DETERMINATION OF THE PARTICLE SIZE AND SHAPE OF PHARMACEUTICAL GRANULES USING DYNAMIC IMAGE ANALYSIS

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There are many applications in the pharmaceutical industry involving simple to complex granules produced using various processes. The physical characterization of the granules can be important for understanding and controlling the manufacturing process and quantifying product quality. Many techniques exist for performing the particle size analysis of granules including sieve analysis, laser diffraction, and others. In this study dynamic image analysis is used to define the size and shape of granules created through a dry granulation process.

Introduction

Pharmaceutical granules are, from a technical point of view, agglomerates that usually consist of a mixture of a medicinal agent and various excipients. The granules can be prepared by different methods. One of these is dry granulation, a simple and rapid method. Mixtures of powders containing the active substance are compressed with tablet presses or roller compactors to form larger units and are then reduced to the required granule size by using mills or sieve granulators. The different granule sizes produced in this way naturally have irregular shapes. Granulation is often used for obtaining a particular mixture quality as well as for improving the flow and compression properties of the powder mixture. A more recent field of application is the use of such dry granules as an independent form of drug, which release the active substances as uniformly as possible throughout a certain period (8 – 12 hours). These so-called retard drug forms benefit the patient by having longer administration intervals and accordingly a reduced administration frequency when compared with conventional drug forms.

Model

The example given below uses dry granulation to granulate the anti-asthmatic agent theophylline together with ammonium methyl methacrylate copolymer (Eudragit® RS PO) and ethyl cellulose (Ethocel® Standard 10 FP Premium). The two last-mentioned are used to form a matrix, that is inert to physiological liquids, in which the active substance theophylline is embedded. The quality-

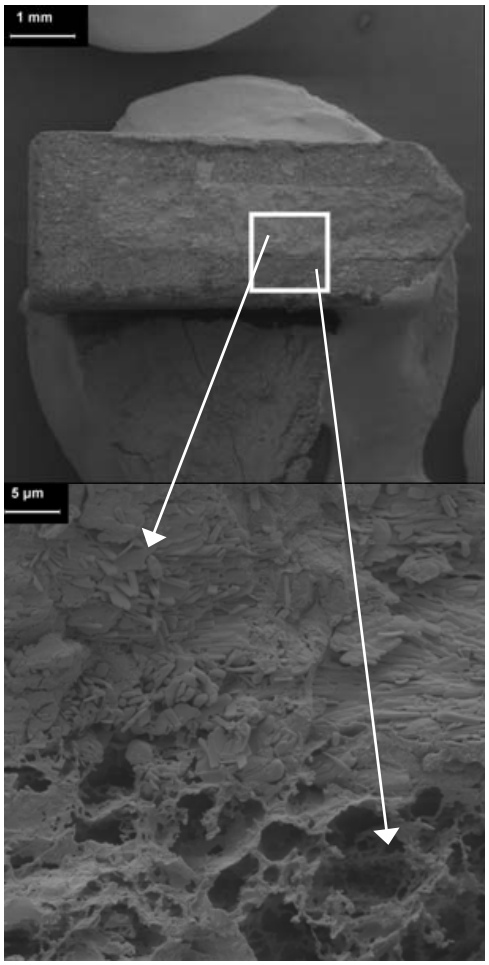


Figure 1: Diffusion front in a drug after 10 hours release. Top: 2 areas can be recognized: a) inner (lighter) area, structure with active substance and b) outer (darker) area, structure without active substance. Bottom: Magnification of the transition zone. Upper half: Active substance not yet dissolved; lower half: active substance has been dissolved and the structure is empty.

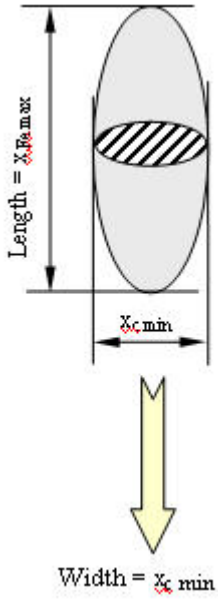
determining parameter of the granules obtained in this way is the amount of active substance released from the granules per time unit. This release takes place in two steps: first water wets the active substance located on the surface and dissolves it. Then the dissolved active substance molecules leave the matrix system by diffusion. Initially, the diffusion paths are short as the active substance is close to the surface. In time these diffusion paths become increasingly longer as the diffusion front moves toward the interior of the particles so that the amount of active substance released per time unit decreases. Fig. 1 shows the diffusion front after 10 hours' release.

The greater the surface area in relationship to the volume of the individual particles, the quicker the active substance will be released from the matrix. Small granules have a large surface area in comparison to their volume. This means that, in comparison to large granules, more solvent molecules can attack and the active substance will be released more quickly. In order to be able to predict this release behavior a knowledge of the surface area and volume of these irregularly shaped particles together with their distribution is required.

Methods

In order to investigate the predictability of the system described the granules obtained are separated into 5 different fractions with the following sizes: 2-2.8 mm / 1.4-2 mm / 1-1.4 mm / 0.71-1 mm / 0.5-0.71 mm. Their *in-vitro* theophylline release behavior was studied as a function of their particle size and shape. The aim is to correlate these parameters to develop a model for predicting release profiles from unknown granule fractions.

The individual granule fractions are inhomogeneous particle collectives that are very different as regards their shape and size. This means that classification using a simple spherical model (sphere diameter = class midpoint of the sieve fraction) or conventional image analysis systems is not possible. Compared with these, the CAMSIZER dynamic image analysis system is an efficient alternative and allows a rapid, non-invasive determination of the particle size and shape for pourable bulk goods. In the CAMSIZER a vibratory feeder transports the granules to a free-fall feed shaft equipped with a light source and 2 high-resolution CCD cameras with different image scales. During the free fall of the sample the individual particles of the granule fractions are recorded by the cameras and evaluated in real time. This is a non-destructive method; the measuring time per run is about five minutes. In addition to image analysis, parameters such as mean particle size, length, width, length/width ratio, roundness, symmetry and convexity, a surface/volume ratio (S_v) can also be determined. For the calculation of the surface/volume ratio (S_v) various calculation models are available: the sphere and various ellipsoids (Fig. 2).



$$V_{Ellipsoid} = \frac{x_{Femax} \cdot (x_{cmin})^2 \cdot \pi}{6}$$

Figure 2: Ellipsoid calculation model

The measuring and evaluation of the studied theophylline matrix granules produced elongated and symmetric particles, so that the calculation of the surface/volume ratio was based on an ellipsoid. This ratio was determined for all size classes and represents the granule fraction with respect to these two parameters.

Results

There is a mathematical relationship between the rate of active substance release and the surface/volume ratio of the granules. If the cumulative amount of released theophylline is considered as a function of time then different release profiles are obtained for the various size fractions. These can be described by using the Weibull function.

Weibull Function:

$$D(t) = 1 - e^{-\left(\frac{t}{k_{63,2\%}}\right)^{d}}$$

The reference parameter ($k_{63.2\%}$) is the time at which 63.2% of the active substance that it originally contained has been released from the granule. The release profiles and their associated $k_{63.2\%}$ values are shown for the 5 different size fractions in Fig. 3 and Table 1. As the release from large particles is slower than that from small particles because of the smaller surface/volume ratio, the value for the parameter $k_{63.2\%}$ increases as the size of the granule increases.

A requirement for the validity of the model is that the surface area and volume of the individual particles do not change during the release process. This is ensured by the added excipients. By determining the surface/volume ratio (see S_v values in Table 2) with the CAMSIZER for the various fractions it is possible to make a correlation between the release parameter $k_{63.2\%}$ and the image analysis data. As shown in Figure 4, there is a linear relationship between $k_{63.2\%}$ and the surface/volume ratio. With this straight-line equation and the Weibull function the release profile can be predicted for any granule fractions, provided that the size and surface/volume ratios are known.

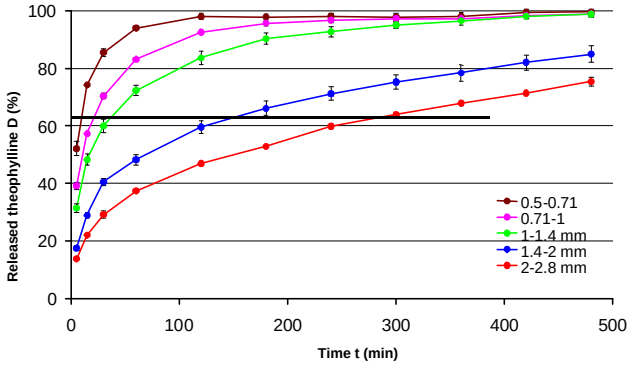


Figure 3: Release rate as a function of granule size for the 5 fractions studied. The smaller the granule, the greater the amount of theophylline released. t is the time in minutes and d a formulation-dependent constant with the value 0.5

Granule fraction (mm)	$k_{63.2\%}$ - Parameter (min)
0.5 – 0.71	10
0.71 – 1	27
1 – 1.4	39
1.4 – 2	154
2 – 2.8	300

Table 1: $k_{63.2\%}$ values for 5 granule fractions

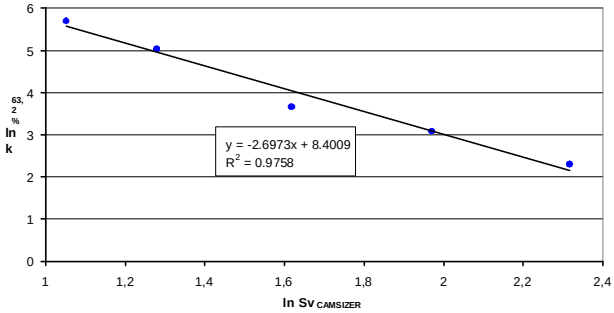


Figure 4: Shows the relationship between the surface/volume ratio S_v (determined with the CAMSIZER®) and the Weibull parameter $k_{63.2\%}$ determined via the release profile.

Granule fraction (mm)	Sv CAMSIZER
0.5 – 0.71	10.14
0.71 – 1	7.17
1 – 1.4	5.04
1.4 – 2	3.59
2 – 2.8	2.86

Table 2: Granule fraction size and surface/volume ratio show a linear relationship

Summary

Pharmaceutical Granules

The CAMSIZER dynamic image processing system is an efficient and time-saving alternative to conventional image analysis for characterizing the size and shape of inhomogeneous particle collectives. By determining the surface/volume ratio it is possible to describe the individual granule fractions exactly. Data obtained in this way can be correlated with the release parameter $k_{63.2\%}$ and in future will permit a prediction to be made about the release profile of unknown granule fractions.

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