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Contribution to the methodology of optimization and in-process control of some physical properties of pharmaceutical bulk substances and granulates*

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Abstract: Many experts consider drug analysis exclusively as a chemical measuring technique. In the pharmaceutical industry, physical and physico-chemical parameters form an integrated part of the quality specification, because they play an essential role both in quality assurance and in the technical and economic aspects of production on the commercial scale. Such physical and physico-chemical properties are analysed by special, non-chemical methods. In their programme of systematic research in this field, the authors have elaborated new methods to test some essential properties of powders and granulates used in the production of compressed tablets. The following test and production methods have been developed: (i) the determination of flowing–sliding characteristics of granulates based on the measurement of the mass-flow (g s^{-1}) and mass-flow density (g s^{-1} cm^{-2}); (ii) the determination of optimum granulometric parameters with regard to tablet diameter; (iii) the direct determination of the temperature-dependent equilibrium vapour pressure; and (iv) the compression of tablets under controlled temperature.

Keywords: *In-process control; mass-flow density; flowing–sliding characteristics; granulometric optimization; equilibrium moisture content; tablet compressibility temperature.*

Introduction

The scope of pharmaceutical analysis and of drug control is clearly reflected in pharmacopoeias as far as quality specifications are concerned. The standard methods prescribed in these official compendia — as well as the special analytical methods for the individual homogeneous, heterogeneous, incoherent, coherent, plastic, and solid pharmaceutical dosage forms — can be classified as physical, physico-chemical, and chemical. The quality of drugs, standardized through the application of prescribed

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pharmacopoeial methods, can be assured by optimized technologies. Hence, extension of the scope and further development of in-process quality control methods is desirable on practical grounds.

Such methods are useful both at the pre-formulation stage for research work and optimization of technical operations and processes based on engineering calculations, and also at the production stage for systematic continuous and eventually automated control of manufacturing processes on the commercial scale.

Different criteria are applied for the evaluation of pre-formulation, in-process and pharmacopoeial quality control methods. These criteria include: objective and subjective accuracy, time, human resource requirement, automation, simplicity of application and economic feasibility.

In this paper, new methodological possibilities are presented for the testing of a few in-process parameters that are considered important as far as the quality of the finished product is concerned.

The 'Flowing–sliding' Characteristics of Solid Particles

Several workers have studied the flow properties of solid particles and granulates, which play an essential role primarily in the production of hard-gelatin capsules and compressed tablets, as indicated in just a few publications [1–3].

The mass content uniformity, hardness, friability and dissolution rate, and variation of these values within a batch and between different batches, as well as the bioequivalence of tablets, depend on the process technology and on the quality of the granulate. If the granulate composition is disregarded at this stage, it can be concluded from the literature that the parameters affecting the quality of tablets are implicitly included in the flow properties of the granulate.

Many investigators have studied the effect of particle size, particle-size distribution, particle density, bulk density, bed porosity and the diameter of the tablet on the flowability, based on kinetic principles. Others have attempted to measure the adhesion, cohesion and shear forces on the frictional coefficient.

It has been concluded from these tests that the resistance against physical forces evidenced during the flow of the granulate is manifested in a complex variable that can be termed as the 'flowing–sliding resistance'. Exact methods for the selective measurement of the individual forces are not available.

While attempting to find a mathematical relationship among all the important parameters, including particle size, density, geometric shape etc., and conditions such as gravitational force, flow diameter and moisture control, which affect the flow properties of granulates, a new measurement method was elaborated, the principle of which is illustrated in Fig. 1. The test sample II is put into a funnel I. The diameter (d_o) of the circular outflow aperture (III) can be changed. The flow of the sample is controlled by a diaphragm (IV), and the mass of the sample (m, g) is measured as a function of the exposure time (t, s), which can also be changed.

Since the exposure time for the flow of granulate into the cavity of the die depends on the type and speed of tabletting machines, the 'flowability' of these granulates should be studied within practical time limits. Based on the principle described, both the mass-flow ($Q_m = m/t$, g s^{-1}) and the mass-flow density ($Q_m/A = m/t \cdot 1/A$, g s^{-1} cm^{-2}, where A is the surface area) can be very accurately determined as a function of a narrow time interval (0.1–1.0 s).

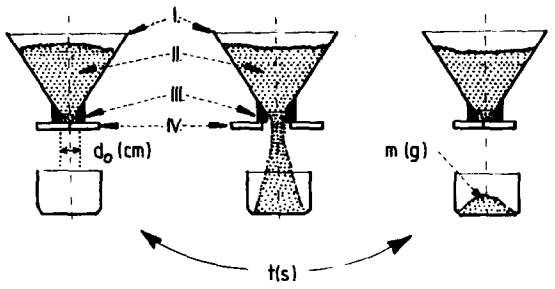

Figure 1
Principle of the mass-flow measurement according to [18] I, funnel; II, test sample; III, circular outflow aperture; IV, diaphragm; d_o, diameter; t, exposure time (s); m, sample mass (g).

In order to facilitate the interpretation of the mathematical analysis of the parameters affecting the 'flowability' of granulates, spherical model materials were selected for the initial tests whose essential parameters spanned a wide range. The samples selected and their characteristics are summarized in Table 1.

Table 1
Samples and characteristics

Samples	Parameters			
	d_s*	ρ_s†	ρ_a‡	d_o(mi)§
Lactose pellets	0.095	1.42	0.74	0.5
Lactose pellets	0.068	1.43	0.76	0.4
Lactose pellets	0.055	1.44	0.77	0.4
Poppy seeds	0.1	1.16	0.61	0.4
Mustard seeds	0.196	1.7	0.76	0.7
Glass beads	0.322	2.47	1.52	1.2
Glass beads	0.409	2.47	1.43	1.2
Lead shot	0.162	11.4	6.33	0.5

* d_s, mean particle diameter (cm).
† ρ_s, particle density determined by picnometry (g cm^{-3}).
‡ ρ_a, bulk density (g cm^{-3}).
§ d_o (min), minimum limits of aperture diameter for the measurement of massflow.

The lactose pellets were prepared in a Fremd-type centrifugal coat granulator. The individual particle size fractions were separated by screening in such a way as to obtain particle size ranges of 0.9–1.0 mm, 0.63–0.7 mm and 0.5–0.63 mm, respectively. The median of each fraction was calculated according to the mass distribution.

The flow functions were determined by a series of measurements, where the aperture diameter d_o was changed by 0.1 cm increments from 0.3 cm (minimum) to 1.2 cm (maximum) and the outflow time was changed by 0.1 s intervals from 0.1 s to 1.0 s. In addition to the above factors, a large amount of data were required to obtain a statistically significant evaluation of the accuracy of measurements and the characteristics of the relationship.

When the masses of the samples flowing through the different apertures were plotted against the exposure time, a series of straight lines described by equation (1):

$$m = Q_m \cdot t \tag{1}$$

was obtained, as illustrated by the graphs of lactose pellets with 0.095 cm average particle size (Fig. 2).

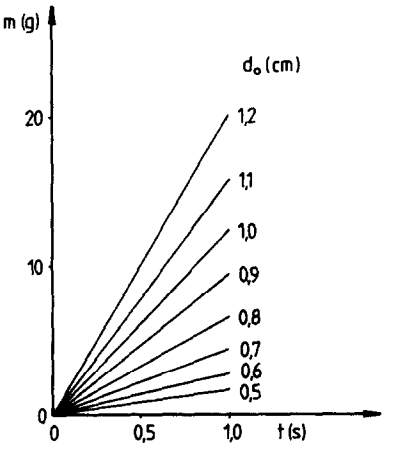

Figure 2
Mass-flow of 0.095 d_s lactose pellets through circular apertures of various diameters (d_o). The correlation coefficients were all close to or equal to 1.00.

Table 2 demonstrates that the mass-flow and mass-flow density as a function of the aperture diameter are characteristic of the test material. The standard deviation of the results (S.D., $n = 10$) was calculated from three parallel series of measurements performed at ten different exposure times for each d_o value.

During the computer analysis of the experimental data, it was found that the mass-flow can be expresssed as an n-degree polynomial of the aperture diameter; the results obtained with a fourth-degree polynomial were consistent among themselves, even at large aperture diameters. Using the least-squares method the following general relationship was constructed:

$$Q_m = \frac{m}{t} = k_1 \frac{\rho_s}{d_s} (d_o - D_{min})^2 \cdot (d_o^2 - k_2 d_o + k_3) \tag{2}$$

where D_{min} is the minimum point of the computed fourth-degree curve, namely the calculated minimum aperture diameter (cm) where the mass-flow is zero; ρ_s is the density of the solid particle (g cm^{-3}); d_s is the mean diameter of the particle (cm); and k_1, k_2 and k_3 are constants characteristic of the test material. The term k_1 represents a possible expression of the 'flowing–sliding resistance'.

In agreement with the literature [2, 4], it is also concluded that the widely used repose angle values [5] do not satisfactorily characterize the flowing properties of the granulates. The authors propose the measurement of the 'flowing–sliding resistance' both for the optimization of formulation and for in-process control of the physical properties of granulates.

The Possibility of Optimizing Granulometric Parameters with Regard to Tablet Diameter

The tests described above were evaluated on the basis of the mass-flow of granulates. During these investigations, attempts were made to establish a simpler, more practical

Table 2
Measured and calculated data of mass-flow (Q_m)* and mass-flow density (Q_m/A)

Samples		d_o 1.2	1.1	1.0	0.9	0.8	0.7	0.6	0.5	0.4
Lactose pellets	Q_m	19.82	15.80	12.30	9.62	6.50	4.45	2.78	1.80	—
d_s = 0.095 cm	± SD†	0.12	0.7	0.8	0.76	0.01	0.09	0.10	0.15	
	Q_m/A	17.5	16.8	15.8	15.0	13.0	11.7	9.92	9.47	
Lactose pellets	Q_m	20.97	16.80	13.20	10.17	6.75	4.70	3.12	1.96	0.80
d_s = 0.068 cm	± SD	0.06	0.1	0.2	0.08	0.05	0.06	0.04	0.05	0.01
	Q_m/A	18.6	17.8	16.9	15.9	13.5	12.3	11.1	10.3	6.66
Lactose pellets	Q_m	21.15	17.15	13.30	10.57	6.86	4.75	3.19	1.97	0.85
d_s = 0.055 cm	± SD	0.81	0.6	0.4	0.04	0.05	0.05	0.08	0.08	0.02
	Q_m/A	18.7	18.2	17.1	16.5	13.7	12.5	11.4	10.4	7.08
Poppy seeds	Q_m	16.33	13.30	10.40	7.83	5.67	3.59	2.28	1.42	0.64
	± SD	0.85	0.6	0.2	0.09	0.05	0.05	0.09	0.06	0.06
	Q_m/A	14.4	14.1	13.3	12.2	11.3	9.45	8.14	7.47	5.33
Mustard seeds	Q_m	17.45	13.55	10.10	7.12	5.30	3.30	—	—	—
	± SD	0.86	0.2	0.1	0.04	0.09	0.01	—	—	—
	Q_mA	15.4	14.4	12.9	11.1	10.6	8.68			
Glass beads	Q_m	25.55	—	—	—	—	—	—	—	—
d_s = 0.322 cm	± SD	4.48	—	—	—	—	—	—	—	—
	Q_m/A	22.6	—	—	—	—	—	—	—	—
Glass pearls	Q_m	24.75	—	—	—	—	—	—	—	—
d_s = 0.409 cm	± SD	3.76	—	—	—	—	—	—	—	—
	Q_m/A	21.9	—	—	—	—	—	—	—	—
Lead shot	Q_m	212.9	162.0	121.0	86.32	66.59	44.39	28.24	20.08	—
	± SD	12.2	6.3	5.0	5.1	0.88	0.21	0.33	4.35	—
	Q_m/A	188.4	172.3	155.1	134.8	133.2	116.8	100.8	105.7	

* Terms defined in text.
† SD = standard deviation (n = 10; see text).

mathematical relationship between the mass-flow density and aperture diameter or particle size, respectively. Several test functions were analysed, among which a surprisingly good linear relationship was found between the aperture diameter (equal to the diameter of the die, in practice) and the granulometric properties, as seen from the following equation:

$$\frac{Q_m}{A} = c_1 \frac{d_o^2}{d_s} + c_2 \tag{3}$$

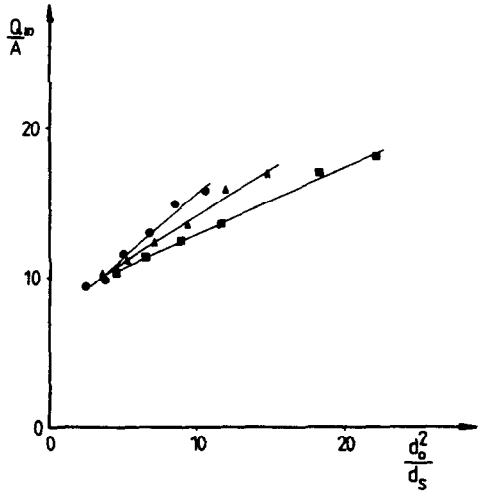

Figure 3
Relationship between the mass-flow-density and diameter aperture (d_o) or particle size of lactose pellets with different mean particle size d_s: -●-● 0.095 cm; -▲-▲- 0.068 cm; -■-■- 0.055 cm.

and illustrated by the graphs of lactose pellets in Fig. 3. It should be noted that equation (3) could be considered as a possible approximation to equation (2). The two material constants of equation (3) could also be interpreted on the basis of test functions, among others, as follows:

$$c_1 = \rho_s \cdot j, \tag{4}$$

where j is a potential coefficient of the dimensionless 'flowing–sliding resistance'; furthermore:

$$c_2 = J \cdot \mathbf{g} \left(1 - \frac{\rho_s - \rho_a}{\rho_s \cdot \rho_a}\right) \tag{5}$$

where **g** is the gravitational constant (9.81 m s^{-2}), J is a constant characteristic of the granulometric properties, and ρ_s and ρ_a are the particle density and bulk density, respectively.

The correlation-coefficients (r^2), the values of material constants c_1 and c_2, the valid limits of d_o for a linear relationship, and the constants j and J are indicated in Table 3.

The measurement of the mass-flow and mass-flow density of granulates within the described limits may be used as a practical tool for the optimization of formulations and also for in-process control of production. The method offers a new possibility to relate

Table 3
Calculated data from equation (3) for mass-flow density

Sample	r^{2*}	c_1†	c_2†	d_o limits‡	j§	J
Lactose pellets d_s = 0.095 cm	0.98	0.87	7.07	1.0–0.5	0.613	2.04
Lactose pellets d_s = 0.068 cm	0.99	0.63	7.85	1.0–0.5	0.440	2.08
Lactose pellets d_s = 0.055 cm	1.00	0.45	8.45	1.1–0.5‖	0.313	2.18
Poppy seeds	0.97	0.69	5.70	1.1–0.5	0.595	2.61
Mustard seeds	0.98	1.37	5.67	1.2–0.7	0.806	2.13
Lead shot	0.98	12.67	76.6	1.2–0.5	1.11	8.40

* r^2 = correlation coefficient squared.
† c_1c_2 = constants.
‡ d_o limits = limits of aperture diameter within which the regression is linear.
§ j = potential coefficient of 'flowing–sliding resistance'.
‖ An unusually high value was observed at 0.9 cm aperture diameter and was omitted from the regression analysis.
J = constant characteristic of granulometric properties.

the tablet diameter with the optimum mean particle size or particle density in addition to the apparent density parameters, which hitherto could only be determined empirically by time-consuming experiments. Investigations are continuing with the objective of clarifying the physical semantics of the material constants related to the granulometric properties. Although these studies have not yet been completed, the proposed method is already considered applicable for in-process control.

Direct Method for the Determination of the Temperature-Dependent Equilibrium Vapour Pressure

Moisture content is an important parameter of solid pharmaceutical dosage forms, particularly tablets, and might affect the 'flowability' of powders [6] and granulates [7], their compressibility [8], and the dissolution properties [9] and stability [10] of tablets. The in-process control of moisture content therefore plays an essential role both in assuring the quality and in process economics of the finished products. The moisture content of a solid-phase system establishes a temperature-dependent equilibrium with the humidity of the surrounding atmosphere. Hence the equilibrium moisture content should be studied as a function of temperature. The well-known sulphuric acid hygrometers [11] are suitable for such experiments. The air is recycled through the test sample in a closed system and the mass of equilibrium water vapour is determined directly by titration with concentrated sulphuric acid, using manometric end-point indication. If the sulphuric acid hygrometer is provided with a temperature-controlled jacket, the equilibrium moisture content of the solid-phase sample can be determined at atmospheric pressure as a function of the temperature. According to the available experimental data, the equilibrium moisture content of some solid-phase drugs and intermediates shows irregular changes as a function of temperature. The characteristics of such irregularities must be known both for the manufacture and quality assurance of the finished product and for the control of the moisture content through technological means. The equilibrium moisture content of such a system also changes as a function of atmospheric pressure. For this reason vacuum-technique methods [12] could be applied

only to the determination of equilibrium moisture contents that are not sensitive to pressure.

Instead of sulphuric acid hygrometry the so-called sorption-optical hygrometer [13] can be used to follow continuous changes of the equilibrium moisture content, including automated process-control of moisturing and drying operations in fluidized bed equipment.

This new measurement technique permits the continuous determination of the relative humidity of the air both in a static system and in intensive streams within a few seconds, theoretically in a temperature range between −180°C and 300°C and between zero to 100% relative humidity limits. The instrument can be used for the automation of the production process and it also assures the optimum equilibrium moisture content of the product.

The simultaneous application of a nuclear magnetic resonance hygrometer has also been found useful for such purposes. A small, portable instrument [14] has been developed for the accurate and selective determination of free and adsorbed water and water of crystallization in solid-phase systems in about 30 s, using only a few grams of sample; some measured data are presented in Table 4. This instrument is particularly suitable for in-process control.

Table 4
Moisture content of various prepared potato starch samples by different methods

Method	Moisture content (%)	RSD(%)*
Karl Fischer	8.1 10.2 12.0 14.5 18.7 22.2 25.3	2.5
Thermoanalytical	9.0 11.1 13.0 16.0 19.5 24.0 26.6	8.3
NMR-hygrometer	7.9 9.9 11.9 14.8 18.7 23.0 25.4	3.5

* Relative standard deviation for 6 parallel measurements (%).

The Possibility and Practical Significance of Compressing Tablets Under Controlled Temperature

Very little attention has been paid so far to the optimum temperature of tablet compression, in spite of the fact that the ability of some granulates to form tablets depends on the compression temperature [15]. This observation is not surprising if the linear relationship between the volume of the tablet and reciprocal value of the compression force per unit area is taken into account. Such a relationship can be shown to exist with the volume and pressure variables [15] of published data for magnesium carbonate tablets [16]; and for lactose, sulphadiazine, lactose–aspirin and aspirin tablets respectively. Essentially, this means that the compression of some tablets can *formally* be described by the Boyle–Mariotte law, since the product of a fixed mass of a gas and its pressure is a function of temperature for thermodynamic reasons.

In addition to the potential contribution of this observation to the theory, some very important practical points can be derived from this relationship. The 'sticking' of the granulate to the punches might cause trouble during tabletting and reduction of the temperature by 10°–15°C might sometimes solve the problem. Another undesirable phenomenon is the 'capping' or separation of the tablet into layers, which can eventually be corrected by increasing the temperature.

The quality assurance and trouble-free production of some tablets therefore depend on, among other factors, the optimum moisture content of the granulate and on the optimum temperature of compression. The availability of controlled-temperature tabletting machines [15] might contribute to better in-process control and automated regulation of the compression.

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