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THERMOANALYTICAL METHODS IN PHARMACEUTICAL TECHNOLOGY

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A short survey is given of some aspects of the application of thermoanalytical methods, especially differential thermal analysis (DTA), differential scanning calorimetry (DSC) and thermogravimetry (TG), in solid-dosage technology. The usefulness of these methods in the prediction of drug-excipient compatibility, studies of solid-dispersion systems, the analysis of enantiomers and racemates, measurement of the time of tablet disintegration, the analysis of drug formulations and studies of the processes of grinding and drying of drugs is discussed.

Keywords: enantiomers and racemates, drugs, pharmacy, solid-dosage technology

Introduction

In recent years, thermoanalytical methods, especially DTA, DSC and TG, have played an important role in the solution of a variety of scientific and industrial problems in pharmacy. They are finding increasing applications for the determination of the temperatures of phase transitions of drugs and the values of their thermodynamic constants, the determination of phase diagrams and purity, the evaluation of compatibility among the components of dosage forms, the qualitative and quantitative analysis of drug formulations, stability tests and the determination of kinetic parameters. Accordingly it has been decided to present new, selected examples of the practical application of thermoanalytical methods in solid-dosage technology.

Prediction of drug-excipient compatibility

Incompatibility is defined as an interaction between two or more components which produces changes in the chemical, physical, microbiological or therapeutic properties of the drug formulation [1]. Chemical incompatibility is usually due to redox, acid-base,

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hydrolysis of combination reactions. On the other hand, physical incompatibilities involve changes in solubility, adsorption of a drug onto an excipient or the formation of a eutectic mixture.

DTA and DSC are very useful analytical tools during the prediction of physico-chemical incompatibility [2]. Screening is performed by recording separately the pure excipient and the pure drug at a standard heating rate, usually in a nitrogen atmosphere. A simple additive superimposition of these curves is then compared with the DTA (DSC) curve obtained from a well-mixed 1:1 mixture of the drug and ecxipient. In the simplest case, the thermal properties of the mixture are the sum of those of the individual substances. An interaction might be identified from the DTA (DSC) curves through changes in transition temperature, peak shape, peak area and transition presence. If there are no differences between the theoretical and experimental mixture curves, thermoanalytical methods do not reveal an interaction between the drug and the excipient. It can be suggested that there is no physico-chemical incompatibility.

The use of DSC to predict interactions in capsule dosage forms was studied by Botha *et al.* [3]. They reported findings on salicylamide, ascorbic acid, pyrilamine maleate and phenylephrine hydrochloride combined with lactose as filler and with colloidal silica and sodium starch glycolate as other excipients. Ascorbic acid is compatible with colloidal silica because the physical mixture of drug-excipient shows no significant differences as compared with the individual substances. It can therefore be concluded that these two substances may be used together in drug formulations. The physical mixture of ascorbic acid and sodium starch glycolate reveals that the excipient is incompatible with ascorbic acid.

Solid dispersion systems

The bioavailability of poorly water-soluble drugs is limited by their dissolution rates. Since the dissolution rate is directly proportional to the surface area, the dissolution rate may be increased by decreasing the particle size of the drug. A greater surface area of a drug can very often increase the rate of its gastrointestinal absorption and the amount of drug absorbed from a drug formulation.

The reduction of the particle size of drugs is generally achieved by mechanical micronization processes. The resultant micronized particles can have disadvantages, especially as concerns aggregations and agglomerations. Sekiguchi and Obi [4] proposed the use of solid dispersions as a novel method for reducing particle size. Solid dispersions may be obtained by dispersion of one or more active ingredients in an inert carrier or matrix in the solid state [5]. The methods utilized in their preparation include melting, use of a common solvent or the melting-solvent method.

The solid-dispersion techniques were used by Ford [6] to prepare granules containing indomethacin and PEG 6000. Their granule structure was examined by scanning electron microscopy and compared with the structures of granules of similar composi-

tion prepared by solvent deposition, aqueous granulation and preliminary compression techniques. The indomethacin-PEG 6000 distribution was found to be dependent on the preparative technique used. The rapid and complete dissolution of indomethacin was achieved only from tablets containing the solid-dispersed drug. Solid-dispersion systems of nifedipine with different carriers were also investigated by Sumnu [7, 8]. The results showed that the rate of dissolution of nifedipine can be greatly increased by the use of a coprecipitate technique with carriers, especially PEG 4000, PEG 6000, PEG 10000, K-25, K-30, K-90, polyvinyl pyrrolidone and urea. DTA and X-ray diffractometry showed that binary mixtures of nifedipine with PEG and urea were eutectic mixtures.

Analysis of enantiomers and racemates

Some chemical substances contain asymmetric carbon atoms and therefore exhibit two diastereoisomeric pairs of enantiomers, the *trans* and *cis* pairs. Only one pair of enantiomers is used in therapy. The second pair is pharmacologically less active and is a potential impurity of the active form.

The aim of thermoanalytical studies is to characterize the enantiomers and the racemates in the solid state and to build up the phase diagrams of the respective binary systems [9, 10]. Moreover, the possibility of determining the racemic low-active enantiomer content as the main impurity in the high-active enantiomer is also investigated. DSC, X-ray diffractometry, IR and solid-state NMR spectroscopy are employed as primary sources of information.

Since physical characterization for the development and process validation of pharmaceuticals is crucial for both satisfactory drug formulation and batch reproducibility, Bettinetti *et al.* [9, 10] performed studies on the thermal properties of sobrerol enantiomers and racemates. DSC analysis data, especially the enthalpy of fusion, melting point and heat capacity, allowed use of the Schroeder-Van Laar equation in its simplified form to construct theoretical phase diagrams for the *cis*- and *trans*-sobrerol pair.

Varshney *et al.* [11] report the application of DSC for the detection and quantitative determination of the less-active *meso* isomer in *dextro*-ethambutol hydrochloride. A DSC scan of the *dextro* isomer containing 5% of the e *meso* isomer shows two peaks. The first indicates the heat required to disrupt the solid-solid interaction and the second peak indicates the enthalpy of melting of the mixture. The enthalpy of the solid-solid interaction is linearly related to the content of the *meso* isomer in *dexrto*-ethambutol. On the other hand, a linear relationship is also observed between the enthalpy of fusion and the content of the *meso* isomer. Even as low as 0.2% of the *meso* isomer can be detected. Quantitative evaluation is reliable in the range of 1 to 5%.

Measurement of tablet disintegration

The disintegration time of a tablet is one of the most important characteristics by which the quality of a tablet is evaluated. Drugs released from a tablet pass through two processes: tablet disintegration and dissolution of the dispersed particles. The processes are affected by many factors, including tablet structure, particle size and rate of dissolution. General methods which have been used for disintegration measurement cannot elucidate the disintegration and dissolution process in detail.

The pharmacopoeias of several countries contain the methods of testing this property. These methods are very simple as concerns finding the outline of tablet distribution, but the values are not related directly to physical phenomena, especially the increase in surface area and the dissolution of a crystalline drug substance contained in a tablet during its disintegration.

Nogami *et al.* [12, 13] proposed a new method, using thermal analysis for the detailed investigation of tablet disintegration. By this means, the continuous variation in the surface area of a solid drug can be studied and each stage of the disintegration and the physical process is easily and distinctly recognized. This method was applied to an uncoated tablet and a granule and is useful when the tablet ingredient dissolves or reacts with the testing solution.

A typical result of the thermal analysis of tablet disintegration shows that the process is divided into four stages:

i) A rise in temperature is not seen and the original form of the tablet remains in the liquid.

ii) An increase in surface area an a temperature rise are observed during disintegration. The smaller particles dissolve in the reaction liquid and the difference between the increase and decrease in surface area is measured. The amount of particles dissolved may not be high when the tablet disintegration within a short period.

iii) An increase in surface area during disintegration may not be recognized and the rate of temperature change is lower for a good tablet. The disintegration almost reaches the final stage and dissolution is a rate determinant for the decrease in surface area. If a large granule disintegration in this period, an irregular decrease may be observed.

iv) All particles are dissolved and the surface area becomes zero. The change in temperature follows the cooling constant of the reaction system.

Analysis of drug formulations

Estimation of the drug value is of the highest importance. The pharmaceutical legislation foresees checking of the compliance of the final form of drugs with the quality standards established for them. This obliges the producers to control the quality of the

raw materials used in the manufacture of drug formulations and to check both the production process and the final product.

The programme of analytical studies involves checking of the appearance and designation of the final product package, organoleptic examination, verification of the content of drug in a container, determination of the loss on drying, the contents of ash and drugs, and microbiological assay. This is very difficult due to the specific character of drugs associated with the diversity of their forms. Moreover, it requires a good knowledge of the technology of drug formulations.

Checking of the qualitative composition of drug formulations by thermoanalytical methods is based on the verification of the identity of the components via their thermal properties. Wesolowski [14] showed that as the content of a particular component in samples is changed, the thermal decomposition of a mixture in granulate, tablet and dragee form is primarily due to the decomposition of the main component. As the content of this gradually decreases, the overall thermal effects of decomposition of the mixture become less dependent on the decomposition of this component. It is understandable that subtle effects due to the decomposition of a component present in minor amounts very frequently cannot be reflected in the DTA, TG and DTG curves. It influences only the parameters of the overall effects, such as the temperatures of the beginning, end and extremum of the peak, and the height, width at half-height and area of the peak.

The identification of drugs is most conveniently accomplished by comparing the temperature ranges, areas and shapes of the DTA peaks of drug formulations with those of authentic standard compounds.

The quantitative determination of the drugs in drug formulations depends on their concentration and the type of thermal decomposition process used [15, 16]. A high content of drug facilitates its quantitative determination because its thermal decomposition steps are better differentiated in the TG and DTG curves, and in such a case any effect of other components is correspondingly diminished. On the other hand, the least suitable are the thermal processes which take place over a broad temperature range. Decomposition frequently occurs over the temperature range of decomposition of the tablet mass, accompanied by a high loss in weight.

In order to apply DSC for determination of the native protein in drug formulations, Izutsu *et al.* [17] studied the dependence of the denaturation enthalpy observed via DSC analysis on the amount of β-galactosidase. The denaturation enthalpy was measured for various amounts of lyophilized β-galactosidase powder, which was the most highly purified enzyme available, and also a β-galactosidase powder formulation. The observed enthalpy was proportional to the amount of β-galactosidase in both cases. The linear relationship indicates the possibility of using the denaturation enthalpy to determine the native protein, though large standard errors were observed in the case of the powder formulation.

Processes of grinding and drying

Many drugs are known to crystallize with water molecules as an integral part of their crystal structure. The pharmaceutical hydrates display marked alterations in several physico-chemical properties, especially chemical stability or dissolution rate, during their processing or on exposure to relative humidities of varying degrees. The crystallinity of such compounds can easily be degraded by mechanical forces, with a resulting decrease in chemical stability of the drug substances.

Kitamura *et al.* [18, 19] studied the effect of grinding on the physico-chemical properties of cefixime trihydrate by DSC and TG, X-ray diffractometry and scanning electron microscopy. It was confirmed that the interaction between the water molecules and cefixime molecules was weakened by grinding. The crystal lattice damage induced by grinding significantly affected the chemical stability and also the discoloration. The results suggest that kinetic study is very useful for an estimation of the effects of mechanical stress on drug substances.

The crystallization of the active ingredient in a tablet can result in prolonged disintegration, cracks and an altered appearance, and may possibly influence the bioavailability. Ando *et al.* [20] investigated the possibility of crystal growth when tablets containing anhydrous theophylline and a hygroscopic material were stored in an atmosphere of high relative humidity. The DSC scans and X-ray diffraction patterns of the tablets at 90% RH showed that anhydrous theophylline was converted to the hydrate. This conversion at very high humidities may possibly by influenced be the addition of hygroscopic excipients.

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Zusammenfassung — Es wird ein kurzer Überblick über einige Aspekte der Anwendung von thermoanalytischen Methoden, insbesondere von DTA, DSC und TG in der Feststoffdosierung gegeben. Weiterhin wird die Nützlichkeit dieser Methoden bei der Voraussage der Bindemittelverträglichkeit, bei der Untersuchung disperser Feststoffsysteme, bei der Analyse von Enantiomeren und Racematen, bei der Messung der Tablettenzerfallszeit, bei der Analyse der Arzneimittelformierung und bei der Untersuchung von Mahl- und Trocknungsprozessen bei Arzneimitteln diskutiert.