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Energetics of tablet disintegration

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Summary

A recent physical analysis of the disintegration phenomenon expresses the disintegration force in terms of an exponential expression containing an expansion rate constant, k, and an exponent, n, which varies depending on the composition of the tablets tested. It is shown that the expansion rate constant, k, is strongly dependent on experimentation temperature and that it can be analyzed using an Arrhenius-type expression. Thus, an activation energy can be calculated. Experimental results of disintegration of tablets prepared from calcium diphosphate dihydrate and containing various swellable disintegrants are presented and analyzed.

Introduction

The process of tablet disintegration has been modelled in recent publications from our research group (Caramella et al., 1987, 1988; Colombo et al., 1988) as a coupled phenomenon of detachment of particles (layers) from the solvent/tablet interface (interface-controlled mechanism) and diffusion of particle layers away from the interface (diffusion-controlled mechanism). Thus, we have shown that the overall disintegration force measured by an experimental apparatus such as that described by Caramella et al. (1986) is given by Eqn. (1):

$$\frac{F}{F_\infty} = 1 - \exp(-kt^n) \qquad (1)$$

Here F is the disintegration force measured as a function of time t, F_∞ is the maximum disintegration force developed and measured, n is an exponent characteristic of the controlling disintegration mechanism (Colombo et al., 1988), and k is an expansion rate constant.

The rate constant can be readily determined from the half-life, θ, of the process by setting $F/F_\infty = 0.50$. Thus, Eqn. (2) is obtained

$$k = \ln 2/\theta^n \qquad (2)$$

Whereas in a previous publication (Colombo et al., 1988) we offered a complete analysis of the significance of the exponential term n, we now recognize that the kinetic term k incorporates significant information on the energetics of the disintegration phenomenon. It is, therefore, the intention of this work to provide a thorough analysis of this parameter.

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Energetics of Tablet Disintegration

General description

As described before, the expansion rate constant, k, can be compared to that observed in nucleation phenomena. It is therefore described in terms of a general Arrhenius expression

$$k = k_0 \exp\left[-\frac{\Delta E}{RT_d}\right] \tag{3}$$

Here k_0 is a pre-exponential constant independent of temperature and T_d is the disintegration (experimentation) temperature.

The activation energy of the overall process ΔE, can be determined from a single graphic representation of the logarithm of k vs T_d^{-1}. However, further molecular insight into the meaning of this activation energy can be obtained by recognizing that the disintegration process is the composite of a diffusion-controlled mechanism with activation energy ΔE_1, and an interfacially controlled mechanism with an activation energy ΔE_2. Therefore, one may write:

$$k = k_0 \exp\left[-\frac{\Delta E_1}{RT_d}\right] \exp\left[-\frac{\Delta E_2}{RT_d}\right] \tag{4}$$

Diffusional mechanism

The activation energy, ΔE_1, for the diffusion-controlled mechanism of the disintegration process is directly related to the molecular diffusion of macromolecular chains or other excipient molecules from the system. Such a process is much promoted when the disintegrant is in its rubbery state, i.e. in a state where the relative mobility of the chains is high. Thus, ΔE_1 can be related to the glassy/rubbery transition temperature, T_g, of the overall tablet system. The Williams Landel–Ferry equation (Ferry, 1984) best describes this transitional behavior.

$$\Delta E_1 = \frac{4135 T_d}{51.6 + T_d - T_g} \tag{5}$$

This equation clearly indicates that a decrease of the glass transition temperature, T_g, at constant experimentation temperature, T_d, will lead to a decrease of the activation energy for the diffusional process. This is clearly correct, since a depression of T_g due to the presence of a significant quantity of water leads to greater ease of molecular rearrangment (diffusion).

The effect of water content on the T_g for mixtures of one polymer with water is given by Eqn. (6):

$$\frac{1}{T_g} = \frac{w_p}{T_{g_p}} + \frac{1 - w_p}{T_{g_w}} \tag{6}$$

Here T_{g_p} is the glass transition temperature of the polymer in the absence of any other components, T_{g_w} is the glass transition temperature of water (Franson and Peppas, 1983), and w_p is the weight fraction of water in the tablet. For a system with several components exhibiting individual glass transition temperatures T_{g_i} and appearing in weight fractions w_i each, an analogous expression for the overall tablet can be written:

$$\frac{1}{T_g} = \sum_{i=1}^{n} \frac{w_i}{T_{g_i}} + \frac{\left(1 - \sum_{i=1}^{n} w_i\right)}{T_{g_w}} \tag{7}$$

In fact, Okhamafe and York (1984) have shown that such component influence on the total T_g is possible for pharmaceutical preparations.

Experimentally, the overall T_g value can be determined by running a differential scanning calorimeter thermogram of the tablet mixture.

Interfacial mechanism

The interfacial activation energy, ΔE_2, may be expressed by parameters characteristic of tablet dimensions and the thermodynamics of disintegration. For this purpose, let us consider a monolayer of surface particles of the material (Fig. 1) in the disintegrating tablet with thickness, l. The surface free energies of the end plane and the peripheral area are σ_e and σ_s, respectively.

Then, the energy ΔE_2 can be expressed in terms of the previous parameters and the enthalpy of

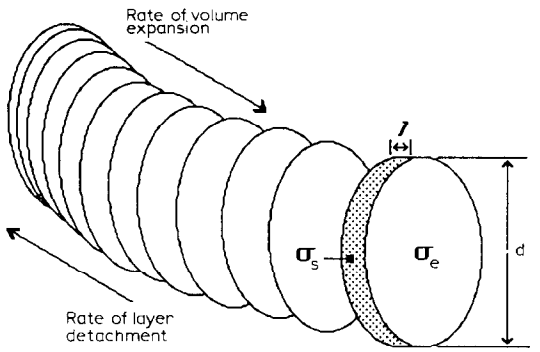

Fig. 1. Parameters of interfacial monolayer mechanism, of a tablet with diameter d and monolayer thickness l.

formation, ΔH_m, of the system (Avrami, 1940)

$$\Delta E_2 = \frac{4l\sigma_s\sigma_e}{\Delta H_m} \frac{T_g}{T_d - T_g} \tag{8}$$

Again, the glass transition temperature is important in this phenomenon. For high values of T_g, the activation energy is low and the phenomenon is almost spontaneous. For low values of T_g, the material is close to its transition at experimentation temperature and a large activation energy is required for the interfacial detachment.

Overall mechanism

By combining equations 4, 5 and 8 one is able to express the expansion constant, k, in a logarithmic form as follows:

$$\ln k = \ln k_0 - \frac{4135}{R(51.6 + T_d - T_g)} + \frac{4l\sigma_s\sigma_e T_g}{\Delta H_m R(T_d - T_g)T_d} \tag{9}$$

The numerical coefficients are such that the universal constant R is expressed in units of $R = 1.987$ cal/mol · K whereas the enthalpy of formation, ΔH_m, is expressed for a tablet of known thickness and molar composition.

As mentioned earlier, one method of analyzing the disintegration energetics is by plotting ln k versus $1/T_d$. Such a diagram (according to Eqn. 3) would give the value of the total activation energy, ΔE, and the preexponential constant, k_0. An alternative method based on Eqn. 9 would be to plot the term $\ln k + 4{,}135/R(51.6 + T_d - T_g)$ versus the term $T_g/R(T_g - T_d)T_d$. Then, the intercept will be $\ln k_0$ and the slope will be $4l\sigma_s\sigma_e/\Delta H_m$. Calculation of individual parameters of this term is possible, provided certain assumptions are made.

For example, following Fig. 1, the thickness, l, of one particulate monolayer of disintegrating material may be considered equal to the average size (particle diameter, for spherical particles) of the particles used to make the compressed tablet. In addition, in the actual disintegration force experiment, the surface area of the base is equal to the area of the tablet and significantly bigger than the perimetric area of one monoparticulate layer. Thus, it may be assumed that the ratio of surface free energies is related to the ratio of areas (where d is the tablet diameter). Therefore:

$$\frac{\sigma_e}{\sigma_s} \cong \frac{\pi d^2/4}{\pi dl} = \frac{d}{4l} \tag{10}$$

Consequently, the slope of this graph may be represented by

$$\text{slope} = \frac{4l\sigma_s\sigma_e}{\Delta H_m} = \frac{d\sigma_s^2}{\Delta H_m} \tag{11}$$

Finally, the enthalpy of tablet formation, ΔH_m, may be calculated from other sources and is related to the applied pressure during compaction. Therefore, using Eqns. 10 and 11 we can calculate σ_s and σ_e, and we can eventually classify all systems tested according to their energetic properties for disintegration.

Materials and Methods

Model tablet systems were prepared by mixing a disintegrant and a model substance with a lubricant. Calcium diphosphate dihydrate (Emcompress, Mendell, Carmel, NY) as a model substance (always 500 mg per tablet) was mixed with 4 w% (20 mg) of one of the following compounds as disintegrants: cross-linked sodium carboxymethyl-

cellulose (Ac-di-sol, Eigenman and Veronelli, Milan, Italy); sodium starch glycolate (Primojel, Deimos, Milan, Italy); crosslinked poly(*N*-vinyl-2-pyrrolidone) (Polyplasdone XL, GAF, Milan, Italy) and microcrystalline cellulose (Avicel PH101, Gianni, Milan, Italy). A quantity of 1.5 w% (7.5 mg) of magnesium stearate was added as a lubricant and the components were mixed in a mixer (Turbula, model T2G, Backhofen, Basle, Switzerland) and compressed at 20 °C and 50% RH with a mean force of 25 ± 0.5 kN, using a reciprocating tablet press (Kilian Co., Cologne, F.R.G.) employing flat punches of 11.28 mm diameter.

Measurement of the disintegration force was done in water at 7, 20, 30, 37 and 40 °C, using the apparatus and method described by Colombo et al. (1980).

In addition, the glass transition temperatures of the various disintegrants were determined using a differential scanning calorimeter (Mettler, model TA 3000) at 5 K/min.

Results and Discussion

Analysis of the temperature-dependent disintegration

All tablets prepared were tested at 5 temperatures, and the force of disintegration was measured as a function of time up to the maximum disintegration force, F_∞. The normalized data were plotted as a function of time and analyzed as described before (Caramella et al., 1988), using Eqn. 1.

The analysis of all the data obtained is presented in Table 1. It is evident that the exponent n that describes the overall disintegration phenomenon varies from 0.56 to 0.74 for Ac-di-sol and Polyplasdone XL, from 0.92 to 0.98 for Primojel,

TABLE 1

Analysis of time-dependent disintegration phenomenon for tablets prepared with 94.5 w% calcium diphosphate dihydrate, 1.5 w% magnesium stearate and 4 w% disintegrants

Disintegrant	Temperature (°C)	Expansion constant $k(s^{-n})$	Exponent n	Maximum disint. force $F_\infty(N)$
Polyplasdone XL	7	0.120 ± 0.001	0.74 ± 0.004	37.6 ± 2.2
	20	0.145 ± 0.021	0.72 ± 0.038	35.4 ± 1.9
	30	0.143 ± 0.001	0.73 ± 0.010	34.6 ± 0.9
	37	0.157 ± 0.001	0.72 ± 0.010	30.8 ± 0.7
	40	0.160 ± 0.000	0.71 ± 0.010	33.1 ± 0.9
Ac-di-sol	7	0.104 ± 0.004	0.56 ± 0.060	53.3 ± 0.5
	20	0.114 ± 0.027	0.68 ± 0.100	53.0 ± 2.1
	30	0.115 ± 0.003	0.66 ± 0.010	43.8 ± 0.2
	37	0.133 ± 0.008	0.64 ± 0.005	43.0 ± 2.3
	40	0.169 ± 0.013	0.59 ± 0	43.7 ± 1.0
Primojel	7	0.028 ± 0.002	0.98 ± 0.110	24.6 ± 0.5
	30	0.050 ± 0.006	0.95 ± 0.060	27.8 ± 2.2
	37	0.049 ± 0.005	0.96 ± 0.017	27.2 ± 1.8
	40	0.061 ± 0.015	0.92 ± 0.070	28.6 ± 1.7
Avicel PH101	7	0.012 ± 0.006	1.36 ± 0.140	7.2 ± 0.3
	20	0.017 ± 0.007	1.30 ± 0.070	6.0 ± 0.7
	30	0.022 ± 0.012	1.25 ± 0.100	6.4 ± 0.6
	37	0.042 ± 0.025	1.09 ± 0.170	6.9 ± 0.8
	40	0.036 ± 0.008	1.09 ± 0.050	6.5 ± 0.1

All values are the average of 3 experiments ± S.D.

and from 1.09 to 1.36 for Avicel. Therefore, and according to our previous analysis (Caramella et al., 1988), the disintegration phenomenon is diffusion-controlled for tablets containing the first two disintegrants, whereas for tablets containing Primojel and Avicel it is more influenced by an interfacial mechanism. This conclusion agrees with our previous observations that as the hydrophilicity of the disintegrant increases the expansion constant decreases. Indeed, Primojel has the highest equilibrium weight degree of swelling of the 3 amorphous disintegrants tested (Caramella et al., 1984). The case of Avicel is somewhat different because this disintegrant is semicrystalline; it will be further discussed below.

To determine the overall activation energy of disintegration, ΔE, the data of Table 1 were plotted in logarithmic form. By performing linear regressions of ln k vs $1/T_d$ for each set of tablets, the values of ΔE were determined as reported in Table 2. A typical curve for Polyplasdone XL-containing tablets is shown in Fig. 2.

The activation energy for Avicel-containing tablets is 4 times bigger and of Primojel-containing tablets is twice that of tablets containing either Polyplasdone XL or Ac-di-sol. These results are in physical agreement with the values of n of Table 1. In a diffusion-controlled situation (e.g. Polyplasdone) with expansion constant 4–10 times greater than that of an interfacially controlled disintegration (Avicel), the energetic contribution necessary for the activation process should be significantly reduced. In fact, since Polyplasdone

TABLE 2

Activation energy for disintegration of tablets prepared with 94.5 w% calcium diphosphate dihydrate, 1.5 w% magnesium stearate and 4 w% disintegrant

Disintegrant	Activation energy ΔE (kcal/mol)	Correlation coefficient r
Polyplasdone XL	1.41	0.953
Ac-di-sol	2.01	0.830
Primojel	3.76	0.972
Avicel PH101	6.40	0.950

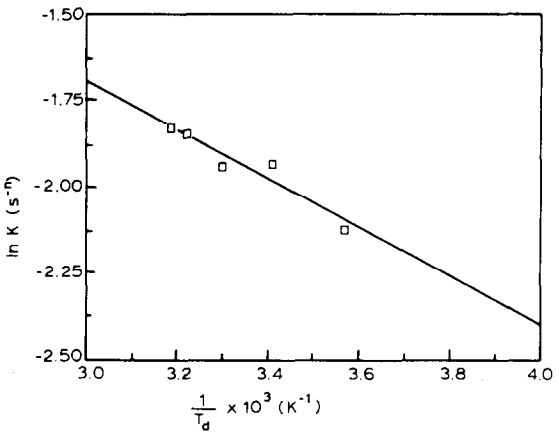

Fig. 2. Variation of the logarithm of the expansion constant (in s^{-n}) with inverse disintegration temperature for Polyplasdone XL-containing Emcompress tablets.

is a better disintegrant than the others, it has the lowest activation energy.

The activation energies calculated are typical of diffusional phenomena (where the activation energy varies from 1–15 kcal/mol), indicating that, even in the case of Avicel-containing tablets, diffusion plays a certain role. In fact the activation energy values are in the lower limit of diffusional energies, indicating "spontaneity" or ease of occurrence of this phenomenon.

Surface energetics of disintegration

A further analysis of the energetic characteristics of these systems was followed in order to characterize the importance of such phenomena as the swelling characteristics of the disintegrant and the surface energies of the particles of the overall systems. Equation (9) was used for this analysis.

First, the glass transition temperature, T_g, of the mixtures tested was determined by using Eqn. 6. Since some of the properties of the disintegrants have been previously associated to their swelling characteristics (Caramella et al., 1984) we calculated first these values using $T_{gw} = 149.1$ K for water (Franson and Peppas, 1983) and the T_{g_p} values for the amorphous polymers tested as presented in Table 3. Avicel was not further analyzed because it is a semicrystalline disintegrant and neither Eqn. 6 nor the WLF equation can be used.

TABLE 3

Surface energetics of disintegration using swelling characteristics of disintegrants in tablets containing 94.5 w% calcium diphosphate dihydrate and 1.5% magnesium stearate

Disintegrant	Degree of swelling q(g/g)	Glass trans. of disintegrant T_{g_p}	Glass trans. of swollen system T_g (K)	Slope of Eqn. 9 (kcal/mol)	σ_s (kcal/mol)	σ_e (kcal/mol)
Polyplasdone XL	6.2	313.1	162.7	2.31	0.63	16.22
Ac-di-sol	7.7	333.1	160.1	2.23	0.62	16.00
Primojel	13.0	333.1	155.8	1.04	0.42	10.90

The necessary value of w_p was calculated from the data of Caramella et al. (1984) which give the amount of water in the polymer, q, in g water/g dry polymer, for the 3 disintegrants tested. It can be easily proven that

$$w_p = \frac{1}{1+q} \tag{12}$$

Then, from Eqns. 6 and 12, the values of T_g were calculated as shown in Table 3. Plots were made of $\ln k + 4.135/R\ (51.6 + T_d - T_g)$ vs $T_g/R(T_g - T_d)T_d$ and the slopes of these curves were determined by linear regression. Fig. 3 indicates one of these curves for Polyplasdone-containing samples and Table 3 includes the values of the slopes.

From the values of the slopes, the surface free energy of the peripheral area, σ_s, was calculated using Eqn. 11. Here $d = 1.28$ mm is the diameter of the tablets. The value of ΔH_m was determined from data of Ragnarsson and Sjögren (1985),

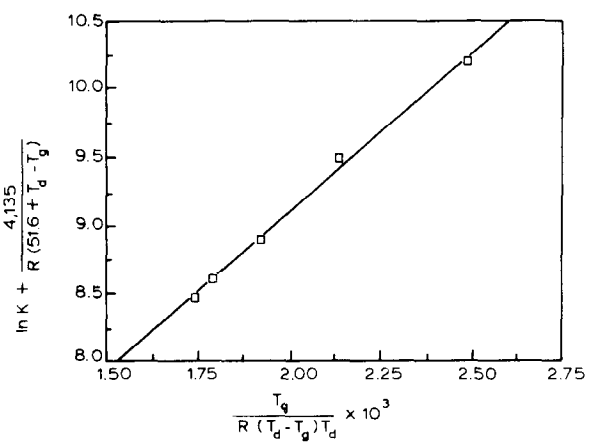

Fig. 3. Energetic analysis of Polyplasdone XL-containing Emcompress tablets using Eqn. 9.

which indicate that during compaction of similar tablets at 250 MPa, a net work of 7.3 J was measured for a tablet with thickness of 4 mm containing 0.00536 mol of Emcompress. The final value was $\Delta H_m = 1.93$ cal · m/mol.

Finally, the value of the end surface free energy, σ_e, was calculated from Eqn. 10 using $l = 110$ μm, which is the average size of the particles used in these studies. Both values of σ_s and σ_e for all the systems studied are summarized in Table 3. We observe that the surface energy is significantly *lower* for tablets prepared with Primojel rather than with the other two polymers as disintegrants. A lower surface energy indicates greater ability and ease of "delamination," i.e., of the interfacial mechanism of disintegration.

Consequently, the surface free energy of a monoparticulate layer of a mixture of the specific disintegrant with a model substance can become a strong indicator of the interfacial mechanism of the disintegration process. Knowledge of this parameter will lead to an understanding of the temperature effect on the overall disintegration process as well as at the diffusional contribution to this phenomenon.

Relative importance of mechanisms

The importance of each mechanism on the overall disintegration phenomenon was finally determined by calculating the ratio of the diffusion-controlled and interface-controlled activation energies, $\Delta E_1/\Delta E_2$, using Eqn. 14 and the definition of the two terms using Eqns. 5 and 8. Therefore, and with appropriate transformation for the units,

$$\frac{\Delta E_1}{\Delta E_2} = \frac{1.02\Delta H_m(T_d - T_g)}{l\sigma_s\sigma_e T_g(51.6 + T_d - T_g)} \tag{13}$$

TABLE 4

Relative importance of diffusion-controlled activation energy, ΔE_1, and interfacially controlled activation energy, ΔE_2 for disintegration of tablets containing 94.5 w% calcium diphosphate dihydrate, 1.5 w% magnesium stearate and 4 w% disintegrant

Disintegrant	Disintegration temperature (°C)	$\Delta E_1/\Delta E_2$	Percentage of diffusional mechanism (%)
Ac-di-sol	7	7.77	88.6
	20	7.96	88.8
	30	8.12	89.0
	40	8.26	89.2
Primojel	7	1.76	64.0
	20	1.81	64.3
	30	1.84	64.9
	40	1.87	65.0

The results for two disintegrants are presented in Table 4. Clearly, for Ac-di-sol-containing tablets where the disintegration analysis using Eqn. 1 gave values of n between 0.56 and 0.66 (indicating a diffusional mechanism), the contribution of the diffusional mechanism is around 89%, as judged from the analysis of the activation energies.

However, for tablets containing Primojel, where the exponent n was between 0.92 and 0.98 (indicating the importance of the interfacial mechanism), the percentage drops to 65% diffusional and 35% interfacial mechanism. Therefore, analysis of the energetics of the parameter k, indicates what the value of the exponent n should be, and vice versa.

Conclusions

We have shown that the process of tablet disintegration may be analyzed in terms of an exponential expression containing an exponent characteristic of the mechanism of disintegration and a kinetic expansion constant. The latter may be expressed in terms of temperature using an Arrhenius expression. This analysis can be used to quantify the energetics of tablet disintegration, measure the activation energy for the diffusion-controlled or interface-controlled mechanism, and finally determine the surface free energy of disintegrating tablets.

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