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Optimization of glibenclamide tablet composition through the combined use of differential scanning calorimetry and D-optimal mixture experimental design

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Abstract

A systematic analysis of the influence of different proportions of excipients on the stability of a solid dosage form was carried out. In particular, a D-optimal mixture experimental design was applied for the evaluation of glibenclamide compatibility in tablet formulations, consisting of four classic excipients (natrosol as binding agent, stearic acid as lubricant, sorbitol as diluent and cross-linked polyvinylpyrrolidone as disintegrant). The goal was to find the mixture component proportions which correspond to the optimal drug melting parameters, i.e. its maximum stability, using differential scanning calorimetry (DSC) to quickly obtain information about possible interactions among the formulation components. The absolute value of the difference between the melting peak temperature of pure drug endotherm and that in each analysed mixture and the absolute value of the difference between the enthalpy of the pure glibenclamide melting peak and that of its melting peak in the different analyzed mixtures, were chosen as indexes of the drug–excipient interaction degree.

Keywords: Glibenclamide; Preformulation studies; D-optimal mixture experimental design; Differential scanning calorimetry; Drug–excipient interaction

1. Introduction

Careful selection of the excipients, integral components of all pharmaceutical products, is essential for the development of stable and effective dosage forms. Preformulation studies, aimed at the assessment of drug–excipient compatibility and identification of suitable dosage form composition, are recognized as an essential phase of the development process. Excipients are often regarded as "inert", although it is known that they can interact with drugs, giving rise to changes in their stability, solubility, dissolution rate and bioavailability [1–3]. Therefore, in order to accelerate drug development, it would be very useful to obtain knowledge rapidly about potential physical and chemical interactions between drugs and excipients. However, despite the importance of drug–excipient compatibility testing, no generally accepted method is available for this purpose.

Differential scanning calorimetry (DSC) has shown to be an important tool at the outset of any solid dosage form preformulation study to quickly obtain information about possible interactions among the formulation components, according to appearance, shift or disappearance of endothermic or exothermic peaks and/or variations in the corresponding enthalpy values in thermal curves of drug–excipient mixtures [4–7]. Moreover, DSC technique offers significant advantages over the conventional techniques of isothermal stress testing, in terms of the absence of long-term storage of samples, requirement of minimal amounts of compounds, rapid measurement and relative experimental simplicity. However, at present, DSC compatibility studies are generally carried out by comparing the thermal curves of the pure drug and examined excipients with those of the corresponding 1:1 (w/w) binary mixtures. In real formulations, instead, all the

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components and the drug are present together at the same time in complex heterogeneous mixtures and in ratios very different from 1:1 (w/w). Thus, the information obtained by classic DSC studies may be misleading, and have a limited predictive value, since it does not reflect the actual situation. It should be considered that the effect of an excipient may be strongly dependent on its relevant amount in the mixture and that the compatibility assessed in binary mixtures cannot allow for possible interactions which might occur in multicomponent mixtures, also as a consequence of mechanical treatments (such as grinding or tableting) undergone during the manufacturing process [8].

For an efficient development of stable formulations, a two-step procedure should therefore be recommended. First, classic rapid excipient compatibility screening on binary mixtures should be performed using the DSC technique; then, further studies on complete model formulation with the selected excipients, each at a realistic level, should be conducted to verify the actual stability of the drug in the final dosage form and identify the most suitable mixture composition in order to maximize drug stability. However, the second step of the proposed procedure might appear difficult to correctly and efficiently realized due to the large number of test mixtures to be prepared and analysed in order to cover, as much as possible, the different possible combinations. A favourable solution is to set up experiments according to statistical experimental design [9–11]. If the planned strategy is ideal, it is possible to obtain the desired results as quickly as possible, avoid carrying out unnecessary experiments, ensure that the results are as precise as possible, and provide a model and optimisation of the phenomena studied [9]. In particular, when the measured response is assumed to depend only on the proportions of the ingredients present in the mixture, it is possible to use experimental mixture design [12]. A mixture experiment is a special type of response surface experiment in which the factors are the components of a mixture and the response is a function of the proportions of each ingredient. The mixture components cannot range in an independent way since their sum has to be equal to 100% and specific experimental matrices and mathematic models have to be used. This approach is suitable for pharmaceutical blending problems allowing investigation, with the least number of experiments, of the effects of changes in mixture composition and selection of the optimal composition for achieving the prefixed target [12–16].

In the present study, a 20-run D-optimal mixture design was applied to the evaluation of compatibility of glibenclamide (selected as model drug) in a complete tablet formulation. After a preliminary screening, carried out by DSC analysis on 1:1 (w/w) drug–excipient binary mixtures, four classic tablet excipients (natrosol as binding agent, stearic acid as lubricant, sorbitol as diluent and cross-linked polyvinylpyrrolidone as disintegrant) were evaluated, each in adequate concentration ranges, in view of their different specific functions in tablet production. The mixtures of active ingredient and excipients were prepared according to the 20-run D-optimal mixture design. The goal was to find the mixture component proportions corresponding to the optimal drug melting parameters, i.e. its maximum stability. The responses, selected as indicative of the presence of drug–excipient interactions, were the peak temperature of drug melting endotherm and the relative enthalpy per unit of mass. Finally, the calculated empirical models were plotted as contour diagrams for revealing the optimal formulation.

2. Materials and methods

2.1. Materials

The active ingredient glibenclamide (GLI) was kindly offered by Guidotti Laboratori S.p.A. (Pisa, Italy). The excipients were as follows: hydroxyethylcellulose (Natrosol, Eigenmann & Veronelli, Milano, Italy); sorbitol (Carlo Erba, Milano, Italy); stearic acid (Fluka AG, Buchs, Switzerland); cross-linked polyvinylpyrrolidone (PVPXL) (Merck-Schuchardt, Munich, Germany).

2.2. Software

NEMROD-W software package [17] was used for generation of the experimental design and statistical evaluation of experimental data.

2.3. Preparation of samples

Each material was sieved and the respective 75–150 μm granulometric fraction was selected. Physical mixtures of GLI and the various excipients were prepared by 20 min blending in a turbula mixer. The total amount of the mixture was kept constant, and the relative amounts of the different excipients varied according to the experimental plan of the mixture design provided for by the NEMROD-W software. Tablets were produced by direct compression of mixtures. Uniformity of blending was verified by DSC measurements of three samples taken from a same mixture. For each combination, tablets of a constant weight (160 mg) were prepared using a laboratory hydraulic press for IR spectroscopy at a force of about 3 t for 2 min. The compacts obtained were then broken up and sieved, the 75–150 μm granulometric fraction being collected.

2.4. Differential scanning calorimetry

Samples of individual substances, as well as mixed systems of GLI and excipients, were weighed (Mettler M3 Microbalance) directly in pierced Al pans (5–10 mg) and scanned between 30 and 200 °C with a heating rate of 10 K min^{-1} under static air, using a Mettler TA4000 apparatus equipped with a DSC 25 cell. The instrument was calibrated using Indium as a standard (melting point, 156.61 °C; enthalpy of fusion, 28.71 J g^{-1}).