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Mini Review

Principal Component Analysis in Drug-excipient Interactions

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Abstract

Studies about the interaction between active pharmaceutical ingredients (API) and excipients are so important in the pre-formulation stage of development of all dosage forms. Analytical techniques such as differential scanning calorimetry (DSC), Thermal gravimetry (TG), and Furrier transform infrared spectroscopy (FTIR) are commonly used tools for investigation regarding compatibility and incompatibility of APIs with excipients. Sometimes the interpretation of data obtained from these techniques is difficult because of severe overlapping of API spectrum with excipients in their mixtures. Principal component analysis (PCA) as a powerful factor analytical method is used in these situations to resolve data matrices acquired from these analytical techniques. Binary mixtures of API and interested excipients are considered and produced. Peaks of FTIR, DSC, or TG of pure API and excipient and their mixtures at different mole ratios will construct the rows of the data matrix. By applying PCA on the data matrix, the number of principal components (PCs) is determined so that it contains the total variance of the data matrix. By plotting PCs or factors obtained from the score of the matrix in two-dimensional spaces if the pure API and its mixture with the excipient at the high amount of API and the 1:1mixture form a separate cluster and the other cluster comprise of the pure excipient and its blend with the API at the high amount of excipient. This confirms the existence of compatibility between API and the interested excipient. Otherwise, the incompatibility will overcome a mixture of API and excipient.

Keywords: API; Compatibility; DSC; TG; Interactions

Introduction

In a dose shape, an API comes in coordinate contact with other components (excipients) of the formulation that encourage the administration and release of an active substance as well as keep it safe from the environment [1,2]. Although excipients are pharmacologically inert, they can interact with the drug in the dosage form, there by affecting the physical stability of the drug product, such as sensory properties, slowed dissolution rates, or chemical properties that cause drug degradation [3,4]. Excipients need to be carefully selected to form a robust and effective dosage form to facilitate administration, improve patient compliance, promote drug release and bioavailability, and extend shelf life [5,6]. Therefore, the compatibility detection of API and excipients or other active ingredients is considered one of the mandatory factors and is at the forefront of research in pharmaceutical science and technology. In addition, under the prototype of drug development quality design, it is expected that the physical and chemical interactions in the dosage form will be fully understood and encouraged by the U.S. Food and Drug Administration and various regulatory agencies around the world. The emergence of thermal analysis methods in the initial steps of pre-formulation research has greatly facilitated the early prediction, monitoring and characterization of API incompatibility, thereby avoiding expensive material waste and significantly reducing the time required to achieve the correct product formulation of the API [7,8].

Regularly utilized analytical techniques for investigation the compatibility comprises thermal methods such as differential scanning calorimetry, thermogravimetric analysis [9,10], differ-

ential thermal analysis, isothermal microcalorimetry [11,12], hot stage microscopy [13] and other analytical methods like powder X-ray diffraction [14,15], Fourier transform infrared spectroscopy [16], scanning electron microscopy [17] and high-performance liquid chromatography [18].

Sometimes interpretation of data obtained from the mentioned analytical techniques is difficult because of overlapping of the peaks of APIs with excipients. In this situation, factor analysis method can be a powerful method to process and resolve data in a better and more precise way.

Factor analysis (FA) is fitting a set of latent variable models and methods to data. One of the FA methods is principal component analysis (PCA). The purpose of PCA is finding the subs pace in the space of the variables where data has the most variance. The primary variables, generally correlated, are linearly transformed into a fewer number of uncorrelated variables namely principal components (PCs). PCA obeys the following:

$X = T_A \cdot P_A + E_A$

Where X is a N×M matrix of data, T_A is the N×A scores matrix including the projection of the objects in the A PCs sub-space, P_A is the M×A loadings matrix comprising the linear combination of the variables indicated in each of the PCs, and EA is the N×M matrix of residuals [19].

PCA can be utilized to recognize the relationships among variables of high variance. As shown by Jackson [20], the understanding of the data set under analysis will be useful [21].

In this review PCA is used as a factor analytical method to interpret the data matrixes of mixture of APIs with excipients and it is helpful to predict drug-excipient interactions.

Case studies

Study about interaction between Theophylline and some excipients such as Arabic gum, glucose, sorbitol and sucrose showed incompatibility using factor analysis method on DSC data [22]. In this experiment, binary mixtures of theophylline with excipients were prepared at 9:1, 7:3,1:1, 3:7 and 1:9 molar or mass ratios (the first number of the ratio shows the content of theophylline in the mixtures). In FA calculations, the variables were DSC parameters such as enthalpies, onset temperatures, peak temperatures, peak heights and peak widths. The samples were considered as theophylline, excipients and their mixtures at ratios of 9:1, 7:3, 1:1, 3:7and 1:9. Figures 1-6 show the DSC curves of theophylline with excipients at different ratios.

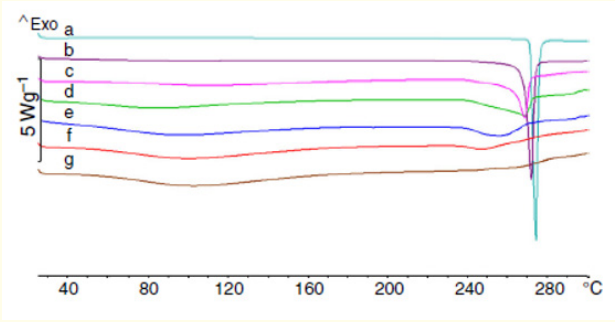

Figure 1: DSC curves of a Theophylline, Arabic gum and their mixtures at API/excipient ratios b 9:1, c 7:3, d 1:1, e 3:7, f 1:9.

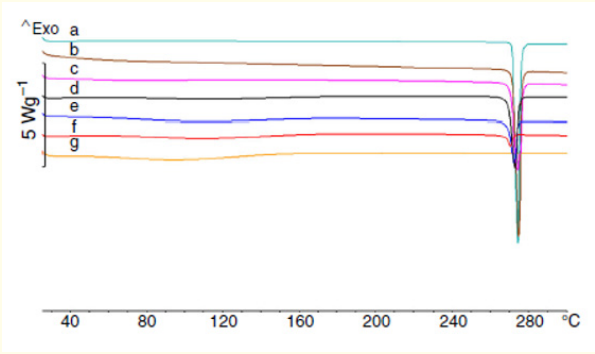

Figure 2: DSC curves of a Theophylline, g Microcrystalline Cellulose and their mixtures at API/excipient ratios b 9:1, c 7:3, d 1:1, e 3:7, f 1:9.

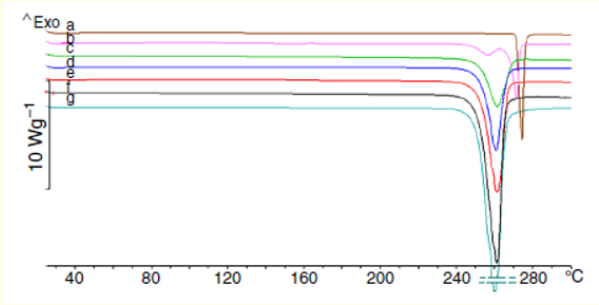

Figure 3: DSC curves of a Theophylline, Glicocol and their mixtures at API/excipient ratios b 9:1, c 7:3, d 1:1, e 3:7, f 1:9.

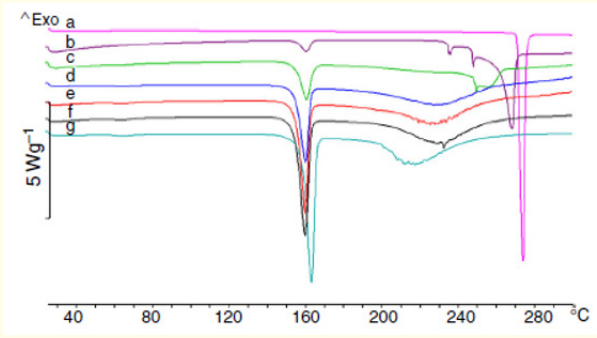

Figure 4: DSC curves of a Theophylline, g Glucose and their mixtures at API/excipient ratios b 9:1, c 7:3, d 1:1, e 3:7, f 1:9.

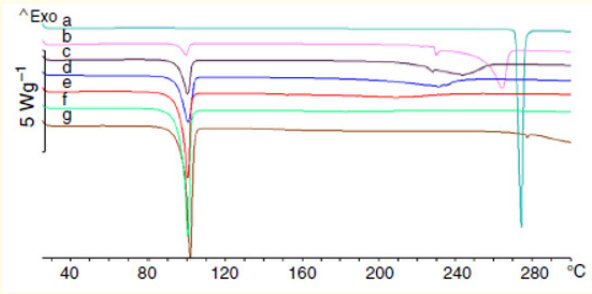

Figure 5: DSC curves of a Theophylline, g Sorbitol and their mixtures at API/excipient ratios b 9:1, c 7:3, d 1:1, e 3:7, f 1:9.

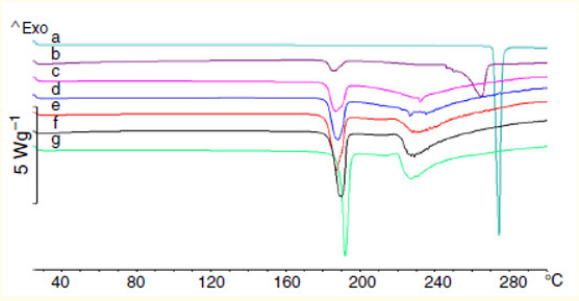

Figure 6: DSC curves of a Theophylline, g Sucrose and their mixtures at API/excipient ratios b 9:1, c 7:3, d 1:1, e 3:7, f 1:9.

Sometimes it is difficult to predict compatibility or incompatibility between mixture ingredients in the DSC data, e.g., theophylline mixtures with glicocol orarabic gum. In these situations, factor analysis methods such as principal component analysis (PCA) are a solution to determine compatibility. The results of FA can be seen on a two-dimensional score plot. The localization of both ingredients and their blends on the FA plot demonstrates compatibility or incompatibility.

If the API with mixtures at most amount and the 1:1 blend form a separate cluster and the other cluster comprises of excipient with blends with its most amount; this indicates that compatibility between ingredients is obvious. The score plot of theophylline with microcrystalline cellulose and sorbitol are shown in figure 7 and figure 8, respectively.

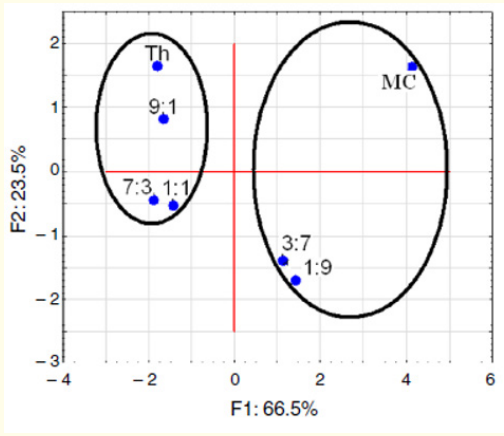

Figure 7: FA score scatter plot for DSC data: Theophylline (Th), Microcrystalline Cellulose (MC) and their mixtures at the ratios:9:1, 7:3, 1:1, 3:7, 1:9.

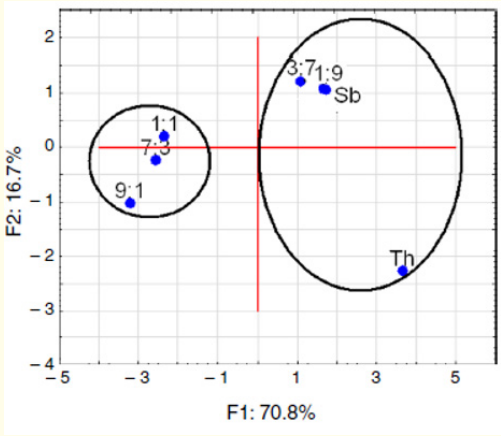

Figure 8: FA score scatter plot for DSC data: Theophylline (Th), Sorbitol (Sb) and their mixtures at the ratios: 9:1, 7:3, 1:1, 3:7, 1:9.

According to these score plots, theophylline is compatible with microcrystalline cellulose and is incompatible with sorbitol. Table 1. Shows that which excipient is compatible with theophylline.

Matrices	Theophylline mixtures	Theophylline mixtures
1	Arabic gum	Incompatibility
2	Microaystalline cellulose	Compatibility
3	Glicocol	Compatibility
4	Glucose	Incompatibility
5	Sorbitol	Incompatibility
6	Sucrose	Incompatibility

Table 1: Results obtained using FA for interpretation of the DSC data for theophylline mixtures.

In another study the compatibility of hydrocortisone as an API with excipients such as mannitol, starch, lactose, methylcellulose, β-cyclodextrin, meglumine, chitosan, magnesium stearate and polyvinylpyrrolidone was investigated. PCA and cluster analysis methods were applied on the matrixes of thermal gravimetric data. Hydrocortisone was incompatible with β-cyclodextrin and magnesium stearate. The results were confirmed by other methods like DSC, IR and X-ray powder diffraction [23]. figure 9 and figure10 represent TG traces of hydrocortisone with chitosan and magnesium stearate at different mole ratios, respectively.

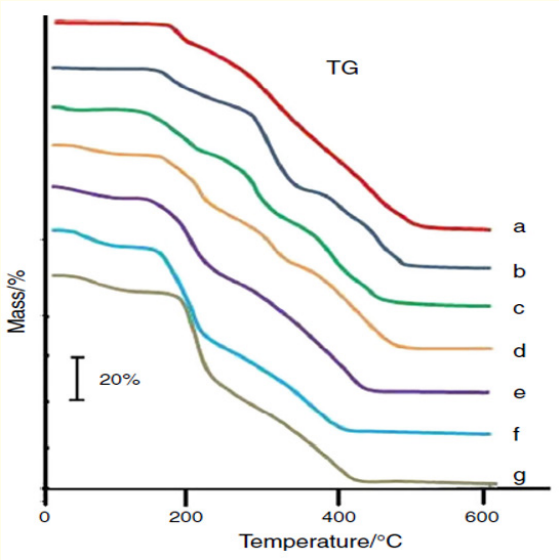

Figure 9: TG traces of: (a) Hydrocortisone, (g) Chitosan at Drug/Excipient Ratios: (b) 9:1, (c) 7:3, (d) 1:1, (e) 3:7, (f) 1:9.

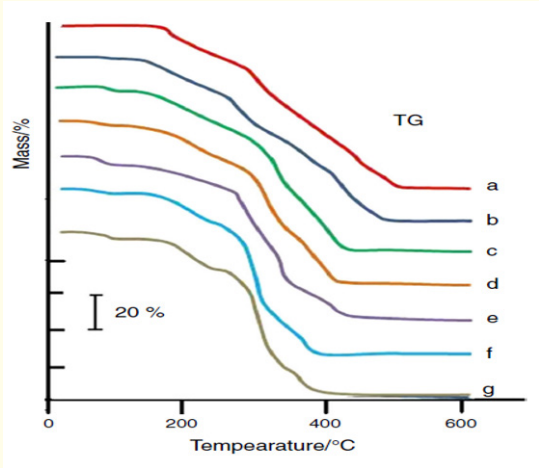

Figure 10: TG traces of: (a) Hydrocortisone, (g) Magnesium Stearate and their mixtures at drug/excipient ratios: (b) 9:1, (c) 7:3, (d) 1:1, (e) 3:7, (f) 1:9.

By applying PCA on data matrixes from figure 8 and figure 9, PC2 versus PC1 was graphed. Figure 11a and figure 11b show two-dimensional score plot of hydrocortisone with chitosan and magnesium stearate, respectively.

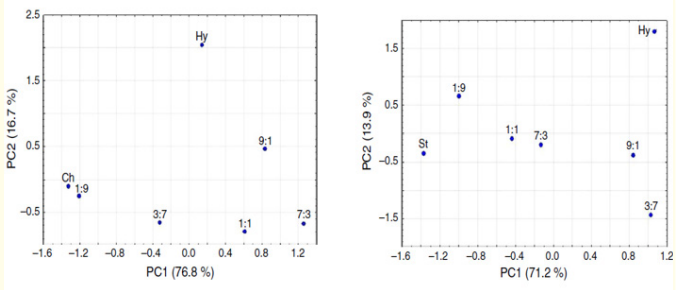

Figure 11: PCA score biplot for the first two principal components for Hydrocortisone (hy), Chitosan (Ch) and their mixtures at drug/excipient ratios: 9:1, 7:3, 1:1, 3:7, 1:9 and b PCA score biplot for the first two principal components for Hydrocortisone (Hy), Magnesium Stearate (St) and their mixtures at drug/excipient ratios: 9:1, 7:3, 1:1, 3:7, 1:9.

Figure 11a shows that two partitioned clusters were formed. One comprises chitosan and a blend with its high content, whereas the other includes hydrocortisone and its blend with a high amount of API. This classification indicates hydrocortisone and chitosan are compatible. Distribution of points in the score plot of figure 11b shows that hydrocortisone and its mixture with the high amount of API (9:1) are not close to each other. Also, Mg stearate and its blend with the high amount of excipient (1:9) are not in the same group. Therefore, hydrocortisone and Mg stearate are incompatible. The same method was used for the other excipients. Table 2 shows the results of PCA on data matrixes obtained from different excipients with hydrocortisone at different ratios.

Matrices	Excipients	PCA	CA
1	Mannitol	+	+
2	Lactose	+	+
3	Starch	+	+
4	Methylcellulose	+	+
5	β-cyclodextrin	-	-
6	Meglumine	+	+
7	Chitosan	+	+
8	PVP-30	+	+
9	Magnesium stearate	-	-

Table 2: Results obtained by using multivariate statistical techniquesas supporting tools for interpretation of the TG curves of mixtures with hydrocortisone.

+, Compatibility; -, incompatibility

Conclusion

In this review a simple, fast and precise method was used to investigate the compatibility of API with excipients. The method was based on application of principal component analysis as a powerful chemometric method on data matrices obtained from DSC, TG and FTIR analytical techniques. By plotting score points, the compatibility is confirmed if the API and its mixture with the excipient at the high amount of API put in one group and the excipient and its mixture with API at the high amount of excipient placed in another group. This method helps the formulation scientists to select appropriate excipients with lowest possibility of interaction with API.

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