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REQUIREMENTS FOR THE PRODUCTION OF MICROTABLETS: SUITABILITY OF DIRECT-COMPRESSION EXCIPIENTS ESTIMATED FROM POWDER CHARACTERISTICS AND FLOW RATES

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ABSTRACT

Eleven direct-compression excipients, namely 3 microcrystalline celluloses, 4 lactoses, 4 co-processed excipients, and 4 mixtures of lactoses with Avicel PH102 SCG were evaluated for possible use in micro tableting. Powder-technological parameters, namely particle size distributions, true and apparent densities, densification behaviour, and mass flow rates from a funnel through very narrow orifices, were determined.
Flow rates required on modern high-speed rotary tableting machines were calculated.
Flow rates may be estimated even for very narrow orifices, and such studies aid in selection of suitable excipients.

Mainly spray-dried lactose preparations with certain, definite upper limits in size distribution, seem to comply with the prerequisites for the production of micro tablets.

INTRODUCTION

Micro tablets are tablets with a diameter equal to or less than 2 mm. They constitute an alternative to pellets produced by conventional methods, since process steps like moisturizing, extruding, spheronizing, and drying may be avoided. Micro tablets have truly identical form and size.
With falling diameter, they approach the form of spheres. Problems in coating and in packing may thus be reduced.
They may be produced on rather conventional tableting machines, utilizing common methods to control the process.

However, for direct compression the raw materials, especially excipients, have to meet special requirements.
The narrow diameter of the die requires excellent flowability as well as a strict limit for the maximum particle size, in order to avoid blocking of the die opening by coarser particles.

Flowability is an important powder-technological property, which affects the performance in sieving, mixing, granulating, and tableting. All these process steps are related to the content uniformity of the final product (1-8).

The JENIKE shear cell has gained remarkable insight into the knowledge on powder flow (9). However, this cell, although intended for routine work, has not been widely accepted to characterize and quantify flowability in pharmaceutical development (10). In contrast, mostly very simple parameters like angle of slope, bulk density, tap density, and derived parameters like the HAUSNER factor and the CARR index, were evaluated by EGERMANN (2) and are widely used.

Recently, HAUER et al. (11) used the densification behaviour of powders in a tapping volumeter for optimizing powder formulations for hard gelatin capsules. HUBER et al. (12) estimated flowability from the surface area of powders, and KAYE (13) related the avalanching behaviour of powders to their flow properties.

All these methods characterize the flow properties of powders in dependence on experimental conditions, on parameters related to the components proper, such as chemical constitution, density, crystalline structure, and on parameters not necessarily specific for the components, such as particle form, particle size distribution, porosity, surface area, moisture content, and the like.
Therefore, the results may not always be directly compared.

Flow properties are also widely determined by directly measuring amounts of powder masses flowing from funnels onto balances or bending bars with time (1, 14-16). A funnel with interchangeable orifices is also used in this study to characterize the flow properties of common modern excipients for direct compression in combination with information on their particle size distribution.

MATERIALS

Microcrystalline celluloses
Avicel PH101 (**AV101**), lot no. 6324; Avicel PH102 (**AV102**), lot no. 7248; Avicel PH102 **S**pecial **C**ourse **G**rade (**AV102S**), lot no. Y233, all by Lehmann & Voss, Hamburg, Germany.

Lactoses
Pharmatose 100M (**PH100M**), lot no. 022317; Pharmatose DCL21 (**DCL21**), lot no. 301319; Pharmatose DCL11 (**DCL11**), lot no. 1007449, all by DMV, BA Veghel, the Netherlands;
Flow lac (**FLOW**), lot no. A9384D832, by Meggle, Wasserburg, Germany.

Co-processed excipients
Cellactose (**CEMCC**), lactose monohydrate with 25 % microcrystalline cellulose, lot no. A9106D431; Cellactose (**CEPC**), lactose monohydrate with 25 %

powdered cellulose, lot no. A4901D508, both by Meggle;
Ludipress (**LUDI**), lot no. 34-0402, by BASF, Ludwigshafen, Germany;
Pharmatose DCL40 (**DCL40**), lot no. 320306, by DMV.

Powder mixtures
Pharmatose 100M with 25 % Avicel PH102 SCG (**PHAV**);
Pharmatose DCL21 with 25 % Avicel PH102 SCG (**DCL21AV**);
Pharmatose DCL11 with 25 % Avicel PH102 SCG (**DCL11AV**);
Flow lac with 25 % Avicel PH102 SCG (**FLOWAV**).

All mixtures were obtained by mixing with a Turbula/T2C (W. Bachofen, Basel, Switzerland) in the original steel vessel (2.4 l volume, filled to 60 %) at 110 upm for 5 minutes.

METHODS

Particle size distribution

A sieving machine (Vibrotronic VE 1000, Retsch, Haan, Germany) with software SP 1000 and a set of analytical sieves according to DIN 4188 was used. 50 to 100 g were sieved for 20 min (FLOW for 25 min) at an amplitude of 1.5 mm. The weights of sieve fractions obtained from 4 runs were averaged and approximated by the RRSB model. The statistical parameters dp_{50} and dp_{99} were used to characterize the size distributions.

SEM

Scanning electron micrographs were obtained (CamScan DV4, Cambridge Scanning Co. Ltd., Cambridge, UK) at 10 kV acceleration voltage.

Bulk density

The method described in the German Pharmacopeia (DAB 10 (17)) was used. 190 to 210 ml powder were gently filled through a funnel with an opening diameter of 5 mm into a graduated cylinder of 250 ml volume. The volumes obtained in 6 runs were read and averaged.

Tap density, densification behaviour

The determination was carried out subsequent to that of the bulk density, (DAB 10 (17)), by means of a tapping volumeter (Engelsmann, Ludwigshafen, Germany) according to DIN 53 194, 3 times. The mean density obtained after 2500 taps is used.

For determining the densification behaviour, the volume in the tapping volumeter was read after 5, 10, 20 to 150, 175, 200, 250, 300, 400, 500, 750, 1000, 1500, and 2000 taps. Three runs were performed with each material.

True density

A gas pycnometer was employed (Stereopycnometer SPY-2, Quantachrome Corp., Syosset, USA), using Helium. Four samples of each material were analysed, each sample was read 2 times.

Flow rate

A special funnel (Figure 1) was made from aluminium with a polished inner surface. The lower end was provided with interchangeable orifices, where their lengths, l, varied with the diameter, D, (9.0, 5.0, 3.5, 2.0 , 1.5, and 1.0 mm respectively) such, to keep the angle of inclination, α, constant.

The mass flown from the funnel (balance type 1907, Sartorius, Göttingen, Germany) and the time (Baud rate 9600) were recorded via an interface RS 232 by a PC (PC 16-16, Siemens AG, Munich, Germany) with the aid of a program written in BASIC. In this investigation the end masses und end times were taken for calculating the flow rates.

Depending on the decreasing diameter of the orifice, from 300 to 8 ml $\pm$ 20 % were filled loosely into the funnel to obtain flow times between about 8 and 80 seconds. With the orifices of 2.0, 1.5, and 1.0 mm, in several cases the flow was only to be started by gently knocking at the wall of the funnel. However, only after subsequent flow without any interupt these data were used.

All flow experiments were conducted at a controlled climate of 22.5 $\pm$ 1°C and 50 $\pm$ 2 % relative humidity.

Since a considerable variance was expected, 8 samples of each material were measured, each one 3 times. The results were averaged.

RESULTS AND DISCUSSION

Predictability of Flow Rates from Parameters calculated from Densities

The values obtained for particle size distributions, true and apparent densities, and parameters derived for compressibility are summarized in Table 1.

The HAUSNER factor is the quotient of the tap density and the bulk density (18), and the CARR index is the difference of the tap density and the bulk density, times 100 over the tap density, in percent (19).

The equation proposed by KAWAKITA to characterize the densification of a powder at low pressure (20), equ. {1}:

$$\frac{P}{C} = \frac{1}{a \times b} + \frac{P}{a} \qquad \{1\}$$

where P is the pressure exerted, C is the volume reduction obtained, i.e. $(V_0 - V/V_0)$ with V_0 as the initial volume and V the volume after the application of pressure P, and a and b are constants, was modified for the evaluation of data from a tapping volumeter by HAUER et al. (11) to equ. {2}, in order to better differentiate the densification behaviour of a material than by the HAUSNER factor or the CARR index:

$$\frac{P}{C} = k_k \times P \qquad \{2\}$$

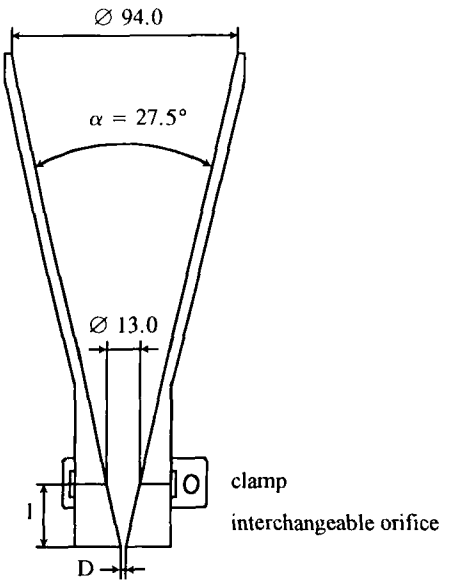


FIGURE 1
Construction of Funnel, Scale in [mm]

where P is the number of taps, C is obtained mathematically as in equ. {1}, but now V_0 being the bulk volume and V the tap volume after the particular tap, and k_k is the KAWAKITA constant (11).

Low values for the HAUSNER factor and the CARR index, as well as high values for the KAWAKITA constant indicate good flowability, since generally the densification behaviour of a powder during tapping is inversely proportional to its flowability: the more the powder can be densified, the lower will be its flowability (19).

The experimentally determined flow rates are summarized in Table 2.
A comparison of Table 1 and 2 shows, that not in every case the rank order obtained from calculated parameters corresponds to that obtained from flow rates. However, low flowability is expected from Table 1 for the materials AV101, AV102, DCL21, and DCL21AV. These materials did not flow at all.

Dependence of Flow Rates on Diameter of Orifices and Prediction

KETCHUM (21) reported a relation between mass flow rate, Q_m [mass/time], and diameter of funnel, D [length], of the form:

$$Q_m \sim D^3 \qquad \{3\}$$

TABLE 1
Powder-technological Characteristics for Particle Size Distributions (dp_{50} and dp_{99}), Densities (true, bulk and tap Densities) (± S.D.), and Densification Behaviour (HAUSNER Factor, CARR Index and KAWAKITA Constant), for various Excipients and particular Mixtures (Abbreviations: see "MATERIALS")

excipient	dp_{50} [μm]	dp_{99} [μm]	true density [g cm^{-3}]	bulk density [g cm^{-3}]	tap density [g cm^{-3}]	Hausner factor	Carr index [%]	Kawakita constant k_K
AV101	48	153	1.602 ± 0.0045	0.28 ± 0.0017	0.43 ± 0.0036	1.52	34.2	3.16
AV102	101	228	1.597 ± 0.0028	0.31 ± 0.0009	0.44 ± 0.0010	1.40	28.8	3.70
AV102S	132	295	1.593 ± 0.0008	0.34 ± 0.0023	0.46 ± 0.0026	1.35	26.1	4.17
PH100M	130	224	1.554 ± 0.0014	0.73 ± 0.0029	0.90 ± 0.0022	1.24	19.1	5.51
DCL21	133	298	1.593 ± 0.0010	0.60 ± 0.0046	0.86 ± 0.0035	1.44	30.5	3.33
DCL11	144	312	1.559 ± 0.0012	0.60 ± 0.0030	0.75 ± 0.0058	1.25	20.0	5.14
FLOW	144	286	1.555 ± 0.0024	0.54 ± 0.0035	0.65 ± 0.0037	1.21	17.2	5.78
CEMCC	167	419	1.579 ± 0.0008	0.49 ± 0.0023	0.62 ± 0.0029	1.26	20.9	4.75
CEPC	225	471	1.581 ± 0.0027	0.36 ± 0.0051	0.48 ± 0.0071	1.32	24.5	4.08
DCL40	178	393	1.603 ± 0.0024	0.61 ± 0.0070	0.80 ± 0.0047	1.32	24.1	4.29
LUDI	195	578	1.532 ± 0.0019	0.50 ± 0.0027	0.63 ± 0.0030	1.26	20.9	4.68
DCL21AV	129	297	1.593[1)]	0.52 ± 0.0063	0.72 ± 0.0021	1.39	27.9	3.77
DCL11AV	132	288	1.567[1)]	0.50 ± 0.0030	0.64 ± 0.0002	1.28	22.1	4.71
FLOWAV	131	285	1.564[1)]	0.48 ± 0.0028	0.59 ± 0.0017	1.24	19.2	5.31

[1)] calculated

TABLE 2
Flow Rates, FR [g s^{-1}] (± S.D.), as experimentally determined from Mass Flow through Orifices with different Diameters

excipient	D [mm] 13.0	9.0	5.0	3.5	2.0
	FR [g s^{-1}]				
AV102S	5.86 ± 0.2648	2.57 ± 0.0137	–	–	–
PH100M	9.85 ± 0.1956	3.98 ± 0.0465	0.92 ± 0.0136	0.34 ± 0.0047	0.080 ± 0.0022
DCL11	14.78 ± 0.1201	6.08 ± 0.0482	1.34 ± 0.0140	0.48 ± 0.0073	0.115 ± 0.0019
FLOW	8.50 ± 0.0834	3.86 ± 0.0959	0.93 ± 0.0118	0.35 ± 0.0050	0.079 ± 0.0013
CEMCC	8.74 ± 0.1559	4.00 ± 0.1959	0.86 ± 0.0254	0.33 ± 0.0073	0.080 ± 0.0012
CEPC	9.08 ± 0.3504	3.70 ± 0.0665	0.86 ± 0.0090	0.31 ± 0.0035	0.065 ± 0.0026
DCL40	11.43 ± 0.2499	5.27 ± 0.1780	1.09 ± 0.0362	0.41 ± 0.0055	0.085 ± 0.0027
LUDI	16.27 ± 0.1770	6.55 ± 0.0309	1.28 ± 0.0267	0.45 ± 0.0039	0.091 ± 0.0013
DCL11AV	11.12 ± 0.0713	4.85 ± 0.1772	1.06 ± 0.0073	0.35 ± 0.0083	0.085 ± 0.0007
FLOWAV	8.97 ± 0.1190	4.03 ± 0.0667	0.87 ± 0.0076	0.33 ± 0.0035	0.075 ± 0.0011

To exactly describe the dependence of experimental flow rate [mass/time] on orifice diameter from 13.0 to 2.0 mm, a polynom of the 4th grade had to be used (equ. {4}):

$$Q_m = a\left(D^3\right)^4 + b\left(D^3\right)^3 + c\left(D^3\right)^2 + d\,D^3 + e \qquad \{4\}$$

The parameters a to e were obtained by a least squares approximation (EXCEL 4.0, Microsoft, Unterschleissheim, Germany) and were used to predict the flow rate for a diameter of the orifice of 1.5 mm. The results are summarized in Table 3.

TABLE 3
Flow Rates, $FR_{1.5, c}$ [mg s^{-1}], calculated for an Orifice of D = 1.5 mm from Results with D > 1.5 mm, Flow Rates, $FR_{1.5, m}$ [mg s^{-1}] (± S.D.) measured at D = 1.5 mm, minimum Diameter, D_{min}, calculated for obtaining Flow, Flow observed at D = 1.0 mm within the first 60 s (+ or -), and Ratios of Diameters ($D_{1.5}$, $D_{1.0}$) and the Parameter dp_{99} from the RRSB Particle Size Distribution

excipient	$FR_{1.5, c}$	$FR_{1.5, m}$	D_{min}	flow	$\frac{D_{1.5}}{dp_{99}}$	$\frac{D_{1.0}}{dp_{99}}$
	[mg s^{-1}]		[mm]			
PH100M	45	50 ± 0.9	1.0	-	6.7	4.5
DCL11	67	68 ± 0.9	1.0	+	4.8	3.2
FLOW	42	49 ± 0.8	1.1	+	5.2	3.5
CEMCC	46	41 ± 0.5	1.0	-	3.6	2.4
CEPC	32	33 ± 1.6	1.2	-	3.2	2.1
DCL40	40	49 ± 1.7	1.2	-	3.8	2.5
LUDI	43	-	1.3	-	2.6	1.7
DCL11AV	52	50 ± 0.4	0.9	+	5.2	3.5
FLOWAV	40	43 ± 0.3	1.1	+	5.3	3.5

Prediction of the Minimum Diameter of the Orifice to obtain Flow

According to KURIHARA (22), the minimum diameter, D_0, of the orifice to obtain flow may be calculated for a powder with a known particle size distribution. However, the equation reported (equ. {5}) resulted in values for orifice minimum diameters, where flow had been observed already even through larger orifices, than those.

$$Q_V = a\left[\left(\frac{D}{dp_{50}}\right)^2 - \left(\frac{D_0}{dp_{50}}\right)^2\right] \qquad \{5\}$$

with Q_V being the volume flow rate [ml min^{-1}] and dp_{50} the mean particle diameter. Instead, plausible values resulted from using a polynomic equation (equ. {6}) and a least squares approximation (EXCEL). Values for Q_V were calculated from the mass registered and the bulk volumes in Table 1.

$$\left(\frac{D}{dp_{50}}\right)^2 = aQ_v^4 + bQ_v^3 + cQ_v^2 + dQ_v + e \qquad \{6\}$$

Calculated values are included in Table 3.

For orifice diameters of 1.5 and 1.0 mm, the experimental results for flow rates coincide well with the calculated values according to {4} for all materials except LUDI and PH100M.

In the case of LUDI, which did not flow even at 1.5 mm, the content of particles within range of 500 to 800 μm (about 1.3 %) may account for the deviation. PH100M has to be considered as a slightly cohesive material regarding it's particle size distribution (2); therefore, flow problems were to be expected.

With decreasing orifice diameter, the maximum particle size, dp_{max}, within the powder gains importance. With the experimental setup used here, a ratio of $D/dp_{99} > 3$ seems to favorable. SCHWEDES summarizes in (9) the opinion several authors, that values for D/dp_{max} between 3 and 6 should lead to bridging, and values up to 10 should lead to irregular flow. However, in this study no bridging was observed; rather blocking of the orifice by wedging of particles was observed.

The form of particles had less effect on the flow, as is derived from comparing the materials FLOW, CEMCC and DCL40 (Figure 2 a-c), where all these materials had good flowability.

What is the Flow Rate required for Micro Tableting?

Theoretical requirements for the flow rate result from the volume of micro tablets (23), which may be calculated for a certain material.

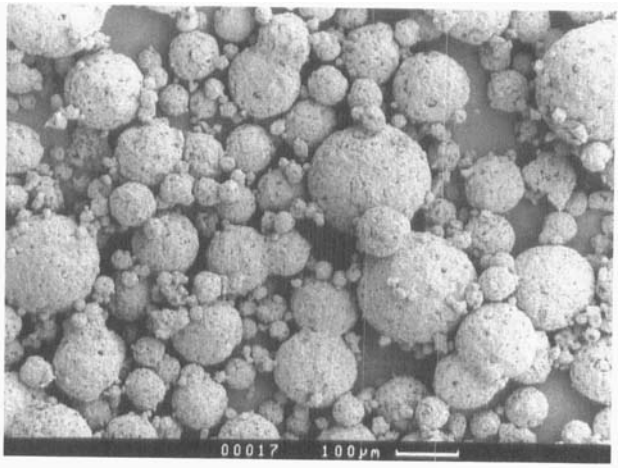
True density is assumed to be 1.6 g cm^{-3}. The degree of densification, $D_{rel,\ max}$, i.e. the quotient of density at maximum densification and of true density, is chosen to be equal to 1 (24). The mass required for a micro tablet is calculated from equ. {7} according to (24):

$$\text{target weight} = D_{rel,\ max} \times \text{volume} \times \text{true density} \qquad \{7\}$$

A typical, modern high-speed rotary tableting maschine (e.g. P2000, W. Fette, Schwarzenbek, Germany), equipped with forced feeding, will theoretically require the minimum flow rates summarized in Table 4.

Mainly the spray-dried lactoses DCL11, FLOW, and mixtures thereof will comply with these requirements, as may be seen from comparing the respective data in Tables 2 and 3, especially with regard to the flow through an orifice of 1.0 mm diameter.

(a)



(b)

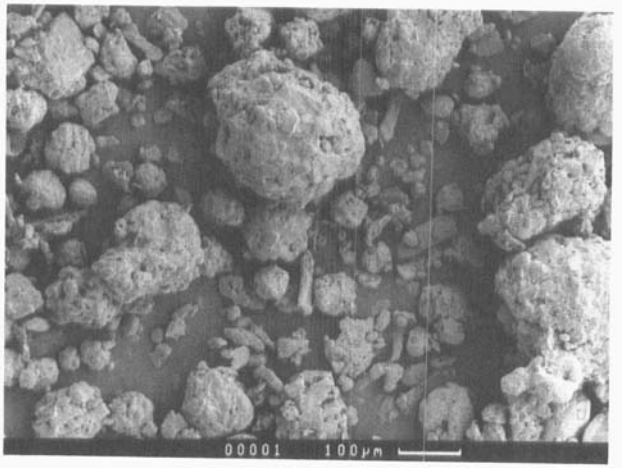


FIGURE 2 a-c
Particle Forms of modern Excipients with high Flow Rates:
spray-dried Lactose Monohydrate Flow lac (a),
co-processed Excipient Cellactose, lot no. A9106D431 (b),
and Pharmatose DCL40, a roller-dried Product (c)

(c)

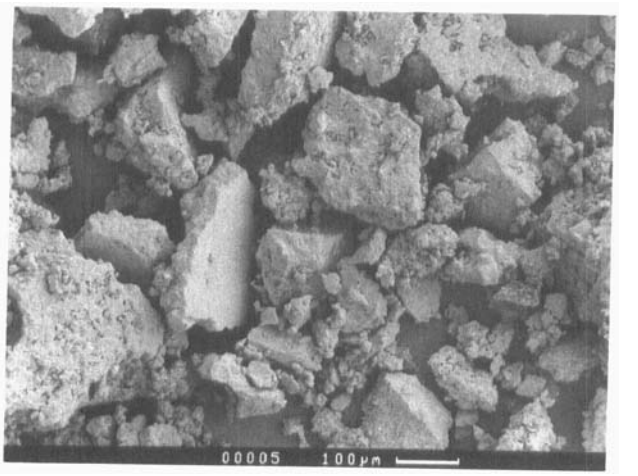


FIGURE 2. Continued

TABLE 4
Minimum Flow Rates of tableting Mass, theoretically required for the Production of Pellet-shaped Micro Tablets at different Rates of Production, relying on free Flow only

micro tablet			speed of die table [upm]		
			30	60	90
			filling time [s][2)]		
			0.436	0.218	0.145
diameter [mm]	volume[1)] [mm^3]	mass [mg]	calculated flow rate [mg s^{-1}]		
1.0	0.64	1.0	2.3	4.6	6.8
1.2	1.10	1.8	4.2	8.3	12.4
1.5	2.14	3.4	7.8	15.6	23.4
2.0	5.06	8.1	18.5	37.2	55.9

1) radius of curvature: 0.7 × diameter according to W. and R. Ritter (23)
2) rotary tableting machine Fette P2000

For all other materials in Table 3, the large maximum particle diameters may cause problems, although they exhibited sufficiently high flow rates through orifices of diameters 2.0 and, with exception of *LUDI*, of 1.5 mm.

The flow rates obtained in this study may not without restrictions be transferred into flow behaviour under conditions for the production of micro tablets: the excipients will have to cover a certain distance within the narrow die; then, even a few larger particles may restrain flow or block the die opening by wedging, etc.

For tablets with larger diameters several authors report (25-27) that, inspite of low flowability of the tableting masses, tableting was successful and tablets of acceptable uniformity of weight were produced, respectivly. EGERMANN cites additional reports on this phenomenom and discusses possible reasons (28, 29): on the one hand, modern tableting machines are equipped with very efficient filling devices, and on the other hand, the slight reduction in air pressure caused by the downward movement of the lower punch may suck the power into the die.
The technical devices may also facilitate flow within a die and can help to prevent filling problems.

CONCLUSIONS

Experimentally determined flow rates for small orifices help to select excipients for micro tableting. Also, in connection with data on the particle size distribution, they provide information on critical diameters of the die to be expected.

Among the materials tested, the spray-dried lactose preparations DCL11 and FLOW, and their mixtures showed advantages, since they freely pass orifices even of only 1.0 mm.
The flow rates of additional materials, namely PH100M and its mixture PHAV, CEMCC, CEPC, and DCL40 are sufficient, when theoretically required flow rates are calculated from the volume of micro tablets and the filling times available on modern rotary tableting machines.

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