Mechanical Activation of Pharmaceutical Systems

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Abstract: Mechanical activation has become a phenomenon of general significance in pharmaceutics. This report describes the extent of activation induced by relevant processes. With the use of the Eyring equation the transformation of structurally stored energy into chemical energy and the implied free enthalpy as well as the excess free enthalpy (activity) were evaluated from the rate of an indicator reaction. A comparison was made between different kinds of milling and tabletting with respect to pharmaceutical conditions. An optimization of these processes was derived.

Mechanical loading of solids causes spatial and thereby energetic disordering of lattice structures. The active mechanical energy that is partially transferred is stored in the form of lattice defects. In this way the solid systems gain an activated state (Fig. 1).

The disordering process is tantamount to a decrystallization and an entropy increase, which are reflected and characterized by an increase of volume (decrease of true density) called the activation volume.

Primarily friction and fracture processes contribute to the change in state (1, 2) transforming maximally 84 to 93 % of the mechanical energy into dislocation and distortion energy of the

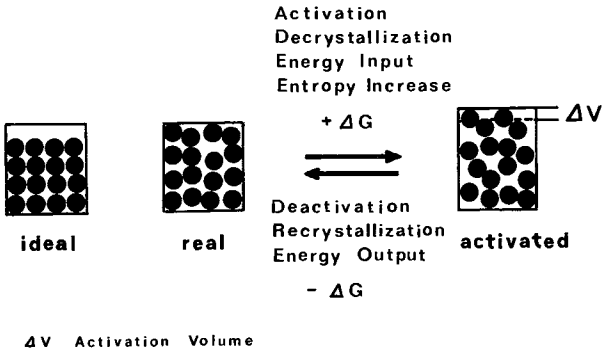

Fig. 1 Principle of activation and deactivation of solids.

lattice elements (3). In 1962 Smekal introduced the term "mechanical activation" for this phenomenon to differentiate it from thermal activation. It represents the most important type of non-thermal activations (1).

Lattice defects introduced mechanically by friction cover only surface layers of 10^{-4} to 10^{-5} cm thickness comprising 100 to 1000 atom layers. The secondary consequences, however, reach far more deeply. Imperfections generally impair monocrystals as a whole. The structural disordering implies an increase of both entropy and enthalpy and thus stimulates the crystal properties according to the intensity of such thermodynamic modification. In the case of comminution only a small part of approximately 10 per cent of the excess enthalpy of the activated product may account for the surface enlarging. The main portion of the excess enthalpy and the modification of properties (contrary to common opinions) can mostly be attributed to the development of thermodynamically unstable states in the lattice and not to the reduction of particle size. If a constant field takes effect, e.g. through the application of a constant stress in the elastic range, it is called a "static activation", whereas a non-constant stress is referred to as a "dynamic activation" (2) (Fig. 2).

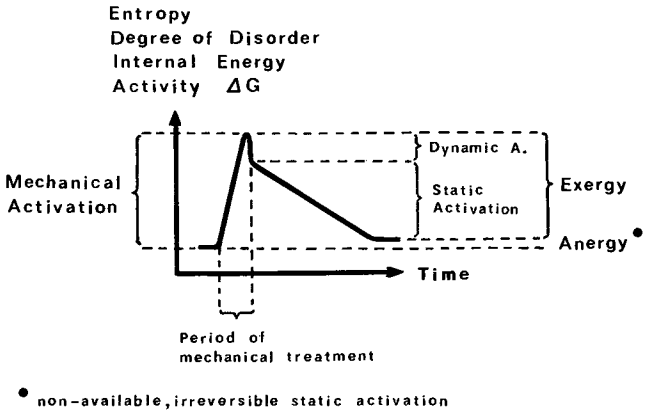

Fig. 2 Definition of the terms used.

Since the activated state is unstable, the process of activation is reversible resulting in a deactivation, recrystallization, entropy loss and energy output of the system (Fig. 1). The reversible part of the stored energy that can be transformed into other types of energy is called "exergy", the irreversible part "anergy". The reverse process continues to thermodynamic equilibrium but never reaches an ideal structure free of defects (Fig. 1).

There are two categories of disorder and instability. One of these concerns the highly excited short-living states with a duration in the range of 10^{-7} to 10^{-3} s, which cause the activation to attain the highest level during the mechanical treatment. These states decay as soon as they are generated. The deactivation of these high-energy structures comes to an end immediately after the removal of the mechanical stress (dynamic activation). The same short duration is required for the destruction of a solid by fracture. Besides these very "hot" and very unstable defects there appear freezed, metastable states (static activation), that have a lower energy and a longer duration of life ranging from 10^{-3} to 10^{6} s (1670 h or 70 d). Vacancies, in general, are healed within less than 10^{-2} s. When the static activation has settled down, a residual activity (residual disorder) will remain (1). The deactivation rate depends upon the reaction conditions (see tempering) and the material properties. For example, the recrystallization of glass lasts thousands of years, when stored under normal conditions.

The phenomenon of mechanical activation proved to be very important in many fields (1–4). It is the basis of mechanochemistry (W. Ostwald, 1919) and of tribology (H. P. Jost,

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1966), since the absorbed excess free enthalpy causes an acceleration of chemical as well as of physical reactions. The first solid reaction induced mechanically was already described in 1892. Investigations since undertaken, however, have included almost exclusively inorganic substances (2), that are rather unimportant with respect to dosage forms.

In pharmaceutics the phenomenon has been explored systematically since 1975 (5). Meanwhile, numerous effects of practical relevance to drug formulation could be attributed to lattice defects produced mechanically (6, 7). After initial scepsis towards the new concepts of Molecular Pharmaceutics other authors also confirmed these results (8–19). In this connection the "Activation Theory of Tablet Formation" was developed (20, 21). Simultaneously, the principles of mechanical activation were transferred to organic substances. However, the thermodynamic values of mechanical activation and their variability involved in pharmaceutical operations have not yet been determined. This question is the topic of the present paper. Hitherto the change of order and crystallinity was taken as a measure of the degree of activation.

The state of activation is characterized by thermodynamic parameters such as enthalpy and entropy (22–24). The enthalpy differences of activated systems generally range between 4.2 and 42 kJ/mol, while the value of entropy may rise to the entropy of fusion. To determine the increased enthalpy levels, calorimetric methods were used (1, 2). We applied a kinetic procedure to evaluate the excess free enthalpy measuring the reverse transformation of potential energy (exergy) into chemical energy by means of an indicator reaction.

Materials and Methods

In accordance with Hüttig (25) the activity of a solid system (A) is defined as the difference of the free enthalpies (Δ G) between the activated (G^+) and non-activated (G) states, i.e. the excess free enthalpy (1, 2):

$$A = \Delta G = G^+ - G.$$

Increasing the enthalpy (H) and the entropy (S) will change the free enthalpy of activation and cause an excess of free enthalpy; thus, according to the Gibbs-Helmholtz-equation

$$\Delta G = \Delta H - T \Delta S.$$

This relationship shows that with respect to the product $T \Delta S$ the enhancement of the concentration of intrinsic defects (entropy, S) corresponds in its consequences to a temperature rise. A thermodynamic equivalence, therefore, exists between the mechanical and thermal activation. In both cases the decisive parameter Δ G exhibits a linear change.
As a consequence of enthalpy increase (Δ H) the energy of activation (E_a) is also increased:

$$E_a \approx \Delta H + R T.$$

Concomitantly, the equilibrium and the equilibrium constant (K) of this reaction are shifted:

$$\Delta G = -R T \cdot \ln K.$$

On the other hand, the equilibrium constant is correlated with the rate constant (k) depending upon the frequency of transformation of activated molecules into non-activated ones (ν):

$$k = \nu \cdot K.$$

In this way thermodynamic parameters meet kinetic ones and make possible the determination of thermodynamic values by kinetic methods. Since in conformity with the laws of thermodynamics

$$K = e^{\frac{\Delta S^\circ}{R}} \cdot e^{-\frac{\Delta H^\circ}{RT}}.$$

Eyring summarized these relationships in the following equation:

$$K = \frac{k_B \cdot T}{h} \cdot e^{\frac{\Delta S}{R}} \cdot e^{-\frac{\Delta H}{RT}} = \frac{k_B \cdot T}{h} \cdot e^{-\frac{\Delta G}{RT}}$$

(k_B = Boltzmann constant)

Hence, the reaction rate is the higher, the smaller (the more negative) ΔG and Δ H are and the larger Δ S is (22). Here it is essential that the relationship allows one to inversely derive from this dependence the free reaction enthalpy and thus the activity of a system (23, 24).
From the transformation of the equation it ensues that

$$-\Delta G = \left(\log \frac{k}{T} - \log \frac{k_B}{h}\right) 2.303\ R\ T.$$

The trials were conducted at room temperature (T = 298 K). Under these conditions the mathematical expression could be simplified as follows:

$$\frac{k_B \cdot T}{h} = 6.2 \cdot 10^{12}\ s^{-1},$$

$$-\Delta G = (\log k - 12.79)\ 2.303\ R\ T \quad \text{and}$$

$$-\Delta G = 5706 \log k - 72980.$$

Therefore, the activity of a system could be directly expressed by the velocity of an indicator reaction.

The oxidation of ergocalciferol has proved to be a suitable indicator reaction (26). The decomposition of the vitamin was enhanced proportionally to the energy stored and available in the solid system.

The experiments were accomplished in two different trial series. Ergocalciferol (10 %) (AB-DDR) was first homogeneously mixed with lactose monohydrate (AB-DDR) in a tumbler. Then the mixture was triturated for 2, 5, 10 and 20 min in a porcelain mortar to examine the influence of the trituration time on the activity of the solids. In another experimental series the same mixture was tabletted with 1, 3 or 6 MPa pressure to form compacts 10 mm in diameter and 200 mg in mass, in order to test the influence of the pressure head.

All samples were stored at room temperature and protected from light. At an interval of 2 or 3 d the ergocalciferol content of the preparations was determined spectrophotometrically (after dissolution in ethanol, at 265 nm). The measurements of both series were compared with those of the corresponding nontreated (non-triturated or non-tabletted) samples. Each value represented an average value of at least three test samples prepared simultaneously.

Results

The experimental observations implied the presence of effects that derive from dynamic as well as static activation. Dynamic activation was indicated by an acceleration of the ergocalciferol reaction during the mechanical treatment, i.e. chemical

effects caused mechanically in the period of direct loading. Definite thermodynamic values, however, could not be obtained, since the active mechanical energy was partially transformed into thermal energy, so that the reaction rate was also influenced by heat. The part of stimulation that was induced by mechanical activation could not be separately determined. The degree of decomposition measured immediately after the operations, therefore, represented only a relative value of dynamic activation.

The static activation, however, could be exactly derived from the gradual release of stored energy after temperature equilibration, on the basis of the different behavior of the mechanically treated and non-treated samples.

Triturating Operations

The decomposition of ergocalciferol that occurred in the trituration period by mechanical (and partially thermal) induction is shown in Table I. The drug decomposition correlates with the loading intensity (trituration time). These values are taken as initial points in the determination of static mechanical activation. The continuation of the decay after removal of the mechanical stress is summarized in Table II. Depending upon the potential of energy input stored structurally the indicator reaction was accelerated. Just as in case of heating, the more intensive was the activation, the more energy was available to the chemical process.

Table I. Drug Decomposition During Mechanical Treatment Determined Immediately after Different Trituration Times (Mixtures of Lactose with 10 % Ergocalciferol).

Trituration Time (min)	Content (%)
0	100.0
2	100.0
5	97.5
10	96.0
20	95.3

Table II. Time Course of Drug Decompositoon Induced Mechanically by Different Triturating Operations (Mixtures of Lactose with 10 % Ergocalciferol; Content Values in %; Initial Content = 100 %)

Storage Time (d)	(s)	Trituration Time (min) 0	2	5	10	20
0	0	100	100	100	100	100
6	518400		97.0	93.0	90.0	88.1
9	777600	93.5	93.3	90.3	86,3	82,2
13	1123200		92.1	86.2	79.7	75.8
21	1814400	90.2	90.2	80.0	73.9	63.1

The graphic evaluation of the measurements in a semilogarithmic plot made clear that a first-order reaction occurred (Fig. 3).

Calculating the slopes of the straight lines the reaction rate was obtained, and the free reaction enthalpies were calculated in accordance with the equations mentioned. The mechanical activations (activities) of the systems, finally, ensued from the differences between the treated and non-treated samples (Table III). Hence, all parameters were affected by the

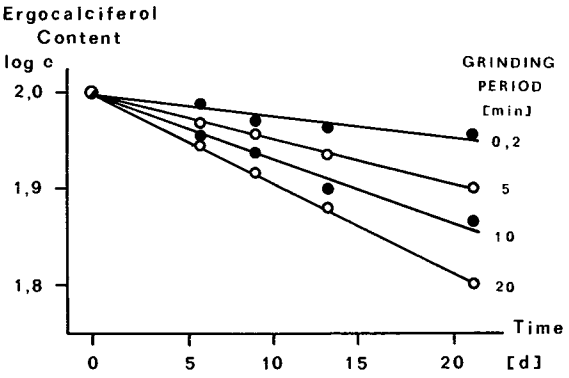

Fig. 3 Course of ergocalciferol decomposition induced by different trituration times.

Table III. Effects of Different Mechanical Loadings Caused by Triturating Operations.

Trituration Time (min)	Reaction-rate Constant (s^{-1})	Free Enthalpy kJ · mol^{-1})	Activity* (kJ · mol^{-1})
0	$6.66 \cdot 10^{-8}$	113.93	0
2	$6.66 \cdot 10^{-8}$	113.93	0
5	$1.27 \cdot 10^{-7}$	112.33	1.60
10	$1.83 \cdot 10^{-7}$	111.42	2.51
20	$2.54 \cdot 10^{-7}$	110.61	3.32

* = Mechanical activation, excess free enthalpy

trituration time. The relationship between the mechanical treatment and the induced activation (excess free enthalpy) is illustrated in Fig. 4. The ability of the system to absorb mechanical energy appears to saturate with time. In the course of advancing disorder the storage of dislocation and distortion energy grows increasingly difficult. A mechanical impact is decreasingly transformed into lattice defects and energy input with increasing activation of the system. Finally, a state will be reached that no longer allows further energy transfer.

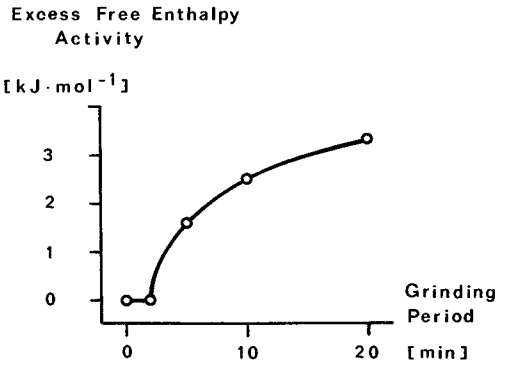

Fig. 4 Dependence of (static) mechanical activation upon trituration time.

Compacting Operations

Similar to the grinding operations (trituration), ergocalciferol decomposition was also registered in the course of tabletting immediately after the stress influence, as a function of the pressure applied. Hence, this correlation can also be used as a chemical method of pressure determination (Fig. 5). The results of the indirect pressure evaluation referred to the dynamic (and thermal) activation and agreed well with the

determination of other effects of activation such as density modification (27–29). Both methods, therefore, made also possible the quantitation of original stress distribution in the tablet during compression (27–29). The shape of the curve demonstrates again that the dynamic activation tends to saturate at a limit value (as is the case with triturations).

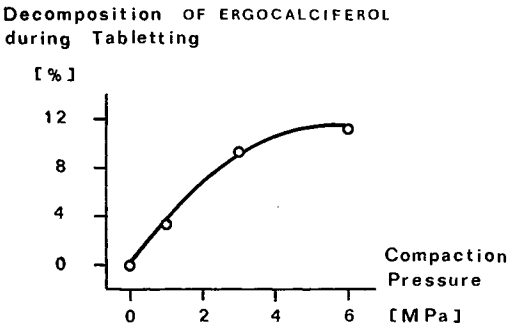

Fig. 5 Dependence of ergocalciferol decomposition during tabletting (especially dynamic mechanical activation) upon compaction pressure.

The further decomposition of ergocalciferol being induced by the release of structurally stored energy follows from Table IV. Again the semilogarithmic plot shows the reaction to be first-order. The straight-line slope (reaction rate) changes in accordance with the mechanical loading applied (Fig. 6). The values derived from the kinetics such as rate constant, free enthalpy and static mechanical activation (excess free enthalpy) are summarized in Table V.

Table IV. Time Course of Drug Decompositon Induced Mechanically by Different Compacting Operations (Mixtures of Lactose with 10% Ergocalciferol; Content Values in %; Initial Content = 100%)

Storage Time (d)	(s)	Compaction Pressure (MPa) 0	1	3	6
0	0	100	100	100	100
7	604800	–	88.2	84.6	66.0
14	1209600	92.1	84.8	78.2	59.4
21	1814400	89.2	84.2	65.2	58.6

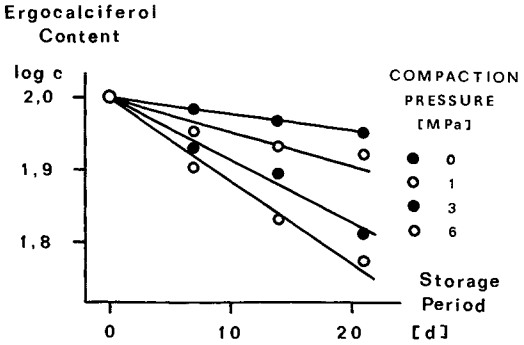

Fig. 6 Course of ergocalciferol decomposition induced by different compaction pressures.

The relationship between the increase of static mechanical activation and the pressure is illustrated in Fig. 7. As seen with grinding there was no linear enhancement af activity, but the activity increased with decreasing sensitivity of the system. The curve, thus, went to a limit equal to the maximal activation. The chemical results again agreed well with the variation of the state of order measured densimetrically (30).

Table V. Effects of Different Mechanical Loadings Caused by Compacting Operations.

Compaction Pressure (MPa)	Reaction-rate Constant (s^{-1})	Free Enthalpy ($kJ \cdot mol^{-1}$)	Activity* ($kJ \cdot mol^{-1}$)
0	$6.35 \cdot 10^{-8}$	114.05	0
1	$1.27 \cdot 10^{-7}$	112.33	1.72
3	$2.35 \cdot 10^{-7}$	110.81	3.24
6	$3.05 \cdot 10^{-7}$	110.16	3.89

* = mechanical activation, excess free enthalpy

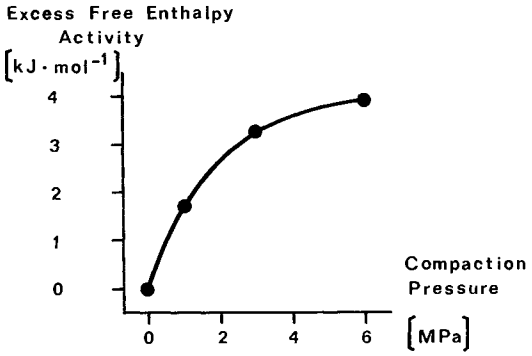

Fig. 7 Dependence of (static) mechanical activation upon compaction pressure.

Discussion

The results of this study document that common pharmaceutical treatment of solids cause a mechanical activation that is expressed in an increased and excess free enthalpy (= Gibbs energy, spontaneity, irreversibility, driving force of isothermal and isobaric processes). The solid system analyzed was independent of the mode of mechanical loading, always reaching the same maximum activation. In the course of simple (manual) grinding operations as well as during compression the excess free enthalpy rose to a value of 4 kJ/mol (extrapolated). The primary structural and the secondary chemical consequences correlated with the intensity of impact. In the system investigated, e.g. trituration for 10 min and tabletting with 2 MPa proved to be equivalent (Fig. 4 and 5). The exponential increases of activation (disordering of structure) agreed, although the mechanical unit operations were quite different. The influence of loading changed with a decreasing sensitivity of the systems: the effect caused by a definite amount of mechanical energy depended upon the degree of order present, and it declined with increasing lattice defects. Finally, a limit value was reached marking the ultimate structural disordering. At this point a thermodynamic equilibrium existed that was characterized by the same amount of defect formation and healing (equal velocity of the forward and backward reaction).

With respect to the economy of applied energy it can be derived that the energy is wasted beyond the limit value. The efficiency of energy utilization decreases even when this border has not yet been reached. As to the "Activation Theory of Tablet Formation" (21) and the correlation between activity and strengthening, this observation means that high compac-

tion pressures are less economical than low ones, and above the saturation value (in the present case 7 to 8 MPa pressure) no further activation and no further increase of tablet strength will be realized. The elevation of pressure then can no longer be transformed into strengthening; crack formation and other fracture phenomena such as capping occur. Therefore, the process of tabletting should be performed with pressure as low as possible.

The logarithmic shape of the curve describing the dependence of mechanical activation (Δ G) upon pressure (Fig. 7) coincides with the well-known correlation between pressure and tablet properties. Thus, the tablet strength increases along with the activation to reach a saturation value. These observations agree with the values of energy uptake derived from pressure-way diagrams of tabletting. Such correlations support the "Activation Theory". In parallel with the course of energy transfer, the apparent and true density (the porosity and the degree of molecular order, respectively) and the ability to disintegrate and to dissolve also vary.

A mere chemical incompatibility between the components or a catalytic effect of lactose on the stability of ergocalciferol is rather improbable. Since the decomposition intensity coincides with the alteration of the activation volume (Fig. 1) (6) and ergocalciferol is sensitive to energy influence, whereas lactose is rather indifferent and stable. It is the reservoir of the structurally stored energy that nourishes the reaction for more than 20 days (Fig. 6), and the reaction rate corresponds to the available energy potential, just as in the case of heating.

The activation values determined for organic substances with a new chemical method agreed well with the results of other authors for inorganic compounds with quite different methods (2). Vibration milling of calcium carbonate, for instance, resulted in an excess free enthalpy between 6.6 and 9.8 kJ/mol; the same treatment of copper yielded the value 7.5, and in the case of nickel 10.8 kJ/mol were observed. The rolling of nickel sheet showed 13.8 kJ/mol. Since "active solids" (2) can also be prepared in quite another non-thermal way, relevant data may complete the picture. The precipitation of calcium carbonate led to an activation between 3.2 and 3.5 kJ/mol; the reduction of nickel salts gave 11.7 kJ/mol; the triboreaction between nickel and carbon monooxide yielded 10.9 kJ/mol.

In conclusion, the following aspects are comparable in their order of magnitude:

- the ability of organic and inorganic substances to be activated;
- the activation by mechanical and non-mechanical operations;
- the activation by pharmaceutical and very different processes such as metallurgical treatments.

Further, a comparison between the mechanical activation and the free enthalpy of polymorphic transformation is of particular interest, since modification transformations pass activated states and can, therefore, be induced by a mechanical treatment (1, 2). Similar to the decay of a static activation, other structural transformations also represent solid phase transitions. For the transformation of graphite into diamond the excess free enthalpy amounts to 2.9; 3.7, and 7.1 kJ/mol at 25, 227 and 927°C, respectively (1).

Comparison of these activation values suggests that the described kinetic method represents a valuable tool that complements established procedures for the determination of electromotive force, equilibrium constant or enthalpy (2). The method is based on the principle that the excess free enthalpy (= activity) causes the system to equilibrate to a stable state, with concurrent release of energy and, thus, an increased reactivity of the system.

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