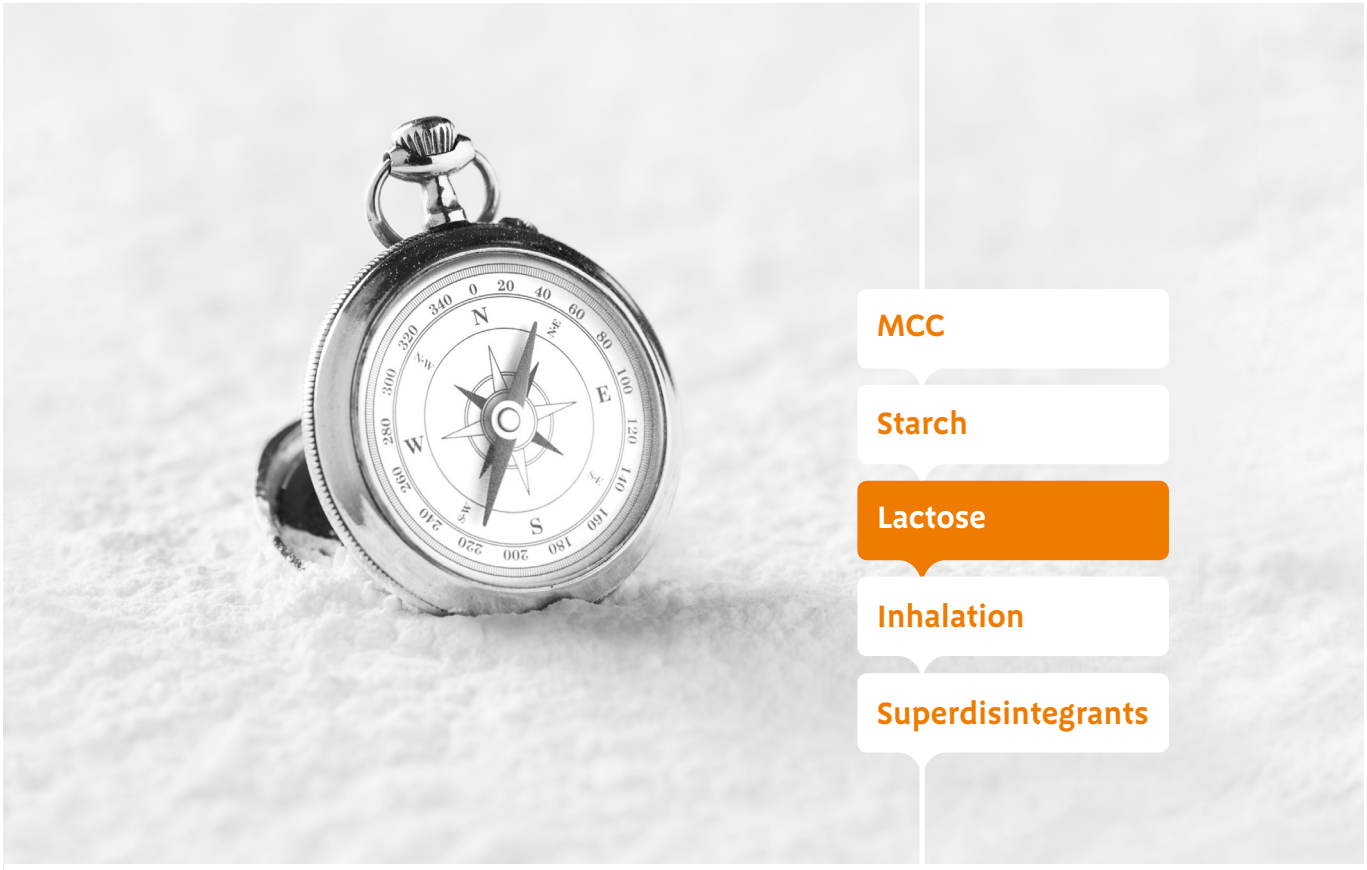
DFE pharma

Introduction to tableting by direct compression



The pursuit of excipient excellence

1 Introduction

Direct compression (DC) is by far the simplest means of production of a pharmaceutical tablet. It requires only that the active ingredient is properly blended with appropriate excipients before compression. Apart from simplicity of formulation and manufacture, the key advantages of direct compression include reduced capital, labour and energy costs for manufacture and the avoidance of water for granulation for water sensitive drug substances.
This guide describes the scope and first principles involved in formulation of tablets by direct compression.

2 Applicability of direct compression

The most obvious factor in determining whether DC is applicable to a certain drug substance is dose. Three key factors for successful tableting are flow and compactability of the compression mix, and drug content uniformity in the mix and the final tablets. All of these factors are likely to be affected by drug dose.
In this guide, low dose is taken to mean 10 mg or below, medium dose is taken to mean 10 mg to 50 mg and high dose is taken to mean above 50 mg.
For low dose drugs, flow and compaction of the compression mix are largely conferred by the excipients and the primary concern is likely to be achievement of good content uniformity in the blend and in the tablets. For medium dose drugs flow of the compression mix may become a critical factor, and for high dose drugs the flow and compaction are highly dependent on the properties of the drug substance (Table 1)

Table 1: *Some factors determining the applicability of direct compression tableting*

Description	**Low Dose**	**Medium Dose**	**High Dose**
Drug Dose	**<10mg**	**10 - 50mg**	**>50mg**
% of a 250 mg tablet	**<4%**	**4 - 20%**	**> 20%**
Content Uniformity	Primary Concern	Not likely to prove a problem	Minimal concern
Flow	Largely taken care of by excipients	Milled drugs may interfere with flow	Highly dependent on the drug properties
Compaction	Largely taken care of by excipients	Unlikely to be a major issue	Highly dependent on the drug properties

The use of direct compression as a manufacturing technique is estimated to be as high as 50% of formulations in the United States [(1)].

3 Excipients for direct compression

Direct compression formulations can be developed with minimal numbers of excipients. Typically the minimum excipients needed are a diluent (filler-binder), a disintegrant and a lubricant. Additional components may include a glidant, a surfactant, pigments and stabilising agents. Commonly used excipients in these categories are listed in Table 2.
Of course some excipients are described as multi-functional.

Table 2: *Commonly used excipients in direct compression formulations*

Function	Common Examples
Diluent	Lactose monohydrate, anhydrous lactose, microcrystalline cellulose, partly pregelatinised starch, mannitol, dibasic calcium phosphate (anhydrous & dihydrate)
(Super)-disintegrant	Croscarmellose sodium, sodium starch glycolate, crospovidone, partly pregelatinised starch, low substituted hydroxypropyl cellulose.
Lubricant	Magnesium stearate, calcium stearate, sodium stearyl fumarate, stearic acid
Glidant	Colloidal silicon dioxide, talc
Pigment	Aluminium lakes, iron oxides
Stabiliser	Buffers such as sodium carbonate and citric acid. Antioxidants such as butylated hydroxyanisole and butylated hydroxytoluene.
Surfactant	Sodium lauryl sulphate, polysorbates

3.1 Diluent

Key to direct compression is selection of an appropriate diluent. This material generally provides the bulk of the tablet and is also responsible for flow and compaction properties. Direct compression diluents are frequently referred to as filler-binders.
The commonest diluents are microcrystalline cellulose (MCC) and lactose, both of which are available in grades especially suited to direct compression. A description of the various types of direct compression lactose available is given in reference 2. Similarly special grades of pregelatinised starch (PGS), mannitol and dibasic calcium phosphate (DCP) make up the remainder of the commonly used diluents. Figure 1 shows the frequency of use of diluents in the most commonly prescribed drugs in the United States of America. Other diluents include tricalcium phosphate and sucrose. The diluents are frequently used in combination.

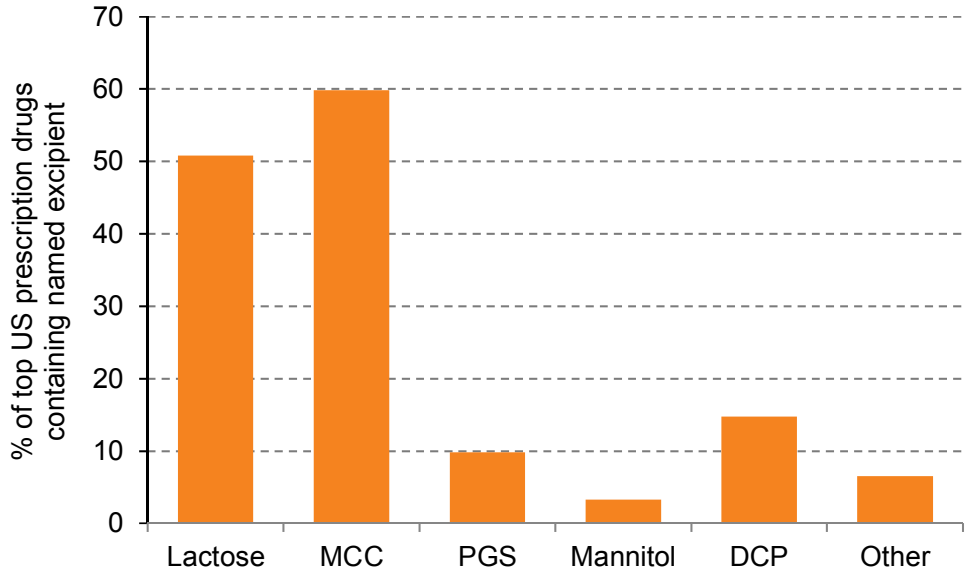


Figure 1: *Frequency of use of diluents in most prescribed drugs in the USA*

Because the diluent is frequently the majority of the formulation, it is important to source these materials to have consistent functional properties. For example the European Pharmacopoeia includes particle size distribution, anomer ratio and bulk density as potential functionality related characteristics of anhydrous lactose.

Figure 2 shows these properties measured on consecutive batches of SuperTab® 21AN (anhydrous lactose) over a 12 month period. A manufacturer of excipients should be able to provide functionality related data for their products to give the tablet developer confidence in the excipient consistency.

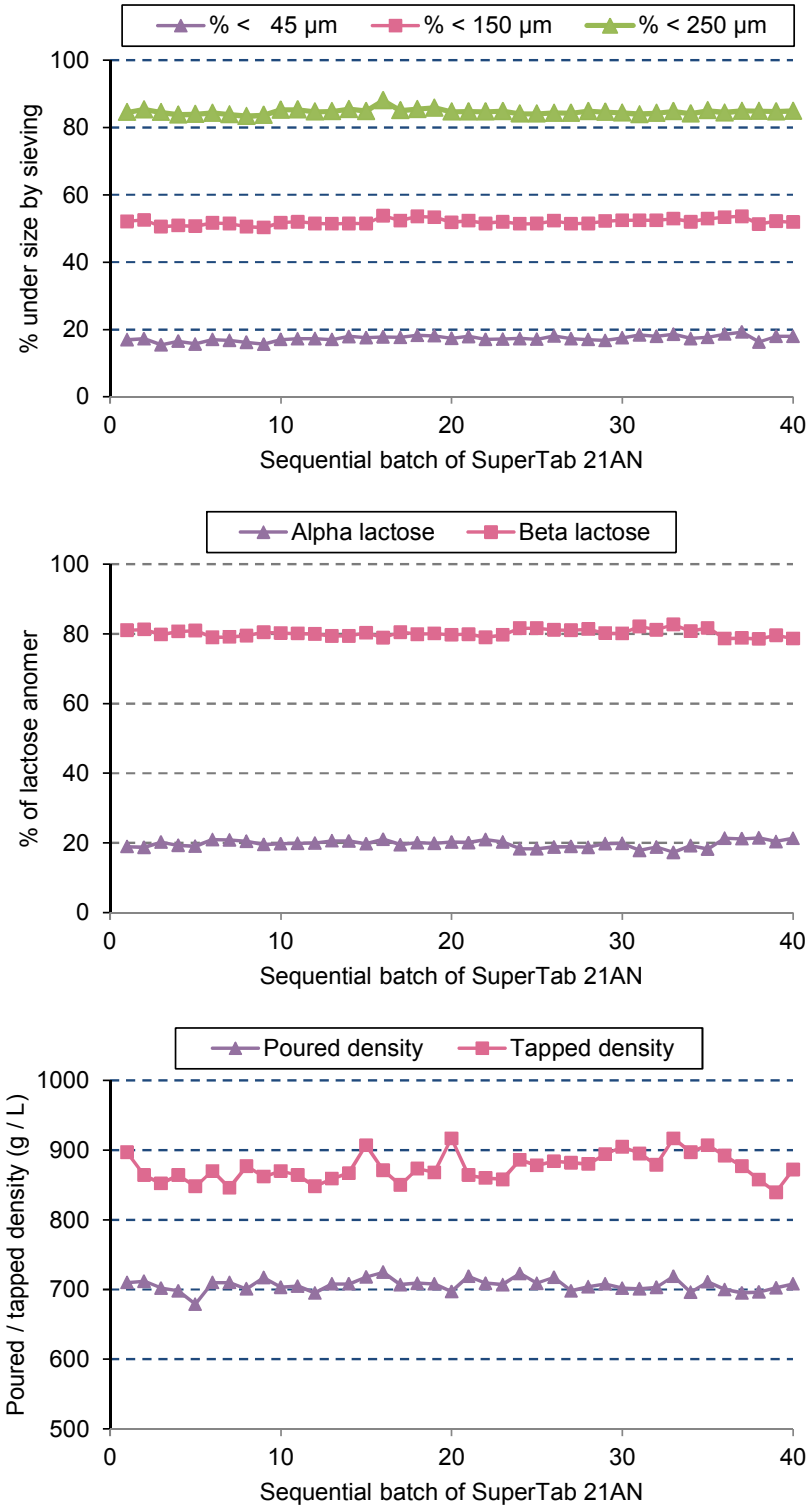


Figure 2: *Some functionality related characteristics of SuperTab® 21AN*

Additionally it is important that tablets developed at small scale can be readily scaled up. Strain rate sensitivity [3] may affect the tableting characteristics of a filler-binder when transferred from a relatively slow laboratory machine to a much faster production machine. In general brittle materials such as anhydrous lactose and DCP have low strain rate sensitivity compared to plastic materials such as MCC and P-PGS. However MCC remains the most compactable filler-binder available and it is frequently used in combination with other filler-binders to give an optimum balance of tableting properties.

3.2 Disintegrants

A super-disintegrant that can effectively disintegrate a tablet when used at low concentrations (typically 2% to 6% by weight) is preferred. Croscarmellose sodium, sodium starch glycolate and crospovidone are the most commonly used superdisintegrants.
The selection of the appropriate disintegrant will depend partly on the drug substance and the selection of the filler-binders. Tablets containing a proportion of microcrystalline cellulose tend to be readily disintegrated by all superdisintegrants, whereas tablets containing a high proportion of dibasic calcium phosphate may require the extra disintegrating power of, say, croscarmellose sodium, especially after storage at accelerated stability conditions.

3.3 Lubricants

Magnesium stearate is used in the vast majority of direct compression tablets with calcium stearate and sodium stearyl fumarate used less frequently. A common problem with metal stearates is their potential to reduce the strength of tablets and to slow disintegration & dissolution if overused or overblended. A lubricant sensitivity index has been proposed [4]. In general problems with magnesium sensitivity are associated with surface area and with compaction mechanism. Materials with low surface area (often crystalline materials) are easily covered with magnesium stearate and hence are most affected. Typically materials that deform plastically tend to be more sensitive to magnesium stearate effects than brittle materials. Therefore starches and microcrystalline cellulose tend to have higher lubricant sensitivity than materials such as anhydrous lactose. Inclusion of colloidal silica can, to some extent, reduce the adverse effects of magnesium stearate [5].

3.4 Glidants

Specialist direct compression filler binders have been developed to exhibit sufficient flow for direct compression, and a glidant will only be needed when the drug is present in sufficient concentration to interfere with flow. Colloidal silicon dioxide added at a typical level of 0.1% to 0.2% will improve the flow characteristics of a compression mix.

3.5 Others

Stabilisers: These are typically used, if necessary, to minimise pH dependent hydrolysis or oxidation depending on the requirement of the drug substance. To promote intimate contact of the drug with the stabiliser it is generally recommended to include the stabiliser in finely divided form at the premix stage.

Colourants: To obtain evenness of colouration in DC formulations the use of insoluble pigments (aluminium lakes and iron oxides) is preferred. Inclusion at the premix stage can minimise “speckling” in the finished tablets. Alternatively the tablets can of course be film coated.

Surfactants: Wetting agents such as sodium lauryl sulphate may be included, especially if the drug substance is hydrophobic.

4 Direct compression strategies for different drugs

4.1 Low dose drugs

The key success factor here is achieving good content uniformity in the compression mix and throughout the tableting run, and the first consideration must be given to drug particle size. If the drug is too coarse, then no formulation approach will yield tablets of acceptable content uniformity. A theoretical approach to calculation of the relationship between drug dose and particle size distribution has been refined and tested with sub-milligram doses of drug [6]. The reference gives a useful guide to the required particle

size distribution of the drug substance for a given drug dose, and shows that direct compression is quite feasible (both in theory and in practice) for very low drug doses.

Thus in considering development of low dose tablets by direct compression then it is necessary first to ensure that an appropriate drug particle size specification is implemented according to the guidance in reference 6.

In practice many drugs are milled or even micronized and will have a particle size distribution suitable for direct compression. Finely milled drugs are frequently cohesive, and agglomerates of drug that find their way into finished tablets can give rise to super-potent unit doses.

An effective mixing strategy for low dose drugs at laboratory scale is to prepare a premix of the active with some of the filler binder and to pass this through a 500 micron sieve. The premix minimises the chance of reagglomeration of the drug after sieving. The following example, abstracted from reference 7, shows why the deagglomeration step is important. In this case the drug was finely milled acetaminophen (NAPA) with a median particle size of 17 microns used as a cohesive tracer (2% in a tablet of 250 mg) and the diluent was SuperTab® 11SD (spray dried lactose). Tablets were compressed over a 30 minute duration and samples withdrawn periodically for single tablet analysis.

The first mixing strategy without a deagglomeration step gave the results in Figure 3a, with a single tablet of 154% potency. The second mixing strategy with the deagglomeration step provides for excellent content uniformity throughout the entire tableting run with no evidence of segregation as shown in Figure 3b. The overall RSD was 1.6% throughout this second tableting run.

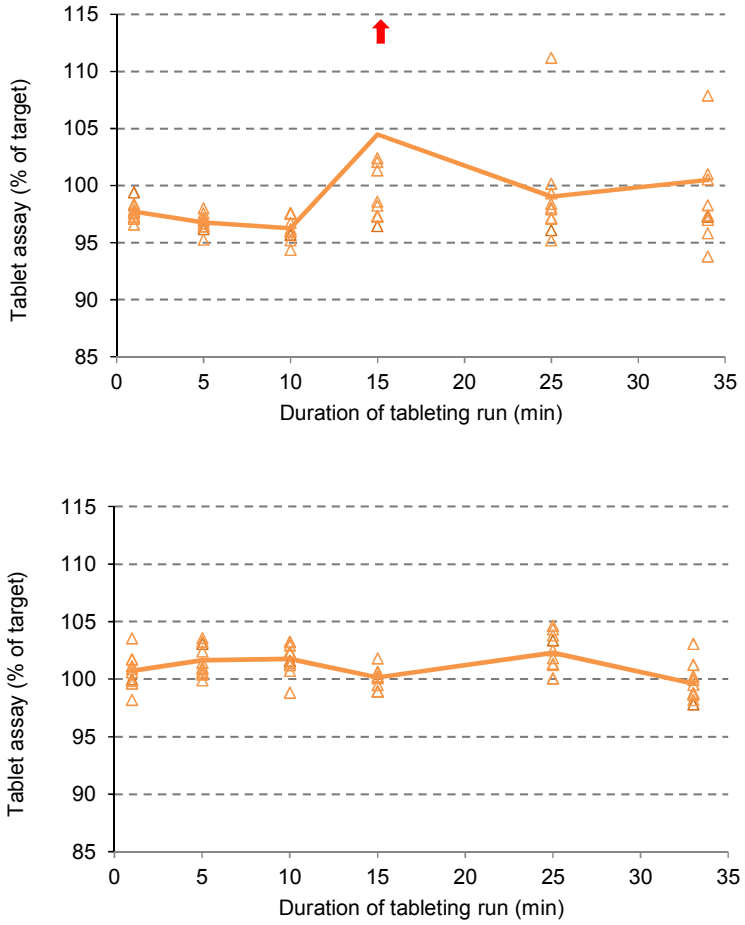


Figure 3: *Tablet assay data for tablets made with (a) a mixing plan without a deagglomeration step (above) and (b) a mixing plan with a deagglomeration step (below).*
The red arrow indicates a tablet outside the range 85% to 115% of target.

In a production environment a sieving or other high shear step (eg Comil) should be included after the premix to de-agglomerate the drug.

An ideal filler-binder for low dose direct compression tablets will also help to minimise segregation of the finely milled drug from the compression mix. It has been suggested that excipients with a rough surface can interact more strongly with drug particles than a smooth surface excipient. The electron micrograph in Figure 4 provides some evidence that drugs can remain associated with granules. The formulation is of directly compressed tablets containing 5% dextromethophan hydrobromide using granulated anhydrous lactose as the filler-binder. The map of bromine atoms shows that the drug appears to remain highly associated with the granules.

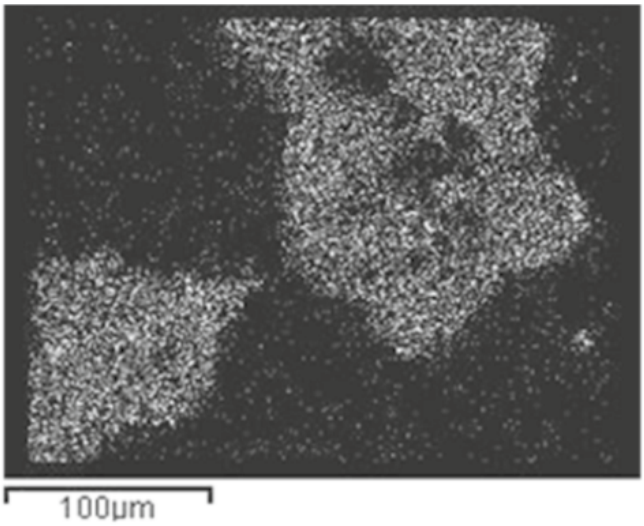


Figure 4: *Map of bromine atoms in the surface of a DC tablet of dextromethophan hydrobromide*

Additionally good content uniformity has been reported when partly pregelatinised starch is used as a filler-binder [8]. It has been proposed that surface roughness and the presence of moisture both contribute to this effect.

4.2 Medium Dose Drugs

Increasing the dose of the drug to the medium range (10 mg to 50 mg) tends first to lead to issues with flow of the compression mix. Compaction tends not to be such an issue because the excipients remain the predominant component of the formulation. Also content uniformity tends to be less of an issue, although it cannot be ignored. Official requirements are that uncoated or film-coated tablets containing less than 25 mg of drug or where the drug is less than 25% by weight must be tested for uniformity by assay rather than by uniformity of weight.

Is it possible to estimate the required flow properties of a compression mix for use on a modern compaction machine?

The data here were generated in our own laboratory. Finely milled paracetamol of finely milled propranolol were blended into a range of lactose DC diluents at levels up to 40% by weight. Various flow related properties were measured and the blends were tableted, when possible, to a target of 250 mg weight using a rotary tablet machine (Rotab) fitted with 9 mm tooling. Tablet weight uniformity was measured. The results are shown in Table 3, where the colours represent the flow characteristic of the blends according to their Hausner ratio, and the numbers in the table are the measured tablet weight uniformity. When the flow was “good” or “fair” (green & yellow cells) then flow was always adequate for tableting and the resulting tablets had good weight uniformity. When flow was “passable” (orange cells) then there were instances of flow related failure and when flow was “poor” or worse (red cells), then in most instances tableting was not possible.

Table 3: *Relationship between Hausner ratio of blends and the weight uniformity of tablets made from the blends. Colours represent the flow characteristic as described by the Hausner ratio and the numbers are the weight uniformity of the resulting tablets.*

Drug concentration	Acetaminophen + SuperTab ®				Propranolol + SuperTab ®			
	11SD	30GR	21AN	22AN	11SD	30GR	21AN	22AN
5%	0.48	0.33	1.14	0.42	0.43	0.47	0.45	0.39
10%	1.11	0.39	0.65	0.48	0.32	0.73	0.50	0.41
20%	No flow	No flow	No flow	No flow	0.45	0.46	1.13	0.62
40%	No flow	No flow	No flow	No flow	0.76	Capping	No flow	No flow

Hausner ratio	1.12 to 1.18	1.19 to 1.25	1.26 to 1.34	1.35 or higher
Flow descriptor	Good	Fair	Passable	Poor or worse

Thus a minimum recommendation is that the Hausner ratio of a compression mix should be at least fair, or preferably good.

4.3 High dose drugs

When the dose of the drug is in this category then the suitability of direct compression is very highly dependent on the properties of the drug substance. Nevertheless some realistic guidance can be given. Again flow and compaction of the compression mix are of key importance.

A useful surrogate for flow of an API is a measure of particle size and size distribution, and particle shape. Useful guidance may be found in literature. For example the size and shape necessary for a direct compression material has been given [9] as:

- D(4,3): Mean diameter by volume >80 µm
- D10: Tenth percentile of size distribution > 30 µm
- D90: Ninetieth percentile of size distribution <1000 µm
- Aspect ratio: <1.5

Alternatively, some flow descriptors based on the relationship between particle size distribution and shear cell measurements have been made (figure 5) where excellent flow is implied when D50 ≥ 80µm and D10 ≥ 10µm. (Note that the flow descriptors are not equivalent to those in Table 3).

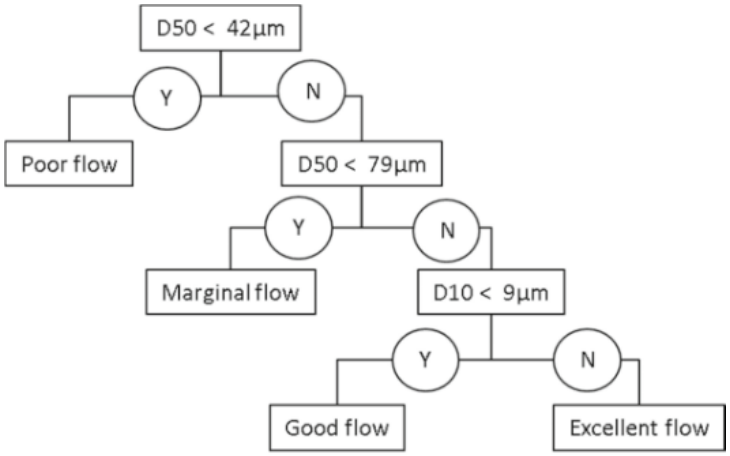


Figure 5: *Relationship of powder flow and particle size distribution (adapted from reference 10).*

These estimates are consistent with data from our own laboratories using ibuprofen as a high dose drug formulation (table 4). Batch A of ibuprofen with D50 = 86 µm & D10 = 19 µm (excellent flow) gave no tableting problems and repeated batches had RSD of weight uniformity from 0.3 to 1.6%. However batch B with D50 = 64 µm & D10 = 17 µm (marginal flow) could not be tableted because of poor flow.

Table 4: *Example high dose formulation (ibuprofen 200 mg)*

Component	mg / tablet	% w/w
Ibuprofen	200	57.14
SuperTab® 11SD	136	38.86
Primojel	10.5	3
Magnesium stearate	3.5	1
Total	350	100

Thus, if a high dose drug does not need to be milled or micronized for reasons other than flow, then a particle size specification based on the guidance above may have sufficient flow for direct compression.

References

1 Evolutions in Direct Compression, D.McCormick, Pharmaceutical Technology, April 2005, 52 – 62.
2 DFE Pharma technical; paper, Direct compression lactose
3 The effect of punch velocity on the compaction of a variety of materials, RJ Roberts and RC Rowe, J. Pharm. Pharmacol., (985, 37, 377 – 384.
4 Film formation by magnesium stearate during mixing and its effect on tableting, GK Bolhuis, CF Lerk, HT Zijlstra and AH de Boer, Pharmacetisch Weekblad, 1975, 10, 317 – 325.
5 Interaction of lubricants and colloidal silica during mixing with excipients. I. Its effect on tableting, CF Lerk, GK Bolhuis and SS Smedema, Pharmaceutica Acta Helvetiae 1977 52(3), 33-39 and Interaction of lubricants and colloidal silica during mixing with excipients. II. Its effect on wettability and dissolution velocity, CF Lerk and GK Bolhuis, Pharmaceutica Acta Helvetiae, (1977), 52(3), 39-44
6 Particle size limits to meet USP content uniformity criteria for tablets and capsules, BR Rohrs, GE Amidon, RH Meury, PJ Secreast, HM King and CJ Skoug, J. Pharm. Sci., 2006, 98, 1049 – 1059
7 DFE Pharma technical paper, Achieving content uniformity in direct compression
8 Formulation of low dose medicines – theory and practice, H Ahmed and N Shah, Am. Pharm. Rev., 2000, *3*(3), 9 – 14.
9 Identifying Candidates fop direct compression using material sparing formulation tools, BC Hancock, AAPS (2004) reported in reference 1.
10 Modelling pharmaceutical powder flow performance using particle size distribution data, MP Mullarney & N Leyva, Pharm Tech, March 2009, 126 – 135.

DFE pharma

Head Office
Klever Strasse 187
P.O. Box 20 21 20
47568 Goch, Germany
T. +49 2823 9288 770
F. +49 2823 9288 7799
pharma@dfepharma.com

www.dfepharma.com

DFE Pharma (#code/month year)