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THERMAL ANALYSIS OF A DRUG-POLYMERIC EXCIPIENT SOLID SYSTEM

*F. Giordano, G. P. Bettinetti, A. La Manna, A. Marini**
and *V. Berbenni**

DIPARTIMENTO DI CHIMICA FARMACEUTICA, UNIVERSITÀ DI PAVIA,
*CSTE — DIPARTIMENTO DI CHIMICA FISICA, UNIVERSITÀ DI PAVIA, ITALY

Differential scanning calorimetry has been applied to the study of the solid system cross-linked polyvinylpyrrolidone/trimethoprim.

Different results have been systematically obtained on co-ground and not co-ground mixtures, suggesting some type of interaction to take place between components as a consequence of co-grinding.

A simple phenomenological model of the interaction is proposed, which quite satisfactorily agrees with thermal data.

It is well-known that drug-excipient interactions can deeply influence the technological and biopharmaceutical properties of solid dosage forms. Thermal analysis and particularly microcalorimetric differential techniques are often employed to evidence such interactions [1, 2].

Cross-linked polyvinylpyrrolidone (PVP-XL) is an amorphous insoluble polymer widely used as a disintegrating agent and binder for tablets [3, 4] and for the preparation of molecular dispersions [5, 6].

Trimethoprim (TMP), whose thermal and structural properties were extensively investigated by some of us [7, 8], is a chemotherapeutic agent commonly used as antifolate drug in combination with sulfonamides [9].

A preliminary investigation of the thermal behaviour of mixtures of PVP-XL and TMP evidenced deep changes in thermal profiles of ground mixtures with respect to those of the pure components, which were ascribed to possible interactions between TMP and PVP-XL [10]. For a better understanding and characterization of such interactions a more detailed DSC study has been undertaken on the system PVP-XL/TMP, whose results are here reported.

It will be shown that a simple phenomenological model of the interaction can be proposed which quite satisfactorily agrees with thermal data.

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Experimental

TMP (recrystallized from EtOH/H_2O 7/3 by volume, form I) and PVP-XL (POLYPLASDONE-XL, GAF, Italy: $d = 1.22$ g cm^{-3}; M.W. > 1,000,000) were sieved and the fractions passing through 60 mesh and recovered over 80 mesh were considered. The respective particle size was finally assessed with a Coulter Counter.

Physical mixtures of PVP-XL (mean particle diameter 210 μm) and TMP (mean particle diameter 229 μm) were prepared in different ratios (ranging from 5 to 60% by weight of TMP) and thoroughly mixed in a turbula apparatus. Samples of the physical mixtures were then ground by hand in porcelain mortar with a pestle. Grinding was stopped when no more change in the thermal traces could be detected.

Thermal measurements were performed by means of a DuPont 1090 Thermal Analysis System equipped with a DuPont 910 Differential Scanning Calorimeter.

Samples were weighed (about 5 mg) into pierced Al pans and scanned at 5 deg min^{-1} under dry nitrogen flux (30 ml min^{-1}) in the temperature range 0–230°.

Results and discussion

Figure 1 shows, together with those of the pure components, the DSC trace of a physical mixture PVP-XL/TMP. As can be seen, the mixture shows a thermal behaviour which is just the sum of those of the pure components. Peaks are due to polymer dehydration and TMP melting and, as expected on the basis of Fig. 1, their relative areas vary according to the mixture composition.

Different results are however obtained for ground mixtures. The DSC traces of some of them are presented in Fig. 2. It can be seen (Fig. 2a) that, while TMP fails to melt at its melting temperature, a new endothermic effect takes place that cannot be directly attributed to any of the pure components (see Fig. 1).

It is interesting to note the evolution of the shape of this peak with increasing the TMP percentage of the mixture: while the onset temperature remains sensibly constant (140°), the peak temperature moves toward higher values both increasing peak asymmetry and area.

Moreover, for mixtures with TMP contents higher than 25% by weight, the overall thermal effect splits into two portions and a peak becomes evident, whose temperature more and more approaches the melting temperature of pure TMP (Fig. 2c). Thus, while no thermal effect directly attributable to TMP can be found on ground mixtures up to 25% TMP content, thermal traces resembling those shown by physical mixtures are obtained with increasing the TMP content above 25% by weight.

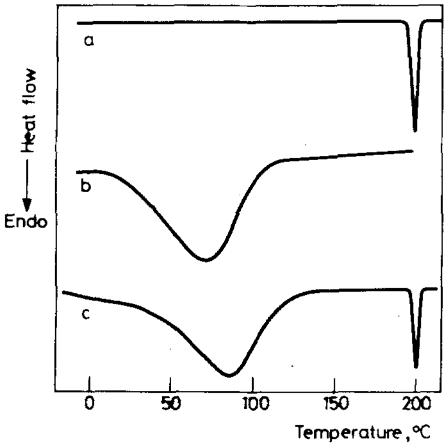

Fig. 1 DSC traces of: a) PVP—XL; b) TMP; c) physical mixture PVP—XL/TMP (TMP content: 25% by weight)

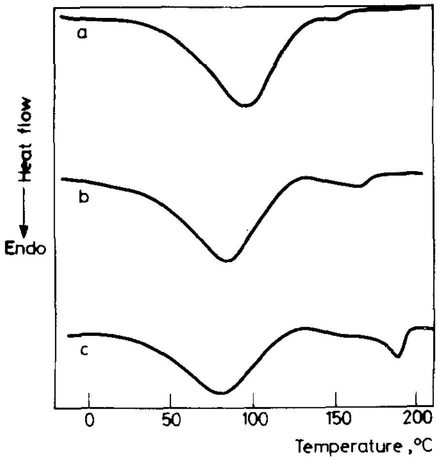

Fig. 2 DSC traces of ground mixtures with different TMP contents by weight: a) 10%; b) 25%; c) 50%

Different behaviours of the mixtures with TMP contents lower and higher than 25% are also obtained during cooling: while the first ones give flat traces, the second ones show a sharp exothermic effect at temperatures around 175°. This confirms that, at least from a phenomenological and qualitative point of view, the 25% TMP composition represents a limiting composition.

What has just been discussed on the basis of a qualitative analysis of thermal data, can be confirmed and extended by a quantitative analysis of the same data.

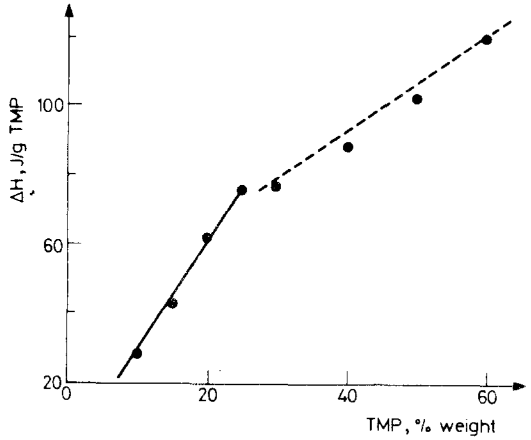

Fig. 3 Specific enthalpy values (enthalpy per unit mass of TMP) as a function of the TMP content of the mixture for the high temperature thermal effect shown by ground mixtures. Points represent experimental values while the solid and dotted lines represent calculated values (see text)

The reaction enthalpy values for unit mass of TMP of the high temperature peak shown by ground mixtures are shown as a function of TMP content in Fig. 3.

It can be seen that the ΔH values increase with increasing TMP content and that the 25% TMP mixture is at the borderline between different dependences of ΔH on TMP content.

In addition to confirming that the 25% TMP composition is of special significance, these results can be of great help in defining a model to explain the thermal behaviour of the ground mixtures.

As the thermal effect we are analysing arises as a consequence of components co-grinding, its presence could very hardly be justified without hypothesizing some type of interaction to take place between PVP-XL and TMP as a consequence of co-grinding.

It must be stressed that this does not mean that the interaction energy can be directly obtained by the thermal effect shown by ground mixtures, but only that it is someway contained in it. Nothing more than this can be said at this point and a complete understanding of the physical meaning of the thermal effect is necessary before conclusions on the interaction energy can be drawn.

This is however all what is needed if a phenomenological model of the interaction process has to be obtained.

As no peak splitting takes place up to a 25% TMP content, it must be assumed that only one and the same phenomenon is responsible for the endothermic effect up to this composition.

The fact that increasing specific enthalpy values are obtained with increasing

TMP content of the mixture (left hand side of Fig. 3) can be explained by assuming a special type of interaction between PVP-XL and TMP whose specific enthalpy changes with changing the relative amount of TMP up to a limiting value after which something new happens.

As it seems that this limiting value is reached with the 25% TMP content, this mixture has been taken as reference and specific enthalpy values have been calculated on its basis (for mixtures with TMP contents lower than 25%) according to the formula:

$$\Delta H_{\text{calc}} = \Delta H_{25} X_{25}$$

where ΔH_{25} = experimental value of ΔH per unit mass of TMP for the 25% TMP mixture; X_{25} = fraction of the 25% TMP mixture ideally present in the analysed mixture.

The results are presented in Fig. 3 (solid line). It can be seen that there is a very good agreement between experimental and calculated values.

Despite its very simple mathematics, however, this equation suggests a quite complex microscopic basis of the interaction process, indicating a well-defined feedback mechanism to be operative between specific enthalpy and mixture composition in a large range of mixture compositions.

This phenomenological conclusion represents a useful guideline for the understanding of the interaction mechanism.

We can at this point try to explain the thermal behaviour of mixtures with TMP contents higher than 25%.

TMP is now present in excess with respect to the interacting ratio, and this excess is responsible for the peak splitting of Fig. 2c.

As the peak temperature of the splitted thermal effect approaches the melting temperature of pure TMP, it seems reasonable to assume that the excess TMP undergoes normal melting. If this is the case, two different specific enthalpies should constitute the overall thermal effect: the first one corresponding to the 25% TMP mixture and the second one to the specific melting enthalpy of the excess TMP.

Such an assumption cannot be directly verified owing to the incomplete separation of the overall thermal effect which makes it impossible to assign reliable areas to the different thermal effects composing the overall one.

As, however, the total area is a well reproducible quantity, an indirect testing can be made on its basis.

It is clear from what has been said up to now that the overall specific enthalpy value should be a weighted mean of two different contributions and should be expressed as:

$$\Delta H_{\text{exp}} = \Delta H_{25} X_{25} + \Delta H_f (1 - X_{25}) \quad \text{(TMP contents} > 25\%)$$

where X_{25} and ΔH_{25} have the same meaning as in the previous equation and ΔH_f is the specific melting enthalpy of pure TMP (melting enthalpy per unit mass of TMP).

The dotted line of the right hand side of Fig. 3 has been obtained by this equation. A reasonable agreement between calculated and experimental values can be seen.

While confirming that the interaction takes place up to a well defined ratio of the interacting substances, these results seem to indicate that the excess TMP does not interact at all. This is probably a too extreme position and it may be that if a weak interaction is associated with the excess TMP, a better agreement between experimental and calculated data can be obtained. Such a minor correction would need a much deeper knowledge of the interaction process than can be obtained by thermal measurements and would however leave unaffected the substantial validity of the phenomenological model proposed.

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References

1 G. P. Bettinetti, C. Caramella, F. Giordano, A. La Manna, C. Margheritis and C. Sinistri, J. Thermal Anal., 28 (1983) 285.
2 M. Wesolowski, Drug Dev. & Ind. Pharm., 11 (1985) 483.
3 S. S. Kornblum and S. B. Stoopak, J. Pharm. Sci., 62 (1973) 43.
4 A. H. Bronnsack, Pharm. Ind., 40 (1978) 1255.
5 B. C. Lippold and R. Lutschg, Pharm. Ind., 40 (1978) 541.
6 F. Carli and F. Garbassi, J. Pharm. Sci., 74 (1985)·963.
7 G. P. Bettinetti, F. Giordano and P. Ferloni, Il Farmaco, Sci. Ed., 35 (8) (1980) 706.
8 G. P. Bettinetti, F. Giordano, A. La Manna, G. Giuseppetti and C. Tadini, Acta Crystallogr., Sect. C: Cryst. Struct. Commun., C41 (8) (1985) 1249.
9 Martindale, The Extra Pharmacopoeia, 28th Edition, The Pharmaceutical Press, London 1982, p. 1457.
10 F. Giordano, G. P. Bettinetti, A. La Manna and G. Giuseppetti, Calorim. Anal. Therm., 16 (1985) 220.

Zusammenfassung — Das feste System von vernetztem Polyvinyl-pyrolidin/Trimethoprim wurde mittels DSC untersucht. Unterschiedliche Ergebnisse wurden systematisch für zusammen und nicht zusammen verriebene Mischungen gefunden, was auf eine Wechselwirkung zwischen Komponenten beim Verreiben hindeutet. Ein einfaches phänomenologisches Modell dieser Wechselwirkung wird vorgeschlagen, das mit thermischen Daten befriedigend übereinstimmt.

Резюме — Методом ДСК изучена твердотельная сшитая полимерная система поливинилпирролидом — триметоприм. Различные результаты были получены для размолотых и не размолотых смесей. Это свидетельствует о некотором взаимодействии между отдельными компонентами, как следствие совместного размалывания. Предложена простая феноменологическая модель такого взаимодействия, полностью согласующаяся с термическими данными.