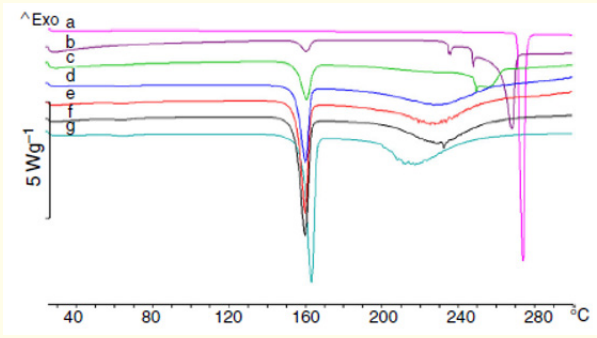

Figure 4: DSC curves of a Theophylline, g Glucose and their mixtures at API/excipient ratios b 9:1, c 7:3, d 1:1, e 3:7, f 1:9.

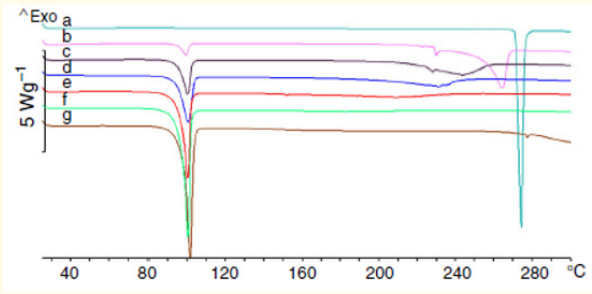

Figure 5: DSC curves of a Theophylline, g Sorbitol and their mixtures at API/excipient ratios b 9:1, c 7:3, d 1:1, e 3:7, f 1:9.

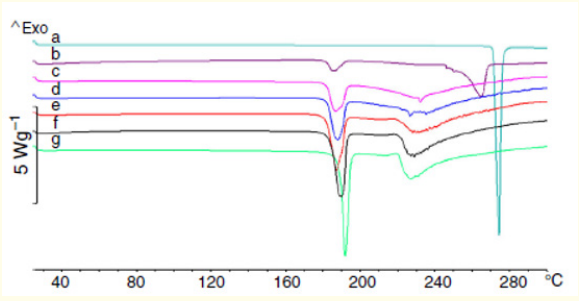

Figure 6: DSC curves of a Theophylline, g Sucrose and their mixtures at API/excipient ratios b 9:1, c 7:3, d 1:1, e 3:7, f 1:9.

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.

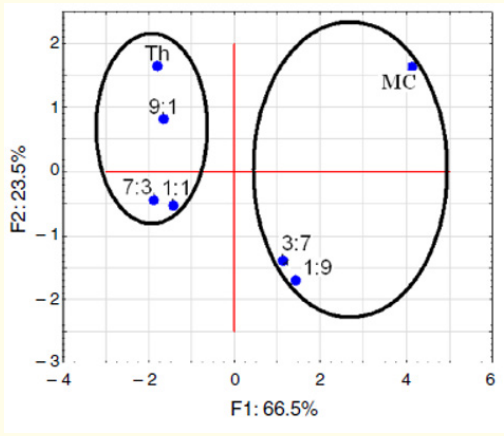

Figure 7: FA score scatter plot for DSC data: Theophylline (Th), Microcrystalline Cellulose (MC) and their mixtures at the ratios:9:1, 7:3, 1:1, 3:7, 1:9.

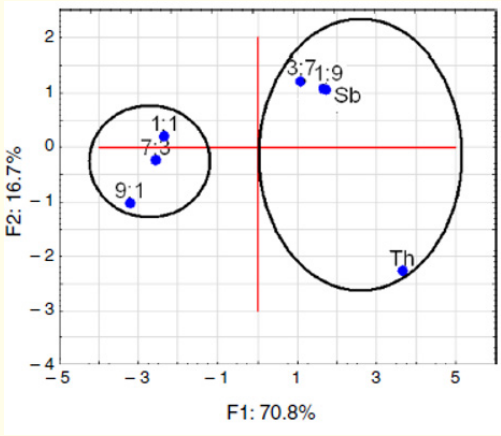

Figure 8: FA score scatter plot for DSC data: Theophylline (Th), Sorbitol (Sb) and their mixtures at the ratios: 9:1, 7:3, 1:1, 3:7, 1:9.

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.

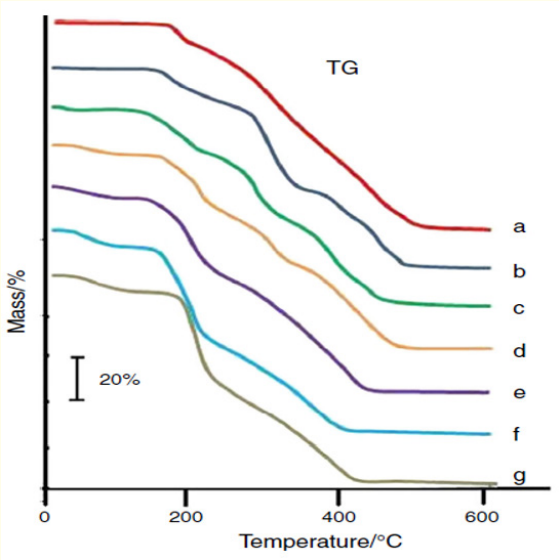

Figure 9: TG traces of: (a) Hydrocortisone, (g) Chitosan at Drug/Excipient Ratios: (b) 9:1, (c) 7:3, (d) 1:1, (e) 3:7, (f) 1:9.

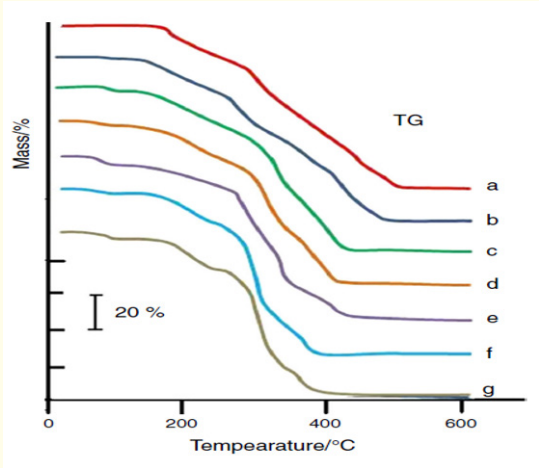

Figure 10: TG traces of: (a) Hydrocortisone, (g) Magnesium Stearate and their mixtures at drug/excipient ratios: (b) 9:1, (c) 7:3, (d) 1:1, (e) 3:7, (f) 1:9.

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.

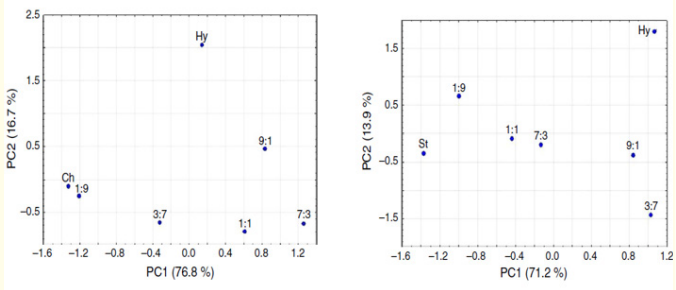

Figure 11: PCA score biplot for the first two principal components for Hydrocortisone (hy), Chitosan (Ch) and their mixtures at drug/excipient ratios: 9:1, 7:3, 1:1, 3:7, 1:9 and b PCA score biplot for the first two principal components for Hydrocortisone (Hy), Magnesium Stearate (St) and their mixtures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

Bibliography

1. AR Fassihi and PHR Persicaner. "Solid state interaction of bromazepam with polyvinylpyrrolidone in the presence of moisture". *International Journal of Pharmaceutics* 37 (1987): 167.

2. K Jackson., *et al.* "Drug-excipient interactions and their effect on absorption". *Pharmaceutical Science and Technology Today* 3 (2000): 336.

3. P Crowley and LG Martini. "Drug-Excipient Interactions". *Pharmaceutical Technology* 13 (2001): 26.

4. FM McDaid., *et al.* "Further investigations into the use of high sensitivity differential scanning calorimetry as a means of predicting drug-excipient interactions". *International Journal of Pharmaceutics* 252 (2003): 235.

5. Z Makai., *et al.* "Evaluation of the effects of lactose on the surface properties of alginate coated trandolapril particles prepared by a spray-drying method". *Carbohydrate Polymers* 74 (2008): 712.

6. B Tita., *et al.* "Compatibility study between ketoprofen and pharmaceutical excipients used in solid dosage forms". *Journal of Pharmaceutical and Biomedical Analysis* 56 (2): (2011): 221.

7. A Marini., *et al.* "Drug-excipient compatibility studies by physico-chemical techniques; The case of Indomethacin". *Journal of Thermal Analysis and Calorimetry* 73 (2003): 529.

8. R Chadha and S Bhandari. "Drug-excipient compatibility screening-Role of thermoanalytical and spectroscopic techniques". *Journal of Pharmaceutical and Biomedical Analysis* 87 (2014): 82.

9. ME Brown., *et al.* "DSC screening of potential prochloperazine-excipient interactions in preformulation studies". *Journal of Thermal Analysis and Calorimetry* 56 (1999): 1317.

10. G Pyramides., *et al.* "The combined use of DSC and TGA for the thermal analysis of atenolol tablets". *Journal of Pharmaceutical and Biomedical Analysis* 13.2 (1995): 103.

11. MA Phipps., *et al.* "Excipient compatibility as assessed by isothermal microcalorimetry". *Journal of Pharmacy and Pharmacology* 50 (1998): 9.

12. EA Schmitt. "Excipient compatibility screening by isothermal calorimetry". in: 53rd Calorimetry Conference, Midland, MI (1998).

13. AW Newman and SR Byrn. "Solid-state analysis of the active pharmaceutical ingredient in drug products". *Dichlorodiphenyl Trichloroethane* 8 (2003): 898-905.

14. R Chadha., *et al.* "Thermomicroscopy and its pharmaceuticals applications". in: A. Méndez-Vilas (Ed.): Current Microscopy Contributions to Advances in Science and Technology edition, Microscopy Book Series, Badajoz, Spain 13 (2012): 1013-1024

15. L Qi., *et al.* "The development of microthermal analysis and photothermal microspectroscopy as novel approaches to drug-excipient compatibility studies". *International Journal of Pharmaceutics* 354 (1-2): (2008): 149.

16. Z Aigner., *et al.* "Compatibility studies of aceclofenac with retard tablet excipients by means of thermal and FT-IR spectroscopic methods". *Journal of Thermal Analysis and Calorimetry* 104 (2011): 265.

17. P Mura., *et al.* "Compatibility study between ibuproxam and pharmaceutical excipients using differential scanning calorimetry, hot-stage microscopy and scanning electron microscopy". *Journal of Pharmaceutical and Biomedical Analysis* 18 (1998): 151.

18. SA Botha and AP Lotter. "Compatibility Study Between Naproxen and Tablet Excipients Using Differential Scanning Calorimetry". *Drug Development and Industrial Pharmacy* 16 (1990): 673.

19. J Camacho., *et al.* "Data understanding with PCA: Structural and Variance Information plots". *Chemometrics and Intelligent Laboratory Systems* 100 (2010): 48.

20. J Jackson. "A User's Guide to Principal Components". *Wiley-Interscience*, England (2003).

21. K Kosanovich., *et al.* "Improved process understanding using multiway principal component analysis". *Engineering Chemical Research* 35 (1996): 138.

22. B Rojek and M Wesolowski. "DSC supported by factor analysis as a reliable tool for compatibility study in pharmaceutical mixtures". *Journal of Thermal Analysis and Calorimetry* 138 (2019): 4531.

23. B Rojek and M Wesolowski. "Compatibility studies of hydrocortisone with excipients using thermogravimetric analysis supported by multivariate statistical analysis". *Journal of Thermal Analysis and Calorimetry* 127 (2017): 543.