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COMPATIBILITY STUDIES OF MULTICOMPONENT TABLET FORMULATIONS
DSC and experimental mixture design

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Abstract

An experimental mixture design was applied to a differential scanning calorimetry (DSC) study performed to evaluate naproxen compatibility in tablet formulations consisting of four classic excipients (sorbitol, sodium carboxymethylcellulose, poly(ethylene glycol) 20 000 and Veegum) each in adequate concentration ranges accounting for the relevant values actually used in pharmaceutical formulations. Twenty-seven different tablets were obtained from as many mixtures prepared according to the experimental design plan and analyzed in a random order by DSC. Statistical evaluation of experimental data enabled correlation of both enthalpy and onset temperature variations of drug melting endotherm (selected as responses indicative of the presence of drug-excipient interactions) with the mixture composition. Variance analysis (Anova) confirmed the reliability of the postulated polynomial model in providing adequate prediction of true system behaviour.

Keywords: compatibility studies, DSC, experimental mixture design, multicomponent tablet formulations

Introduction

Interactions in the solid state between the active ingredient(s) and excipients in pharmaceutical dosage forms can give rise to changes in the stability, solubility, dissolution rate and bioavailability of drugs. Therefore, it would be very useful in the development of new pharmaceutical formulations to have readily available knowledge about potential physical and chemical interactions between drugs and excipients. Differential scanning calorimetry (DSC) has shown to be a powerful tool in the first step of preformulation studies for investigating and predicting physicochemical incompatibility between an active ingredient and pharmaceutical excipients [1–4]. DSC in fact allows rapid evaluation of possible interactions between the formulation components according to appearance, shift, or disappearance of endothermic or exothermic peaks and/or variations in the relevant enthalpy values in thermal curves of drug-excipient mixtures [5–9]. However, at present, DSC compatibility studies of drug substances are generally carried out through the comparison of the thermal curve of the pure drug with the curves obtained from its 1:1 mass/mass individual mixtures with each excipient under consideration. An important limit of this ap-

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proach is that in real formulations all the excipients and drug are present together at the same time and in relevant ratios very different from 1:1 mass/mass. Moreover, processing effects are ignored. Thus, the information obtained by this kind of study may be misleading and have poor predictive value since it does not reflect an actual situation. In fact, it is evident that the effect of an excipient in a binary drug-excipient mixture is strongly dependent on its relevant amount in the mixture; moreover, it may be very different from that in a multicomponent mixture, where multiple excipient interactions may occur, also as a consequence of mechanical treatments necessary for the formulation of dosage forms, which can alter their compatibility with the drug [10]. It should therefore be advisable, after a preliminary screening performed on binary mixtures, to carry out further studies on complete formulations with the selected excipients, each at a realistic level, to verify the actual stability of the drug in the final dosage form.

For these reasons, in the present work we evaluated the possibility of utilizing DSC analysis for compatibility studies of drugs in complete multicomponent tablet dosage forms, with the final aim of optimizing drug stability through a rational selection of the best formulation. Due to the relatively large number of components, it might appear a complex task to investigate the properties of a mixture, especially considering the high number of test mixtures which one should prepare in order to cover, as well as possible, the different, possible ingredient ratios and to find the optimal constituent proportions for the final formulation. Such a situation might be beneficially approached with the use of the experimental design strategies and in particular with the use of mixture designs. This chemometric approach allows investigation, with the least number of experiments, of how changes in mixture composition can affect the properties of the final preparation and to determine the best constituent ratios in order to achieve the fixed goal [11, 12].

Experimental mixture design was therefore used in this study to determine the occurrence of interactions between some pharmaceutical excipients and naproxen (selected as model drug) in a multicomponent tablet formulation, and to find their optimal ratios for the highest drug stability. Based on preliminary screening performed by DSC analysis on 1:1 mass/mass drug-excipient binary mixtures, four classic tablet excipients were selected, i.e. sorbitol, sodium carboxymethylcellulose, Veegum and poly(ethylene glycol) 20000, as diluent, binder, lubricant and disintegrant, respectively. Each one was used in adequate concentration ranges, accounting for their functions in tablet processing. Tablets were then obtained, starting from the different mixtures prepared according to the proportions indicated by the experimental plan of the mixture design. Simultaneous screening of all the examined factors, performed by DSC analysis carried out on the multicomponent mixtures obtained by breaking up and sieving the prepared tablets, should allow determination of the effect of variations in factor levels on the experimental responses, as well as evaluation of possible interactions between factors. The responses, chosen as indicative of the presence of drug-excipient interaction, were the onset and peak temperatures of drug melting endotherm and the relative enthalpy per unit of mass.

Materials and methods

Materials

The active ingredient was Naproxen (NAP) from Sigma Chemical Co. (St. Louis, Mo, USA). The excipients were as follows: sorbitol (Carlo Erba, Milano, I); sodium carboxymethylcellulose (NaCMC) (Dow Chemical, Cincinnati, U.S.A.); poly(ethylene glycol) 20000 (PEG 20000) (Merck–Schuchardt, Munchen, D); Veegum F (Bayer–Italia, Milano, I).

Software

NEMROD-W software [13] was used for generation and evaluation of the statistical experimental design.

Preparation of samples

Physical mixtures of NAP with various excipients were prepared by 20 min blending in a turbula mixer of the components, all previously sieved (75–150 μm). The total amount of the mixture was kept constant, and the relative percentages of the different ingredients varied according to the experimental matrix provided for by the Nemrod software. The homogeneity of blending was checked by DSC measurements of three samples for each preparation. For each combination, tablets of a constant mass (100 mg) were prepared using a laboratory hydraulic press for IR spectroscopy KBr discs 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.

Differential scanning calorimetry

Samples of individual components as well as each drug-excipient mixture were weighed (Mettler M3 Microbalance) directly in pierced Al pans (10–12 mg) and scanned in the 30–200°C temperature range under static air, with a heating rate of 10 K min^{-1}, using a Mettler TA4000 apparatus equipped with a DSC 25 cell.

Results and discussion

Experimental plan

The characteristic features of a mixture are not due to the actual amount of a single ingredient but rather to its proportion in relation to the other ingredients (X_i) as well as to the fact that the components X_i can not be manipulated completely independently since their overall sum must add up to 100% ($\Sigma X_i=1$). This implies that their proportions must lie between 0 and 1 (the mixture total). In this situation, the application of the experimental mixture design defines a regular-shaped experimental region, a simplex, i.e. a geometrical figure with $n+1$ corners in a n-dimensional space (where n represents the number of mixture ingredients). However, in most pratical cases, con-

straints are put on the constituents of a mixture formulation in order to respect the actual amounts of each component commonly used in commercial products.

Table 1 Upper and lower limits of the mixture components

Factor	Lower limit/mass/mass%	Upper limit/mass/mass%
X_1 Naproxen	30	50
X_2 NaCMC	10	20
X_3 sorbitol	10	50
X_4 PEG 20000-Veegum	5	10

These considerations also apply to the case under study, where constituent proportions were restricted in value by upper and lower limits according to the relevant values actually used in pharmaceutical formulations (Table 1). Moreover, two components, PEG 20000 and Veegum, were treated as 'mixture within mixture' (50:50 mass/mass), both in order to simplify the treatment of the mixture problem from five to four factors and owing to the same, low concentration levels of the considered excipients. As a consequence of the illustrated constraints, the experimental region defined by the mixture factors becomes irregular and takes the form of a hyperpolyhedron with eight vertices (Fig. 1). The vertices (8), mid-edge points (12), face centroids (6) and the overall centroid of the hyperpolyhedron define the mixture design-point location, i.e. the points that correspond to the 27 test mixtures that one has to prepare and analyze by DSC in order to establish the compatibility and stability of NAP in the multicomponent formulation and to optimize the component proportions of the final preparation. The center point was determined in triplicate to provide a measure of variability in the DSC response determinations. The coordinates of the points were computed according to the McLean and Anderson algorithm performed

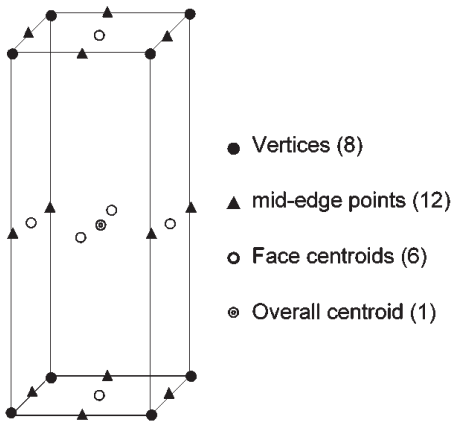

Fig. 1 Restricted experimental regions resulting from different limits in all four factors ($0.3 \leq = X_1 \leq 0.5$; $0.1 \leq X_2 \leq 0.2$; $0.1 \leq X_3 \leq 0.5$; $0.05 \leq X_4 \leq 0.1$)

Table 2 Design point coordinates for the constrained region inside the factor space given by the four-component mixture

Design point	Type of boundary	Mixture component proportions				
		X_1 NAP	X_2 NaCMC	X_3 Sorbitol	X_4 PEG 20000-Veegum	
		mass/mass%				
1	vertex	30	10	50	5	5
2	vertex	30	20	40	5	5
3	vertex	30	10	40	10	10
4	vertex	30	20	30	10	10
5	vertex	50	10	30	5	5
6	vertex	50	20	20	5	5
7	vertex	50	10	20	10	10
8	vertex	50	20	10	10	10
9	mid edge point	30	15	45	5	5
10	mid edge point	30	10	45	7.5	7.5
11	mid edge point	40	10	40	5	5
12	mid edge point	30	20	35	7.5	7.5
13	mid edge point	40	20	30	5	5
14	mid edge point	30	15	35	10	10
15	mid edge point	40	10	30	10	10
16	mid edge point	40	20	20	10	10
17	mid edge point	50	15	25	5	5
18	mid edge point	50	10	25	7.5	7.5
19	mid edge point	50	20	15	7.5	7.5
20	mid edge point	50	15	15	10	10
21	face centroid	30	15	40	7.5	7.5
22	face centroid	40	10	35	7.5	7.5
23	face centroid	40	15	35	5	5
24	face centroid	50	15	20	7.5	7.5
25	face centroid	40	20	25	7.5	7.5
26	face centroid	40	15	25	10	10
27	overall centroid	40	15	30	7.5	7.5

by the Nemrod software. Component concentrations and mixture location in the design space are listed in Table 2. The dependent variables chosen as parameters representative of drug compatibility and stability in the multicomponent formulation were:

Y_1- onset temperature of NAP melting endotherm, °C (T_{onset})
Y_2- peak temperature of NAP melting endotherm, °C (T_{fus})
Y_3- enthalpy of NAP melting endotherm, J g^{-1} (ΔH_{fus})

DSC analysis

The thermal curves of the pure components are shown in Fig. 2. The DSC curve of NAP was typical of a pure crystalline anhydrous substance, showing a single sharp endothermic peak at its melting point, with an onset temperature of 153.4±0.3, a peak temperature of 156.6 ±0.3°C and an apparent heat of fusion of 140±2 J g^{-1} (average of four runs). The thermal curves of Veegum and NaCMC exhibited a shallow broad endothermic band in the 70–130°C range, due to the water evaporation. The thermal curves of PEG 20000 and sorbitol exhibited a sharp endothermic effect, peaked at 68 and 98°C, respectively, due to the excipient melting process. The 1:1 mass/mass combinations of NAP with each of these excipients (thermal curves not shown) re-

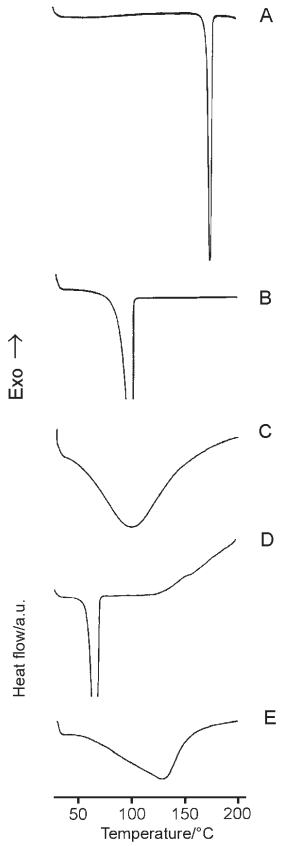

Fig. 2 DSC curves of pure components. A – naproxen, B – sorbitol, C – NaCMC, D – PEG 20000, E – Veegum

flected the characteristic features of the drug melting, suggesting that no problem of compatibility should occur. Tablets (100 mg) were then produced starting from multicomponent mixtures prepared according to the experimental matrix provided for by the Nemrod software (Table 2) in order to also evaluate a possible effect of the sample mechanical treatment [7–9]. Increased drug-excipient contact due to grinding or interaction can greatly alter physical and chemical drug stability [10].

DSC analysis on such drug-excipient multicomponent mixtures, obtained by breaking up tablets and sieving the powders (75–150 μm), were carried out in a randomized order. Typical thermal curves of some of the examined mixtures are shown in Fig. 3. As we can see, they were all characterized by the presence of the drug melting endotherm, preceded by the melting endotherms of PEG 20000 and sorbitol, which appeared particularly broadened due to the superimposition of Veegum and

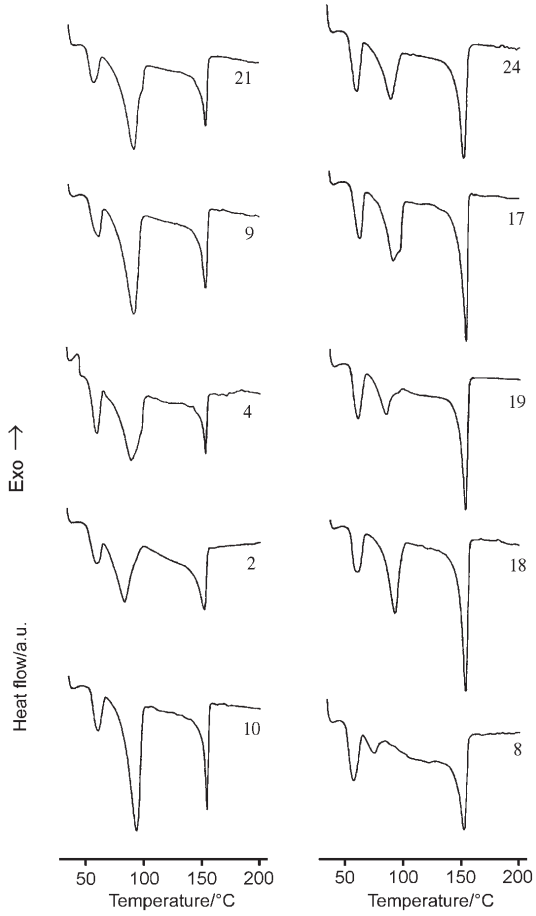

Fig. 3 Typical DSC curves of complete mixtures at low (left) and high (right) concentration level of naproxen. For the mixture compositions, Table 2

NaCMC dehydration band. The melting peak temperature of NAP appeared substantially unaffected by blending and compression with the additive mixtures. However, changes in shape and area of its endotherm were observed and asymmetry of the melting peak was evident and clearly demonstrated by lowering of the peak onset temperature. Both phenomena, indicative of some interaction occurrence, were clearly affected by the relative proportions of the different excipients in the mixture as appears evident by comparing the drug thermal behaviour shown by formulations which all contain the same drug amount.

Data analysis

The parameters of thermal curves selected as response variables are collected in Table 3. For purposes of statistical modelling, the concentration of the various components was normalized so that the lowest concentration of a component was assigned a value of 0 and 1 for the highest. In other words, the original coordinates of the point-mixture were redefined in terms of 'pseudocomponents' in order to make both the construction of the design and the fitting of the model much easier. The selection of the degree of the polynomial model to better fit the experimental reponses (dependent variables) proceeded by following steps. First- and second-order models were initially considered, but only a special cubic model appeared to fit the experimental data well:

$$\eta=\beta_1X_1+\beta_2X_2+\beta_3X_3+\beta_4X_4+\beta_{12}X_1X_2+\beta_{13}X_1X_3+\beta_{14}X_1X_4+\beta_{23}X_2X_3+\beta_{24}X_2X_4+\beta_{34}X_3X_4+\beta_{123}X_1X_2X_3+\beta_{124}X_1X_2X_4+\beta_{134}X_1X_3X_4+\beta_{234}X_2X_3X_4$$

Where – η represents the response; the variable X_1 represents the drug, X_2 NaCMC, X_3 sorbitol and X_4 the 1:1 mass/mass mixture Veegum-PEG 20000; the coefficient β_1 represents the main effect of the variable X_1, the coefficient β_{12} the effect of interaction X_1X_2, the coefficient β_{123} the effect of interaction $X_1X_2X_3$, and so on. The experimental results processed with the Nemrod software enabled the coefficients of the effects of the studied variables on the responses to be calculated. The following equations were obtained:

$$T_{onset}=111.482X_1+79.134X_2+141.132X_3+36.374X_4+185.561X_1X_2+74.06X_1X_3+36.214X_2X_3+276.174X_1X_4+300.534X_2X_4+137.654X_3X_4-66.987X_1X_2X_3-562.133X_1X_2X_4-395.947X_1X_3X_4-38.400X_2X_3X_4$$

$$T_{fus}=147.0866X_1+150.4399X_2+152.4578X_3+118.6888X_4+24.8935X_1X_2+12.0400X_1X_3+1.9732X_2X_3+76.9468X_1X_4+139.9457X_2X_4+46.4534X_3X_4-18.7735X_1X_2X_3-290.9843X_1X_2X_4-75.9466X_1X_3X_4-170.6645X_2X_3X_4$$

$$\Delta H_{fus}=-46.867X_1+243.143X_2+59.828X_3+133.538X_4+81.668X_1X_2+189.396X_1X_3-399.823X_2X_3+256.123X_1X_4-1337.179X_2X_4-242.169X_3X_4+91.990X_1X_2X_3+465.982X_1X_2X_4-681.983X_1X_3X_4+2220.772X_2X_3X_4$$

Table 3 Pseudocomponent settings of the twenty-seven-run experimental mixture design and experimental response values

Mixture	X_1	X_2	X_3	X_4		T_{onset}/ °C	T_{fus}/ °C	ΔH_{fus}/ J g^{-1}
1	0.000	0.000	1.000	0.000	0.000	139.7	152.5	59.95
2	0.000	0.250	0.750	0.000	0.000	130.4	151.3	30.45
3	0.000	0.000	0.750	0.250	0.250	139.9	153.0	30.78
4	0.000	0.250	0.500	0.250	0.250	138.9	152.4	25.30
5	0.500	0.000	0.500	0.000	0.000	146.8	152.9	53.43
6	0.500	0.250	0.250	0.000	0.000	144.4	153.3	74.06
7	0.500	0.000	0.250	0.250	0.250	139.1	152.9	37.61
8	0.500	0.250	0.000	0.250	0.250	143.1	153.1	45.86
9	0.000	0.125	0.875	0.000	0.000	140.2	152.3	39.57
10	0.000	0.000	0.875	0.125	0.125	143.8	152.8	44.18
11	0.250	0.000	0.750	0.000	0.000	147.8	153.4	68.90
12	0.000	0.250	0.625	0.125	0.125	136.2	152.3	36.42
13	0.250	0.250	0.500	0.000	0.000	144.3	152.6	65.48
14	0.000	0.125	0.625	0.250	0.250	139.6	151.6	39.64
15	0.250	0.000	0.500	0.250	0.250	140.5	153.0	33.64
16	0.250	0.250	0.250	0.250	0.250	139.6	152.5	41.83
17	0.500	0.125	0.375	0.000	0.000	142.0	153.0	46.11
18	0.500	0.000	0.375	0.125	0.125	142.4	152.7	52.35
19	0.500	0.250	0.125	0.125	0.125	142.0	152.4	44.29
20	0.500	0.125	0.125	0.250	0.250	143.3	152.7	53.18
21	0.000	0.125	0.750	0.125	0.125	143.4	152.7	33.95
22	0.250	0.000	0.625	0.125	0.125	141.8	153.2	48.32
23	0.250	0.125	0.625	0.000	0.000	141.7	152.7	51.01
24	0.500	0.125	0.250	0.125	0.125	140.6	152.2	38.73
25	0.250	0.250	0.375	0.125	0.125	139.8	152.5	45.68
26	0.250	0.125	0.375	0.250	0.250	137.4	150.4	45.09
27	0.250	0.125	0.500	0.125	0.125	142.0	152.3	56.82
27	0.250	0.125	0.500	0.125	0.125	143.0	152.7	57.38
27	0.250	0.125	0.500	0.125	0.125	141.6	152.5	55.62

The reliability of the selected model was checked by analysis of variance (Anova): the sum of squares due to the lack of fit and the sum of squares due to pure error, each divided by their respective degrees of freedom, were compared in the form of ratio. The *F*-ratio value was not significant for the T_{fus} response, which was practically unaffected by variations in composition percentages. On the contrary. the

ratio analysis showed that both T_{onset} and ΔH_{fus} responses were actually the estimates of the same experimental variance σ^2 (Table 4). It should then be possible to predict the effect of mixture composition variations on drug T_{onset} and ΔH_{fus} and, consequently, to select the proper ingredient ratios leading to the minimum variation of NAP thermal parameters (with respect to the pure drug), revealing minimum drug-excipient interaction, i.e. maximum drug stability.

Table 4 Least squares summary Anova (n=29)

ΔH_{fus}

Source of variation	Sum of squares	Degrees of freedom	Mean squares	F-ratio	Significance
Regression	2.87954 E+03	13	2.21503 E+02	3.7	**
Residual	9.61239 E+02	16	6.00775 E+01	–	–
Lack of fit	7.96175 E+02	13	6.12442 E+01	–	–
Pure error	1.65064 E+02	3	5.50215 E+01	1.11	53.0%
Total	3.84078 E+03	29	–	–	–

T_{onset}

Source of variation	Sum of squares	Degrees of freedom	Mean squares	F-ratio	Significance
Regression	236.92897	13	18.22531	3.88	**
Residual	75.19770	16	4.69986	–	–
Lack of fit	69.47020	13	5.34386	–	–
Pure error	5.72750	3	1.90917	2.80	21.3%
Total	312.12667	29	–	–	–

** $P < 0.01$

Conclusions

Combined use of DSC and experimental mixture design enabled investigation of complex multicomponent solid mixtures in order to establish compatibility between the components. Anova analysis confirmed the reliability of the model postulated by experimental design to provide an adequate prediction of true system behaviour through the correlation of both enthalpy and onset temperature variations of NAP melting endotherm with the mixture composition.

Results of NAP compatibility study in the complete tablet formulation substantially confirmed findings of preliminary screening performed on 1:1 mass/mass binary mixtures, excluding the presence of strong interactions between components also when they were blended all together and compressed. Moreover, additional useful information was obtained by statistical chemometric analysis of experimental data. In fact, the main advantage of this kind of approach was that, in addition to the qualitative information about component interactions provided by classic DSC compatibility studies, a quantitative

analysis of data can be obtained. Therefore, the proposed chemometric approach appears particularly advisable as a final stage of DSC preformulation compatibility testing to assess the actual stability of the drug in the complete formulation and to individuate the best suitable percentages of the formulation components, within the fixed experimental domain, giving drug melting parameters closest to those of the pure drug and therefore corresponding to its optimal stability.

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