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THERMAL METHODS OF ANALYSIS IN SOLID DOSAGE TECHNOLOGY

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ABSTRACT

A survey is given on some aspects of the application of thermoanalytical methods, viz. differential thermal analysis /DTA/, differential scanning calorimetry /DSC/, thermogravimetry /TG/ and derivative TG /DTG/, in solid dosage technology. The review has been preceded by a short characterization of these methods. Further, the usefulness of the thermal methods of analysis in the purity determination, analysis of reaction kinetics of drugs and characterization of suppository and ointment bases has been discussed. The presented studies include also the qualitative and quantitative analysis of solid dosage forms and studies on tablet disintegration. Particular attention has been paid to papers dealing with the possibility of replacing of some expensive and time-consuming methods of classical analysis by rapid and fully automated methods of thermal analysis in control industrial laboratories.

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INTRODUCTION

Thermal analysis is one of the oldest instrumental methods of analysis. It has been nearly one hundred years since Le Chatelier performed first thermoanalytical experiments[1]. The rate of instrument advancement and investigational activity was relatively slow over a number of decades after those initial experiments[2-13], despite the fact that the instrumentation was home-made and factors affecting experimental record were not clearly understood. Results thus tended to be inconsistent. During the 1950's, however, a number of commercially constructed instruments appeared on the market with standardized software and initiated the move towards standarization and comparability of results.

Thermoanalytical methods enable to measure changes of some physical and chemical properties of a substance analysed during its heating at a controlled rate. Initially, they had been used in mineralogy, metallurgy and analytical chemistry only. Actually, these methods have been found useful in the investigations of minerals, ceramics, building materials, cements, glasses, catalysts, liquid and solid fuels, explosives, industrial dusts, plastic materials, polymers, rubbers, textiles and foodstuffs.

Dynamic thermal methods have also gained importance in solving pharmaceutical problems, such as the determination of temperature ranges of phase transitions of drugs and values of their thermodynamic constants, the determination of phase diagrams and purity, the evaluation of compatibility and interactions among the components of drug formulations, as well as the study of solvation, the stability tests

and reaction kinetics of drugs[14-22]. Some of these problems are discussed below.

CHARACTERIZATION OF THERMOANALYTICAL METHODS

Dynamic thermoanalytical methods, especially differential thermal analysis /DTA/, differential scanning calorimetry /DSC/, thermogravimetry /TG/ and derivative TG /DTG/ are the most frequently used in the studies of pharmaceutical materials.

Historically, DTA is one of the oldest methods of thermal analysis. The principle of the DTA is based on measuring of the difference , ΔT, between a sample temperature, T_s, and a neutral reference material temperature, T_i. The temperature difference is recorded as a function of time, t, or temperature, T, by plotting the DTA curve[23-25]:

$$\Delta T = f/t/ = f/T/$$

In the case when a sample temperature maintains on the lower level than that of a reference material, in the sample occurs the process requiring supply of the definite amount of heat. It is characterized on the DTA curve by the negative effect /endothermic peak/. In the opposite situation, the process connected with generation of heat occurs in the sample, and is characterized by the possitive effect /exothermic peak/.

DTA is first of all the method of the phase analysis and for this reason reflects the changes of state occurring in the sample. With its aid those reactions can only be studied which are accompanied by the adequately large exchange of heat with the surroun-

dings, or in the course of which the sufficiently large changes of the specific heat of a sample occur in the sufficiently short time intervals.

In the calorimetric measurements based on the DTA peak area, the quantitative DTA is frequently replaced by the DSC method. The principle of its action is based on the complete compensation, with aid of an electric heating device, of the difference in temperature between a sample and a reference material which is generated during the thermal processes[23,26,27]. In the DSC method, an empty container is used in place of a neutral reference material. The quantity of energy necessary to establish the zero temperature difference between a substance with a container and empty container is recorded.

TG is one of the most frequently used methods of thermal analysis. Over 20 % of published works includes studies carried out by this method. TG differs in substance from that of the DTA and DSC. The TG curve of a sample reflects the mass changes , Δm, its loss or gain, occurring at a controlled heating rate. The changes in weight are recorded as a function of time or temperature, plotting the TG curve:

$$\Delta m = f/t/ = f/T/$$

or also the rate of weight loss , dm/dt, is recorded as a function of time or temperature, yielding the first derivative of TG curve, DTG[23,28,29]:

$$\frac{dm}{dt} = f/t/ = f/T/$$

The TG method ensures a relatively direct quantitative interpretation of the results. On the other

hand, DTG facilitates the interpretation of the TG curve because any change in the rate of weight loss of a sample is seen immediately. This enables a more distinct discrimination of individual stages of the thermal decomposition.

The physical and chemical effects that can be studied by thermal methods of analysis are shown in Table 1. Actually, the most frequent simultaneous registration of the DTA, TG and DTG curves on the same sample is performed presently, because it provides facilitaties for they joint interpretation[30]. The DTA /DSC/ curves enable to find if the definite thermal process has been accompanied by endo or exothermic effect, and with aid of the suitable device to measure its magnitude. On the other hand, the TG /DTG/ curves permit to find the accurate values of the mass changes of a sample and to take advantage of these results to the deduction of the equation of the chemical reaction to be in accord with the thermal decomposition of the pharmaceutical substance.

PURITY DETERMINATIONS

The estimation of purity of pharmaceutical compounds is one of the most important aspects of the drug quality. Many techniques used, such as the phase solubility analysis, are very time-consuming and require large amounts of sample. For these reasons, the interest in purity determination by the DTA and DSC techniques has increased in recent years.

The analysis of the shape, temperature ranges and areas of the endothermic DTA peaks due to melting of organic compounds shows that peak characteristics are

TABLE 1

The physical and chemical effects that can be studied by thermoanalytical techniques.

Physical effects	Thermal effects		Change in weight	
	endo	exo	gain	loss
Crystalline transition	x			
Melting	x			
Crystallization		x		
Vaporization	x			x
Sublimation	x			x
Ad- and absorption		x	x	
Desorption	x			x
Chemical effects	**endo**	**exo**	**gain**	**loss**
Dehydration or desolvation	x			x
Decomposition	x	x		x
Oxidative degradation		x		x
Solid-state reaction	x	x		x
Solid-liquid reaction	x	x		x
Solid-gas reaction	x	x	x	

influenced by impurities. Herington[31] reported four criteria which could be used to differentiate between the purity of organic compounds. These are as follows: /i/ a sample of lower purity begins to melt first, /ii/ the higher the purity the more sudden is the deviation from the straight line when the melting begins, /iii/ the more impure the sample the sooner is the maximum in the curve is reached, and /iv/ the lower the purity, the lower the height of the peak.

Ferrari et al. employed a shape and the temperature range of the DTA peak to evaluate final

purity of material intended for clinical and toxicological use, such as quinethazone, sulphasymazine and thozalinone[32], an amino acid, guanidine, oxazepine base and its succinate, succinic anhydride and succinic acid, thiadiazole base and its hydrochloride , and a pyridin compound[33], biphenyl, hydantoin, imidazolidinone, nitrofurantoin, nystatin and triazole, as well as a variety of methylamino, steroid and thiadiazole compounds[34]. The authors feel that DTA has earned its place along with other current by employed techniques to assist in solving analytical problems with ultra-high-purity pharmaceuticals.

Visser and Wallace[35] have developed a simple, quick and precise method for the detection of o-toluenesulphonamide, an undesired impurity of p-toluenesulphonamide. The method is based on the fact that the two isomers form an eutectic and this can be quantitatized by detecting the energy transition involved in the eutectic formation. The area of an endothermic DTA peak is linearly related to the content of o-toluenesulphonamide in a sample over the concentration range 0.25-5.0 %. Ferrari and Grabar[36] have demonstrated the interaction of two isomers of ethambutol and assumed a mechanism of a solid-solution effect to yield an additional endotherm which is related to the meso isomer concentration. The increase in the size of the endotherm with a corresponding increase in the meso-form concentration has been utilized to determine the isomer over the concentration range 1-4 %. The values obtained on the synthetic mixtures are not too precise but are acceptable owing to small peak areas involved and the lack of satisfactory base-lines.

Bowman and Rogers[37] compared the results of measurements of the melting-point depression of benzophenone contaminated with 4-methylbenzophenone, with the DTA method. The precision of the DTA method was significantly higher than that of the melting-point depression measurement. The DTA method eliminates the need for the precise temperature calibration but greater care is required in weighing out a fixed amount of the active material for dilution with carborundum. Moreover, the DTA, TG and DTG curves of aldrin and dieldrin has also been shown by Flóra[38] to be useful in the determination of these compounds in the presence of each other and the examination of their purity.

More recently, the DSC method has been used for the purity determination of organic compounds by analyzing the peak shape of the melting[39-54]. For more precise determinations, van't Hoff's equation was applied:

$$T_s = T_o - \frac{RT_o^2X_2}{\Delta H_f} \cdot \frac{1}{F}$$

where T_s is the sample temperature, T_o is the theoretical melting point of pure component, R is the gas constant, X_2 is the mole fraction impurity, ΔH_f is the heat of fusion of pure component, and F is the mole fraction of sample melted at T_s.

The fraction of the sample, F, which is melted at any particular sample temperature, T_s, is given by equation:

$$F = \frac{T_o - T_m}{T_o - T_s}$$

where T_m is the melting point of sample.

Rearranging the above equation leads to the following one:

$$T_s = T_o - \frac{T_o - T_m}{F}$$

Consequently, a plot of sample temperature, T_s, versus the reciprocal of the fraction melted, 1/F, should be a straight line of slope equal to the melting point depression. The purity can then readily be calculated from the first equation if ΔH_f is known. A very significant advantage of such a calorimetric determination of purity is that the heat of fusion, which is required for the calculation, is obtained simultaneously.

The method has several limitations, however,[41,43,46-48,52-54]. The first is associated with the derivation of the simplified equation used, as it is applicable only to very dilute solutions and hence to relatively pure samples. Another limitation is that only those impurities which are insoluble in the solid and soluble in the melt are measured because the impurity must concentrate in the liquid phase for the melting point depression to be linearly related to its concentration. In the case of pure compounds, most impurities are similar enough to be soluble in the molten sample, and, fortunately, solid solutions occur infrequently in lower-molecular-weight compounds.

Chemicals that decompose near their melting points cannot be determined. Many compounds reported as being thermally unstable have adequate stability to tolerate determination by DSC, as in this method samples are very pure, very small and kept at the melting point for a short period of time. Also compounds

existing in more than one crystal form cannot be analyzed umless they are previously completely converted to one form. Moreover, the purity of chemicals which have extremely high vapour pressures cannot be determined by this method as they rupture the hermetically sealed pans.

The method based on van't Hoff's equation has been used in the purity determination of many pharmaceutical substances. By comparing the results of purity evaluation obtained by the method of /i/ phase solubility, being commonly regarded as the standard one for evaluation absolute purity, and /ii/ quantitative TLC, it was demonstrated that they give results being in excellent agreement with those obtained by the DSC method for substances of purity in excess of 99 mole-%. This is shown in Table 2. At the same time it is apparent from the NMR and TLC results on the carbamate that impurities of 2 mole-% or more cannot be accurately determined.

ESTIMATION OF REACTION KINETICS

Estimation of kinetic data, such as activation energy, pre-exponential factor and reaction order for thermal decomposition process of drugs can be made either in isothermal or in programmed temperature increase conditions. Most data have been obtained from isothermal experiments. This situation was caused by simplicity of interpretation of these results. It also must be mentioned that when isothermal investigations are used it is difficult to conduct experiments over a wide temperature range.

TABLE 2

Results of purity determination by various methods /from ref. 47/.

dl-13-Ethyl-17α-ethynyl-17-hydroxygon-4-en-3-one			
Sample no.	DSC	Phase solubility	TLC
1	99.4	99.3	99.2
2	99.6	99.5	99.5
3	99.8	99.6	99.7
4	99.8	100	99.8
5	99.1	99.2	99.2
A substituted carbamate			
Sample no.	DSC	NMR[a]	TLC
1	99.7	>99	>99.5
2	99.5	>99	99.5
3	98.6	98.2	98
4	97.4	95.4	95-96
5	96.5	94.4	<95

Key: All values are expressed in mole-%, a is the impurity not detectable by NMR at <1 % level

The thermal decomposition of solid drugs is a very complex process even in the simple case expressed by the equation:

$$A_{/solid/} = B_{/solid/} + C_{/gas/}$$

Zsakó[55] showed that this process takes place in several stages, viz. the chemical act of breaking of bonds, destruction of the initial crystal lattice, formation of the crystal lattice of the solid product

what to consist the formation of crystallization centers and the growth of these centers, adsorption-desorption of the gaseous product, diffusion of the gaseous product, and heat transfer.

The rate of the thermal decomposition is determined by the rate of one or more of these stages. Sometimes, the rate-determining stage at the beginning of the decomposition can lose its significance later and another stage can take its place. Thus, decomposition rate depends not only upon the nature of the studied substance but also upon many other factors, such as particle size, weight of the sample, shape of the crucible, and other.

For the purpose of the calculation the kinetic data from non-isothermal conditions the following equation should be used:

$$\frac{d\alpha}{dt} = A \exp - \frac{E}{RT} f(\alpha)$$

where $d\alpha/dt$ is the decomposition rate, α is the fractional weight of the compound reacted, t is the time, A is the pre-exponential factor, E is the activation energy, R is the gas constant, and T is the absolute temperature.

Since thermal analysis is carried out with a constant heating rate, $\phi = dT/dt$, the substitution $dt = dT/\phi$ can be made, and the following differential equation is obtained:

$$\frac{d\alpha}{f(\alpha)} = \frac{A}{\phi} \exp - \frac{E}{RT} \, dT$$

Some differences in calculating the kinetic data by various authors result from various methods of sol-

ving the first equation. There are two main groups of methods used, viz. differential and integral.

The effect of the kinetics of reaction on the DTA trace has been explored by Kissinger[56]. Curves of reaction rate versus temperature for constant heating rates were used to demonstrate the effect of varying orders of reactions. The Kissinger equation, relates the shift of temperature of the extreme endothermic DTA peak to the heating rate, has been employed for the determination of kinetic parameters of alkali metal salicylates[57] and sodium oxacillin[58]. It has been found that the determination of the kinetic parameters of the thermal decomposition reaction can be easily and conveniently carried out by the use of DTA technique. It might be an efficacious method for studying the stability of solid drugs.

Application of the TG method to estimation of the kinetic parameters has been shown by Horowitz and Metzger[59]. The authors were elaborated mathematical interpretation of the TG traces enables to determine conveniently the kinetic parameters of decomposition reactions. The slope of a straight line plot as a function of the weight fraction left versus the temperature gives the activation energy of decomposition. The good agreement between values of activation energy obtained by this equation and reported literature values for some hydrated salts serves to validate the new approach.

CHARACTERIZATION OF SUPPOSITORY AND OINTMENT BASES

Thermal methods are used for characterization of the process of the melting behaviour of suppository

bases. Significance of the melting bahaviour and its characteristics of fatty suppository bases are of relevance due to the fact that it is one of the most important factors influencing drug release from the suppositories. During storage, the melting range and melting time of bases change so much that the drug release rate in the rectum may be reduced.

Coben and Lordi[60], when examining changes in the initial temperature and height of the endothermic DSC peak showed that DSC in the conjunction with x-ray diffraction and softening time testing are useful as both predictive and ongoing physical stability tests in the evaluation of suppository bases and drug formulations. Bornschein et al.[61] have utilized the temperature range of the DTA peak and melting time for the evaluation of the effect of storage at different temperatures on the release of drugs from the Rosupol-U suppository. Moreover, Müller[62] has used DTA for the purpose of definition of the influence of the particle size of active ingredients on the melting range of the suppository bases. Other factors influencing the melting behaviour of suppository bases are composition of base, chemical form of the drug and the method of the preparation of suppositories[63].

Furthermore, Liversidge et al.[64,65] have used DTA in the examination of binary mixtures of pure monoacid triglycerides to obtain a composition whose characteristics resemble those of commercial bases. It was shown that on storage, the phase diagrams changed due to the conversion of the unstable α- to β'-polymorphic forms of the constituent bases to the more stable β-polymorphic one, causing an increase in the melting point of the mixtures. The effect of storage

time at 295 K on the DTA melting point of pure triglycerides was shown in Table 3.

The problem of the qualitative and quantitative checking of the composition of commercial suppositories by thermoanalytical methods has been studied by Wesołowski[66]. It has shown that the identification of the particular components is more precise when the DTA, TG and DTG curves of the thermal decomposition of suppositories are recorded simultaneously. The use of temperature ranges, areas and shape of the individual DTA and DTG peaks, as well as the corresponding weight losses on the TG curves allows for best comparison. On the other hand, in the quantitative control of the composition only the TG and DTG curves were taken into consideration. The results of these determinations were in good agreement with those calculated from the formulation. It statistical evaluation shows the TG and DTG method to be satisfactorily accurate and precise but with low sensitivity.

Dynamic thermoanalytical methods have also been used in the investigation of the ointment bases and their ingredients. Führer[67] who recorded under linear temperature increase the heat effects of the ointment bases showed the possibility of investigation of the melting range and every kind of conversion in their colloidal structure. Powers and Craig showed that the fundamental informations on the properties and chemical compositions of commercial dental inlay waxes[68] as well as impression waxes[69], can be obtained by analysis of their penetration mode, determined by thermo-mechanical analysis /TMA/, and their solid-solid and melting transformations, determined by DTA. Similar conclusion has been reported by Rootare

TABLE 3

The effect of storage time at 295 K on the DTA melting point of pure triglycerides /from ref. 65/.

Melting point	Initially	After 26 weeks	After 52 weeks
	K	K	K
Tristearin	346.3	347.0	347.4
Tripalmitin	338.0	338.6	339.3
Trimyristin	331.6	332.0	332.0
Trilaurin	318.4	319.2	319.4
Tricaprin	307.4	308.4	308.4

et al.[70] who investigated by the same methods various gutta-percha commercial formulations. On the other hand, studies of the solid-solid transformations conducted by DSC, versus composition of the binary mixtures of paraffin and ester waxes, allowed to evaluate interactions between waxes in commercial dental formulations[71]. TG and DTG were also used simultaneously with DTA by Keserü and Katona[72] in the examination of gelation processes of ointment bases consisting of liquid paraffin and polyethylene.

Based on a study of the melting and the solidification of paraffin, ester and synthetic waxes, Lange and Jochinke[73] were concluded that it is not yet possible to utilize the height of the DTA peak and its position on the curve for identification of different types of waxes. However, Currell and Robinson[74] showed that by comparison of the DTA curves of mixtures of waxes with curves of particular wax and wax-like products, it is possible to identify the com-

ponents of these mixtures. In addition, accurate analysis of the shape of the DTA curves of waxes enabled a choice of the endothermic DTA peak to be made which is useful in distinguishing between paraffin, microcrystalline and polyethylene waxes. A relation between its area and content of waxes in the mixture can be used for estimation of these waxes in a mixture. Simultaneously, the influence of the sample size, its thermal conductivity, the geometry of the crucibles, means of the sample loading in them and the heating rate on the shape of the DTA curves of waxes was also defined. Moreover, a study of montana waxes showed that DTA may be used as a rapid method for evaluation of their chemical composition, and especially for the determination of their resin content[75].

The thermal decomposition of pharmaceutical ointments and creams was studied by Wesołowski[76]. This study has confirmed the possibility of employing thermoanalytical techniques, DTA, TG and DTG for qualitative and quantitative checking of their composition. The simultaneous determination of the content of two or more active components in the ointments and creams is practically impossible. The possibilities of quantitative control of the composition of soft products is supported by Craig et al.[77] and by Boelter[78] who were able to carry out a semi-quantitative analysis of binary mixtures of paraffin and ester or polyethylene waxes by the TG method.

ANALYSIS OF SOLID DOSAGE

In recent years investigations have also been performed on the possibility of utilization of thermal

methods of analysis to the differentiation between particular pharmaceutical preparations, identification of the components contained in them, determination of the content of active principles and mechanically bound and crystallization water. These studies appear reasonable to recommend thermoanalytical methods for the control of technological processes during manufacture of pharmaceutical preparations as well as for the quality control of the manufactured products.

Wendlandt et al. studied the thermal decomposition of internal analgesics[79], antacids[80] and vitamin preparations[81] representing powders, capsules and tablets. These studies confirmed the assumption that possibilities of utilization of the DTA /DSC/ and TG curves in the identification of individual preparations do exist. It assured potential application of the thermal methods of analysis in criminalistic investigations. Preliminary examinations were also carried out of mixtures comprising vitamins and vehicles to demonstrate similarities and dissimilarities between the same preparations manufactured by various producers[81].

Checking of the qualitative composition of drug formulations by thermal methods of analysis is based on the verification of the components identity by their thermal properties. The thermal decomposition of solid dosage forms, representing simple and effervescent powders, dusting powders, capsules, simple and effervescent granulates, internal tablets, tablets for sucking and preparation of effervescent beverages as well as dragees were examined by Radecki and Wesołowski[82-91]. On the basis of the obtained results it has been shown that the fundamental significance

for the identification have endothermic DTA peaks due to first-order phase transformations, particularly melting, evaporation, sublimation and polymorphic transformations[82,84]. The peaks are sharp, high, relatively broad and appear over a narrow temperature range. The parameters of these peaks change proportionally to the content of the active component.

The quantitative determination of the content of active component in a drug formulation is a very important problem. Margomenou-Leonidopoulou et al.[92,93] were the first who suggested the possibility of utilization of the thermoanalytical methods in this field. On the basis of differences in the shape of the DTA, TG and DTG curves of the thermal decomposition of novalgine and N-butylscopolamine hydrobromide, they achieved indication of the content of both components in their model mixture.

Otto[94] studied a Delitex-Pudern powder which is a physical mixture of γ-hexachlorocyclohexane and talc. The results of these calculations are compiled in Table 4. The analysis of the values of the arithmetical average of the content of active component and the confidence interval indicate a close analogy of the measurements based on the endothermic DTA peak with those of the isothermal TG measurements. It shows clearly a good concordance of the values of the arithmetical average of the active component content in commercial powders analyzed.

The quantitative analysis of the composition of pharmaceutical preparations is also a subject of the Radecki and Wesołowski's works[82-91]. The content of the active component was determined on the basis of the loss in weight recorded by the TG curve. The ad-

TABLE 4

Statistical evaluation of the content of γ-hexachlorocyclohexane in Delitex-Pudern powder by isothermal TG and DTA methods /from ref. 94/.

Sample	A	B	C
Isothermal TG /Mettler thermowage/			
$\bar{x}$	0.98	0.80	1.02
s	0.112	0.346	0.236
$\Delta\bar{x}$ /$t_{0.95}$/	0.086	0.266	0.181
DTA /instrument of own construction, ref. 95/			
$\bar{F}_s$	102.8	72.4	107.2
$\bar{x}$	0.98	0.77	1.02
$\Delta\bar{x}$ /$t_{0.90}$/	0.117	0.131	0.148

Key: A is the homogenized mixture containing 20 mg γ-hexachlorocyclohexane and 1980 mg of talc, B and C are the commercially available Delitex-Pudern powders, $\bar{x}$ is the arithmetical average, s is the standard deviation, $\Delta\bar{x}$ is the confidence interval, and $\bar{F}_s$ is the area of the peak.

vantage of this type of analysis is elimination of the time-consuming separation of the active components from vehicles, thus reducing the cost of analysis. The disadvantage of the method is that it cannot be used for determination of the active components which have no distinct thermal decomposition stages, or which constitute less than about 10 % of the total contents. In the later case, this is particularly disadvantageous in view of the fact that the active components are frequently very strong drugs and their determination is of particular importance. It is also difficult to analyse a sample for two active components.

The moisture content markedly affects the stability of active components, excipient materials and finished products, and also complicates the technology of their manufacture. Dávidné Kenéz[96] shows that the moisture content can be interpret in most cases as forming a "non-stoichiometric compound" with smoe ingredients of a pharmaceutical preparation. Experimental examples for illustrating this emphasises that it seems warranted to check the moisture content in pharmaceutical preparations and their ingredients.

The studies carried out by Paulik et al.[97] showed that derivatography can be used as a fast and accurate method of the determination of the moisture content /mechanically bound water/ and crystallization water /due to presence of e.g. lactose/ in pharmaceutical powders and granulates. The total content of the water determined from the TG and DTG curves differs slightly from that determined by the Karl Fischer titration method.

Touré et al.[98] compared three methods used to the determination of the moisture content, a gravimetric method, a chemical method of Karl Fischer titration and a physical one by measuring the dielectric constant. A powdered potato starch and its granulates obtained by wet granulation were used as a material studied. It was shown that the TG method was characterized by the best reproducibility.

TABLET DISINTEGRATION

Disintegration time of a tablet is the most important characteristic by which its quality is evaluated. Disintegration of a tablet is directly respon-

sible for the appearance of medicinal effect. Since the most widely used method is to compress granules into a tablet, the tablet has a secondary structure and is not a simple assembly of microcrystals. Therefore, it is considered that examination of tablet disintegration and its physical process is very important and is required for the elucidation of mechanism of disintegration.

Nogami et al.[99-101] were analyzed the process of disintegration of an uncoated tablet by thermal methods. The beginning of disintegration, the time necessary for the maximum surface area of tablet ingredient, and the time required for a powder to dissolve completely were determined precisely. This method was applied to the tablet of calcium carbonate[99], as well as to the granule and the tablet of basis magnesium carbonate[100].

Medicinals releasing 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 solutions. General methods which had been used for disintegration measurement cannot elucidate the disintegration and dissolution process in detail.

Disintegration of a coated tablet includes an additional factors to that of uncoated tablet. The coating layer must be dissolved prior to disintegration of the tablet core, and release rate of the medicinals in the tablet is affected by the properties of the layer. Nakai et al.[102] were examined the processes of disintegration and dissolution of sugar coated tablets by thermal analysis. The thermogram

clearly showed the disintegration process corresponding to the component of the coating layer. The sugar coated tablet without the water protective film was compared to the tablet with the film, and influence of the film on the medicinal release was examined.

Ueoka et al.[103] were studied the dissolution process of pharmaceutical preparations by using a Dewar vessel type calorimeter. It has been shown that the dissolution rate of a medicine was affected by the particle size of crystal, the compressional pressure and the additives used. On the other hand, Gucluyildiz et al.[104] investigated under isothermal TG conditions the influence of selected tablet components on evaporation of nitroglycerine from the sublingual tablets. The results, confirmed by chemical analysis, showed that the volatility of nitroglycerine was dependent in various ways on the kind of vehicles and concentration ratio in which they were used. It has been shown that the TG method is a simple, rapid and reliable means of screening the influence of vehicles on liberation of the active components from drug formulations containing them.

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