the tubes were stored at exactly 55°C for exactly 511 hours. The tubes were visually evaluated before and after storage, and assayed quantitatively (chromatographically) for content of remaining active ingredient. The total contents of the tubes were used to prevent sampling errors.

RESULTS AND DISCUSSION

Differential Scanning Calorimetry (DSC)

In the evaluation of the DSC curves, the following points have to be considered:

1. In DSC we are dealing with the melting region of the substances. Degradation reactions or transformations

occuring at these temperatures may not take place at room temperature, or, in other words, Arrhenius equations may not be valid.

2. If the curve of the mixture is a simple superposition of those of the single components, an incompatibility is highly improbable.
3. In certain cases the superposition may not be clearly visible; figure 1 for instance shows that the melting peak of the active substance and the excipient lactose coincide.
4. Extra thermal effects in a curve before the peak of the lower melting component, may indicate incompatibility. This applies also when one of the component peaks has disappeared completely.
5. If one of the components degrades before the melting point of the other one it may be possible that the latter substance reacts with the decomposition products. Prediction of incompatibility is impossible then (fig. 2).
6. More reliable conclusions can be made if duplicate samples of the mixtures are stored in the holders at 55°C for 3 weeks and the curves are compared before and after storage. Differences in the curves may indicate incompatibility. In that case a curve should also be taken of a sample stored at 5°C for 3 weeks. If this sample gives the same curve as the sample at zero time, this again is a strong indication of incompatibility.
7. In the latter case it may be worthwile – especially if the excipient is an 'important' one, to investigate further the nature of the interaction, for example by taking curves of mixtures at different concentration, in order to construct a phase diagram.
8. If a eutectic or other mixed melting point entity is formed, a DSC curve characteristic of that new entity is obtained. It would be difficult to state if this new form would negatively affect stability. It should then also be tried to obtain a phase diagram.

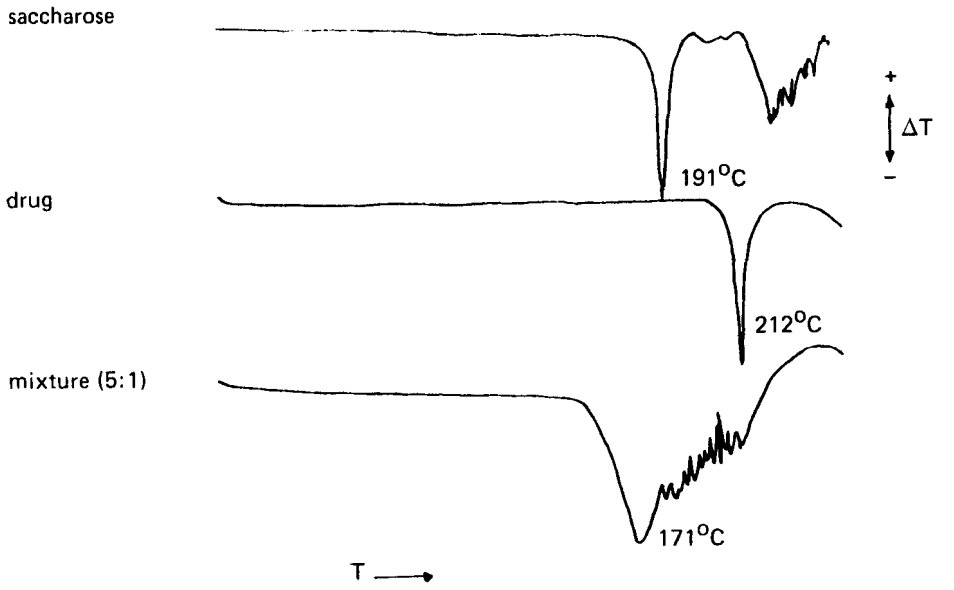

Fig. 2. DSC curves of drug and saccharose

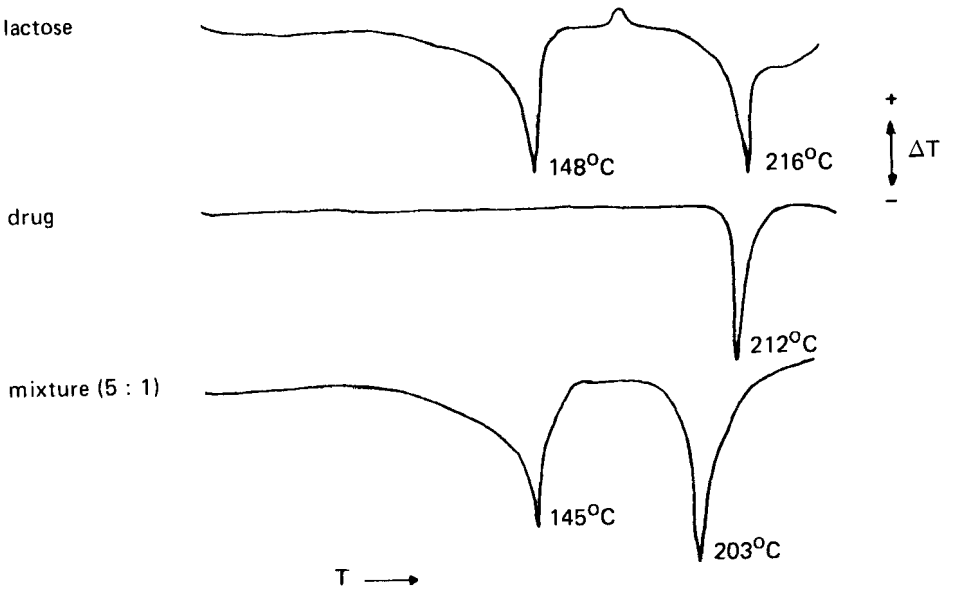

Fig. 1. DSC curves of drug and lactose

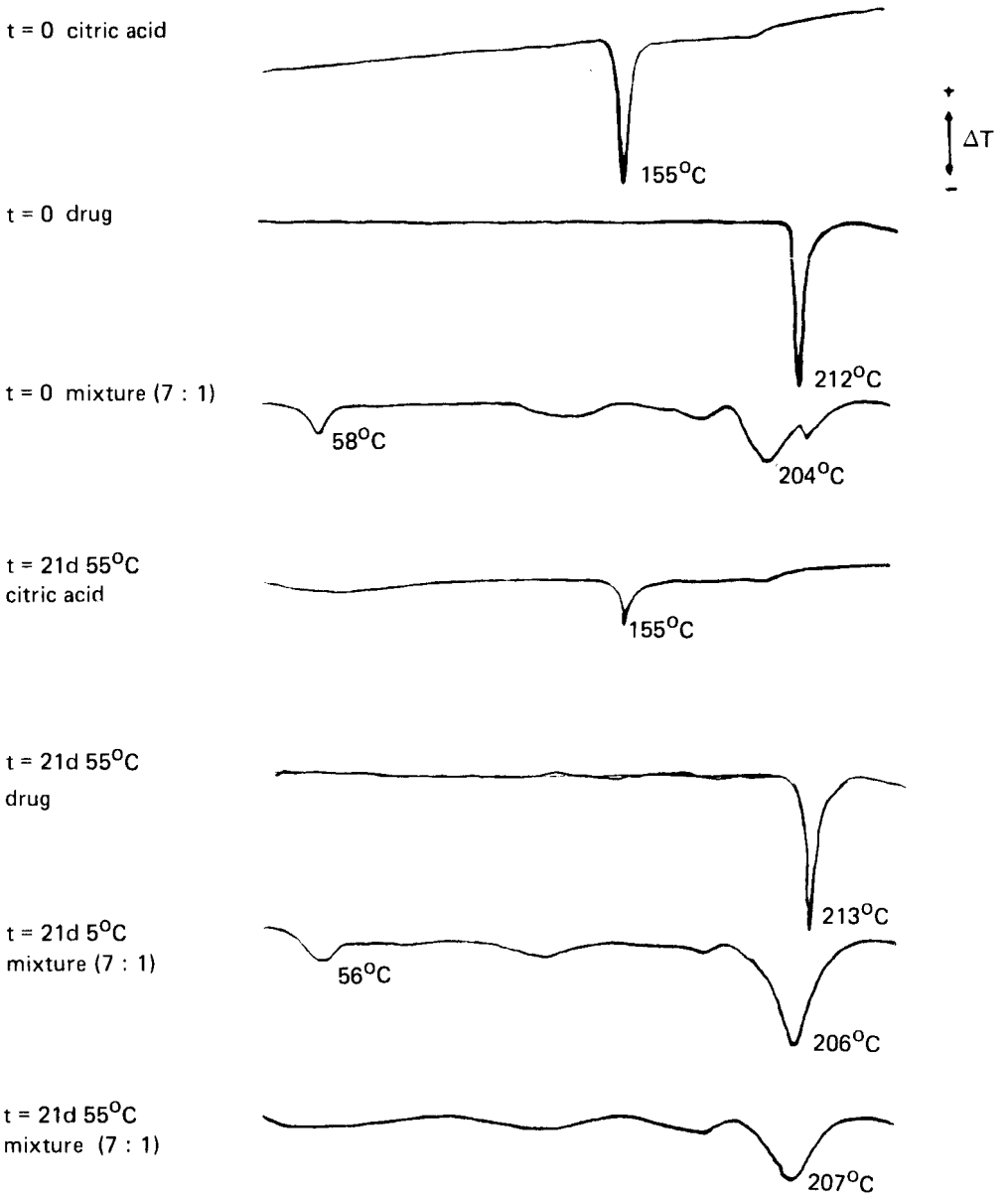

Fig. 3

9. As an example, in fig. 3 the curves with citric acid are given. From these curves we concluded that an interaction between the drug and citric acid was possible.

Isothermal Stress in Test Tubes

Classification on visual observation was done according to a method described by Carstensen et al. (13). Colour and appearance were compared before and after storage at 55°C. We did not try to draw reaction-kinetic conclusions from this classification. Discolouration and change of appearance depend upon the amount of water added, whilst the single components may also change in organoleptic properties during storage. The bearing of the visual observation on the ultimate conclusions about possibility of incompatibilities is only slight.

Of course, the concentration of remaining active ingredient is a much more important criterion. Reaction-kinetic conclusions from these assays have been drawn according to a method described by Kennon (14).

Starting from a requirement of maximum degradation at room temperature, the reaction rate at any higher temperature can be calculated with the Arrhenius equation, if the activation energy is known. The order of the degradation reaction does not play a role. Of course, the activation energy may differ for any decomposition reaction and therefore has to be assumed. The mean value for the activation energy of decomposition in solution is approximately 84 kJ/mole (15). For solid-state reactions it is generally higher. We have chosen for a mean value of Ea = 105 kJ/mole implicating that the temperature dependence of the reactions is relatively high. If, now, the 95 percent retention time at 20°C is 60 months, the reaction rate at 20°C can be calculated. If this value is inserted in the

Arrhenius equation, a value of the pre-exponential factor is obtained which allows to calculate the reaction rate at 55°C, and thus the maximum decrease in content after 0.70 months. If we take another requirement (for example 95 percent retention time at 20°C= 12 months) then with the same activation energy the pre-exponential factor and the reaction rate at 55°C can also be calculated. The classification as given in table 1 is thus found.

When using this method it is essential to realize the assumptions (both kinetic and analytical) which are implicitly made:

1. The storage conditions are exactly 511 hours at exactly 55°C.

TABLE 1

Classification of excipients after isothermal stress in test tubes

Class	Requirement RT95 (20°C) in months	Contents after 0.70 months at 55°C (Ea = 105 kJ/mole) (in percent)
1	> 60	> 94.2
2	> 48 ≤ 60	92.8 - 94.2
3	> 36 < 48	90.6 - 92.8
4	> 24 < 36	86.2 - 90.6
5	> 12 < 24	74.3 - 86.2
6	< 12	< 74.3

2. The initial concentration is 100 percent. This assumption allows us to refrain from analyzing before storage.
3. The Arrhenius equation is valid. Apart from the fact that the assumptions made in the thermodynamic derivation of the equation must hold (like, for example, temperature-independency of activation energy), it also implies that equilibrium or auto-catalytic reactions should not occur, and that the reaction mechanism at 55°C should be the same as at 20°C. The stress temperature of 55°C chosen is a compromise between a) a temperature as high as possible to shorten the duration of the test and b) a temperature as low as possible to prevent side reactions or unrealistic degradations.
4. The activation energies for the interactions between the active drug substance and the excipients should not differ too much.
   To check the validity of this and the former assumption the degradation can be assessed at a second temperature (for example 40°C) and compared with the calculated value.
5. In the calculation, statistical variations in the analytical method are not accounted for. It is assumed that the standard deviation of the analyses is small and always of the same magnitude. At least two duplicate analyses should be done, and if the values found would lead to different classifications, a third tube should be assayed.
6. The amount of water added should not have an effect. An amount of 10 to 20 percent was found to be acceptable.
7. There should also be no effect of the concentration of active ingredient in the mixture. To prevent recovery problems in the extraction of active ingredient prior to chromatographical analysis, the concentration should not be too low. A concentration of 50 percent is acceptable.
8. The active drug substance on its own should be stable under the stress conditions applied.

9. We are well aware of the fact that the purist would certainly condemn this method by questioning the validity of the assumptions. However, it may be argued that if they would be invalid altogether, they are so for all excipients, so that classification of excipients might not be invalidated. This procedure is not meant to determine exact reaction rates and reaction orders or to elucidate reaction mechanisms. It is only tried to make a comparison between different excipients, which is the one and only objective of this type of studies. Indeed, such a comparison must always be made by the pharmacist in evaluating his results and the method described above may help to visualize the logics of his decisions.

CONCLUSIONS

Combination of the results obtained both with DSC and with the isothermal stress test in test tubes allows us to draw conclusions as regards the choice of excipients in solid dosage forms of the investigational drug.

1. Excipients for which both in DSC and in the stress test in tubes indications for incompatibility are found should be avoided.
2. Excipients for which either in DSC or in the stress test in tubes indications for incompatibility are found should preferably not be used.
3. The other excipients which show no indications for incompatibilities are the first choice in the design of a tablet or capsule formulation. Only if for other reasons these excipients would present problems, the use of the substances named under 2 or 1, in order of their classification, should be considered again. In that case, however, extra care should be taken to ensure that

stability of the finished dosage form will be maintained during the intended shelf life.

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