Is direct compression suitable for low dose formulations?

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Introduction

Highly active ingredients are sometimes required in extremely low dose in oral formulations. Over the last decades, the proportion of highly potent drugs has risen from 5% in the 90s to 20% nowadays. Also, for pediatric formulations, low dosage is an important topic. Active pharmaceutical ingredient (API) contents of less than 1% will then cause problems in content uniformity if the most economical process of direct compression (DC) is applied. The pure physical mixture can often not assure stability of homogeneity. For this reason, many formulators switch to more expensive wet or dry granulation processes.

According to textbook knowledge, a mixture has best chances for stability if particles of API and excipients are of the same size range. Modern APIs are more likely to be applied in micronized form. Thus, it was the aim of this study to evaluate if such APIs could create stable mixtures with larger excipient particles and support a direct compression process with good content uniformity. An earlier study has shown the stability of so-called ordered mixtures with spray-dried sorbitol and much smaller API particles [1, 2]. Hersey first introduced the concept of ordered mixtures to explain the behavior of interacting particles in a powder mixture[3].

Materials and Methods

The cited literature dealt with spray-dried sorbitol which was at this time a rare example of direct compressible excipients. Nowadays, mannitol gets much more attention, especially for ethical pharma developments, due to its inertness towards both the patient and the API, its low hygroscopicity and its fast release qualities. So, this study focuses on different DC-mannitols available in the market (Table 1). The model APIs used were ascorbic acid, as an example of a hydrophilic compound, and riboflavin, as a hydrophobic compound. Both APIs were micronized since in most instances a good distribution of a low dose API can only be achieved with small particles.

To evaluate the quality of mixing, the homogeneity was measured on a three-rate blending series by taking 6 samples from the mixtures and analyzing the concentration of API in each (n = 18). The relative standard deviation (RSD) was then at first examined as a function of mixing time (Figure 1 & 2). The content of ascorbic acid was determined in a volumetric analysis by titration with a iodine solution (TitriPUR®, Merck KGaA), and accurate measurement with an RSD of 0.12% for the micronized ascorbic acid. An alternative HPLC method was proven to be inadequate since the ascorbic acid decomposed in solution in the time from preparation until measurement.

To challenge the mixture stability and show strength of adsorption, the mixtures were applied to an air jet sieve and again analyzed after a period of airflow. By this, a certain separation of fine API particles can be assumed if not strongly adsorbed (Figure 3).

In a real life example of a pharmaceutical formulation with a water sensitive low dose drug, the capability of a stable direct compression process has been demonstrated and good content uniformity has been shown.

Excipient/API	Supplier	Particle Size Laser Light Diffraction Dv50 [µm]	Crystal modification	Surface Area Acc. BET-Method [m²/g]
Parteck® M 200 Cat. No. 100419	Merck KGaA	215.8	β	2.89
DC-mannitol spray-dried	A	143.6	α/β	0.60
DC-mannitol granulated	B	286.0	β	0.50
Ascorbic acid* Cat. No. 500078	Merck KGaA	4.52	n.a.	Not determined
Riboflavin* Cat. No. 500257	Merck KGaA	1.72	n.a.	Not determined

Table 1
*The APIs were micronized on a pin mill before using it for the following low dose case study

Results

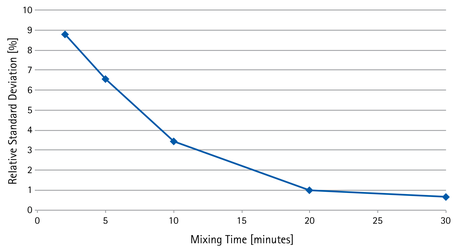

Figure 1. The reduction of the relative standard deviation of the measured API-concentrations with rising mixing times shows how the mixture approaches homogeneity. A time of 30 minutes was chosen as sufficient to view the mixture of DC-mannitol with micronized ascorbic acid as homogenous.

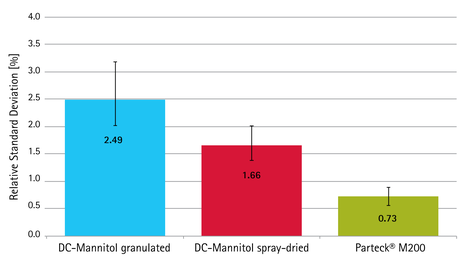

Figure 2. Comparing different DC-mannitols at this mixing time of 30 minutes reveals differences in homogeneity of such mixture with micronized ascorbic acid.

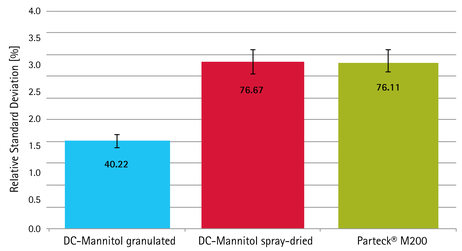

Figure 3. The concentration of ascorbic acid was measured after applying a mixture of 1% API in DC-mannitol for 15 minutes on an air jet sieve (Mesh 40 µm, 2000 mPa). A recovery of 100% would mean a perfectly strong adsorption of API to the carrier. A much stronger adsorption was found for the spray-dried DC-mannitols compared with the granulated quality.

This finding may result from the surface structure of the excipients.

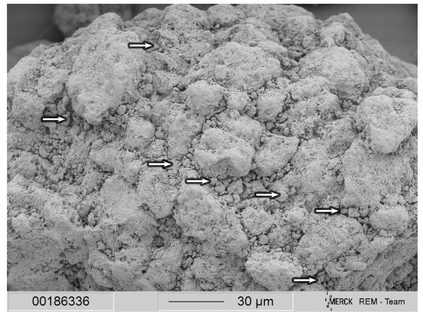

Figure 4. Parteck® M 200 mixed with 1% Ascorbic acid. The micronized API particles are clearly visible (see arrows) in the structure of the porosity of the much larger excipients particles.

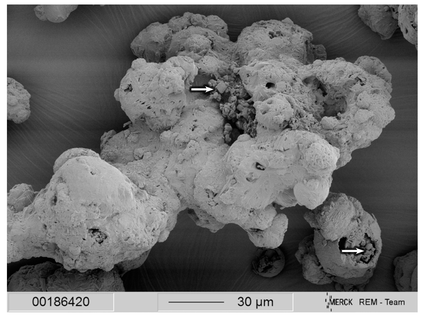

Figure 5. Spray-dried DC-mannitol mixed with 1% micronized ascorbic acid.

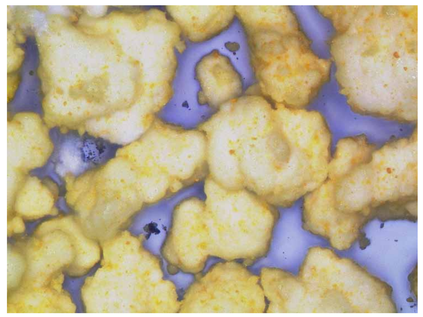

Figure 6. Mixture of Parteck M 200 with 1% micronized riboflavin. Light microscope image with 200x magnification. The yellow particles of API are clearly visible in the porosity of the carrier surface.

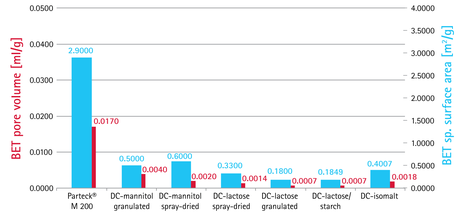

Figure 7. As the API is adsorbed to a porous surface this observed great difference in surface area and porosity may give rise to different behavior in adsorption to micronized APIs. In further studies, this influence on binding capacity has to be examined.

This study has shown that stable mixtures of much smaller API particles with DC-excipients can be achieved. Is this suitable for a direct compression process in a real formulation?

R&D Case Study: Results of a Field Test

This was challenged in an example of a water sensitive R&D-API at only 0.4% in a tablet (0.5 mg API in 120 mg tablet). Wet granulation could not be applied because of the water sensitive R&D-API. So the micronized API (Dv50 10 µm) amount was premixed for 30 minutes with 15% of the total amount of DC-mannitol (Dv50 200 µm), then mixed with the rest of the formulation (see Figure 8) and a test run of 2 hours on a rotary press was performed at two different rotation speeds (40,000 and 80,000 T/h).

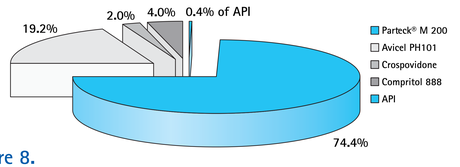

Figure 8.

	40000 Tablets/hour	80000 Tablets/hour
Tablet weight	120.1 mg (RSD 0.6%)	118.8 mg (RSD 0.9%)
Hardness	178 N (RSD 4.1%)	173 N (RSD 4.1%)
Disintegration time	3' 25''	3' 22''

This result was surprisingly good: tablet weight (RSD 0.6–0.9%), tablet hardness (RSD 4.1%) and constant disintegration time. Content uniformity was measured to be ± 1.8%.

Conclusion

The results show clearly that the effect of ordered mixtures can be found with DC-mannitols – especially with spray-dried qualities with a porous surface structure. A stable mixture cannot only be achieved with components of similar particle sizes as textbook knowledge suggests. It's also possible to achieve a stable mixture of micronized API particles (< 15 µm) with a DC-mannitol of a mean particle size of 200 µm. This result can be used to apply direct compression also for low dose applications with very acceptable content uniformity as the example shows. Further work will be invested to study the influence of hydrophobicity on this adsorption effect and the question of adsorption capacity in relation to surface area and pore volume.

[1] I. Nikolakakis, J.M. Newton, J. Pharm. Pharmacol 1989, 41: 145–148
[2] P.C. Schmidt, K. Benke, 1984, Pharm Ind 46 (2): 193–198
[3] J.A. Hersey, 1975 Ordered mixing: a new concept in powder mixing practise. Powder technol 11: 41–44