The Effect of Mixing Time and Excipient Choice on Blend Uniformity

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Abstract

Achieving a homogeneous distribution of all ingredients in a powder blend is crucial for the quality of the final drug product. Blend homogeneity is particularly important in the case of direct tableting, capsule filling, and any application involving loose powders, such as sachets or stick packs.

Apart from the blender design, the most important factors affecting the quality of a powder blend are mixing time and careful selection of inactive ingredients. Both aspects are addressed in this study.

Model formulations were used to determine the minimum mixing time necessary to achieve homogeneous distribution of the model API (ascorbic acid). As a second step, the filler in the model formulation was substituted by an excipient, which was selected based on the findings of the first set of experiments. The optimized blend reached the target homogeneity after considerably shorter blending times than the original formulations.

Introduction

The goal of blending is to achieve homogenous powder blends. Perfect homogeneity, as illustrated in Figure 1b, is merely a theoretical thought. Realistically, the blend quality will – not even after extended blending times – improve beyond a certain level, as illustrated in Figure 1c. Therefore, the blending endpoint is commonly defined as a blending time, which for a given piece of blending equipment and a defined speed, will lead reliably to blend qualities within the plateau zone of the curve shown in Figure 2.

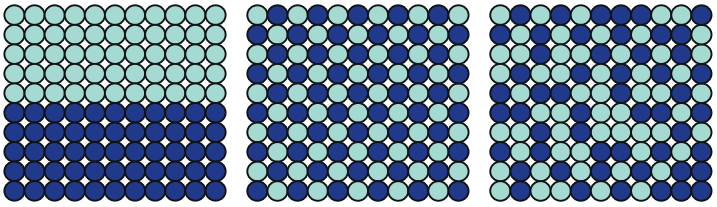


Figure 1: a) before blending b) ideal blend c) realistic blend

The standard blending time in case of the blender used in the JRS Pharma laboratory has previously been defined as 15 minutes. The effect of deviating from the standard blending time will be analyzed through this study, as well as the influence of different excipient particle size and morphology.

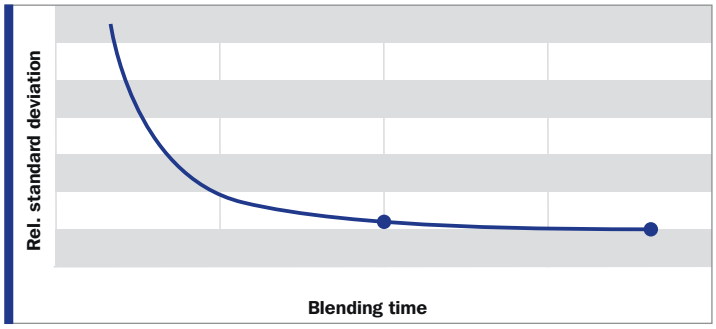


Figure 2: Time-dependent increase in blend homogeneity

Materials and Methods

Powder blends were prepared, using the ingredients listed in Table 1.

Microcrystalline Cellulose, **VIVAPUR® 101**
Microcrystalline Cellulose, **VIVAPUR® 102**
Microcrystalline Cellulose, **VIVAPUR® 12**
Silicified Microcrystalline Cellulose, **PROSOLV® SMCC 90**
Silicified Microcrystalline Cellulose with Sodium Starch Glycolate and Sodium Stearyl Fumarate, **PROSOLV® EASYtab SP**
Sodium Starch Glycolate, **EXPLOTAB®**
Collodial Silica, Aerosil® 200
Ascorbic acid

Table 1

The blender used was a JRS-built, lab-scale freefall blender shown in Picture 1.

Picture 1

Table 2 lists the equipment used in this study.

Equipment	Manufacturer	Type
Free fall Blender	JRS	n/a
Tapped Density	Engelsmann	STAV II
UV Vis Spectrometer	Cecil	CE 10221
Balance	Ohaus	Precision Advanced

Table 2

Blends of the ingredients listed in Table 1 were prepared according to the formulation shown in Table 3. After 10 minutes and 15 minutes (standard blending time), samples were taken from the blending container in the positions indicated in Figure 3.
The content of ascorbic acid in each sample was determined spectrophotometrically at a wavelength of 244.6 nm.

Material	Amount [%]
Binder	76
Sodium starch glycolate (**EXPLOTAB®**)	2
Colloidal silica (**Aerosil® 200**)	2
Ascorbic acid (model API)	20
Total	**100**

Table 3

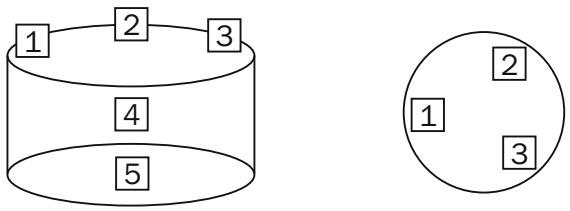


Figure 3: Sampling plan

Results and Discussion

Table 4 summarizes the standard deviations between the samples taken in positions 1 through 5 (see Figure 1) after 10 and 15 minutes, respectively.

Material	Blending time [min]	Ascorbic acid concentration [mg/mL]	Relative standard deviation [%]
PROSOLV® SMCC 90	10	2.13	0.18
	15	2.11	**0.13**
PROSOLV® EASYtab SP	10	2.04	**0.09**
	15	1.95	**0.08**
VIVAPUR® 101	10	2.40	0.27
	15	2.09	**0.04**
VIVAPUR® 102	10	2.21	0.15
	15	1.91	**0.07**
VIVAPUR® 12	10	2.07	**0.10**
	15	2.03	**0.07**

Table 4

The internal acceptance criterion for the relative standard deviation is less than 0.15 %. This was met by all formulations tested after the standard blending time of 15 minutes. **Interestingly, the formulations containing PROSOLV® EASYtab SP and VIVAPUR® 12 passed the 0.15 % mark after only 10 minutes of blending.** Table 5 shows that **PROSOLV®** EASYtab SP and **VIVAPUR®** 12 are characterized by larger particle size and higher bulk density in comparison to the other three excipients tested.

Material	Mean particle size [µm]	Density [g/ml]
VIVAPUR® 12	**180**	**0.30 – 0.36**
PROSOLV® EASYtab SP	**130**	**0.30 - 0.42**
VIVAPUR® 101	65	0.26 – 0.31
VIVAPUR® 102	130	0.28 – 0.33
PROSOLV® SMCC 90	125	0.25 - 037
VIVAPUR® 302	**130**	**0.35 – 0.50**

Table 5

In order to check the validity of these findings, **VIVAPUR® 302,** another MCC grade with high bulk density and larger particles, was tested in the same experimental set up as used before. In this case, however, samples were taken after 2, 4, 6, 8, 10, and 15 minutes.

Blending time [min]	Ascorbic acid concentration [mg/ml]	Relative standard deviation [%]
2	2.5	0.56
4	1.98	0.22
6	1.91	0.20
8	1.82	0.07
10	1.76	0.04
15	1.84	0.10

Table 6: Results for **VIVAPUR® 302**

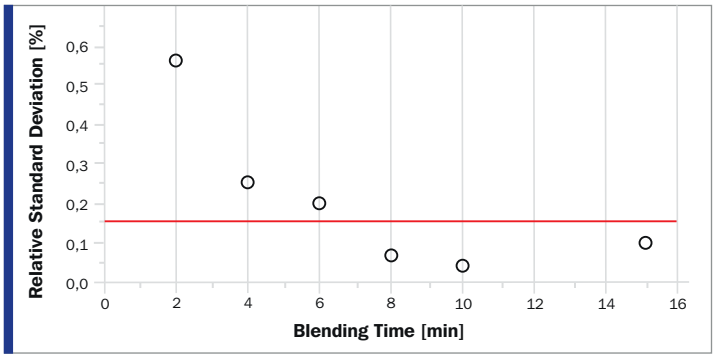
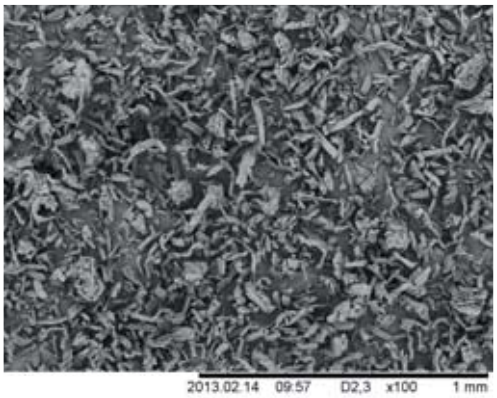
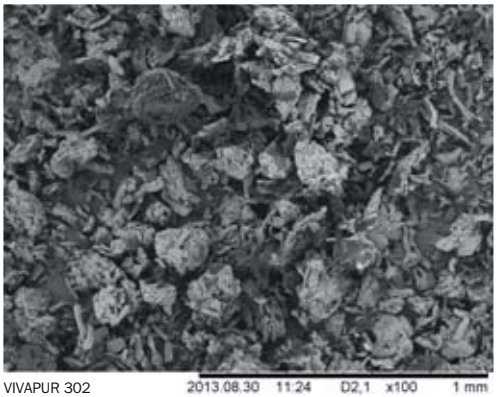


Figure 4

As illustrated in Figure 4, the relative standard deviation of the blend containing **VIVAPUR® 302** drops below the 0.15 % threshold very rapidly and meets the acceptance criterion after a blending time of only eight minutes. **This confirms the assumption, that higher bulk density and larger particle size promote efficient blending.** This finding is further supported by the evaluation of SEM pictures of **VIVAPUR®** 302 and **VIVAPUR®** 101. The micrograph of **VIVAPUR® 302** shows predominantly large spherical particles, whereas **VIVAPUR® 101** consists mainly of small, fibrous particles.



Picture 2: SEM Micrograph of **VIVAPUR® 101**



VIVAPUR 302
lot 530220338

Picture 3: SEM Micrograph of **VIVAPUR® 302**

Conclusion

The tests carried out in this study confirmed the suitability of the standard blending time of 15 minutes. Moreover, it was demonstrated that particle size, shape, and bulk density have a significant impact on the blending process. Material consisting of elongated, fibrous particles required the full 15 minutes of blending time. Coarser, more spherical and denser material, by contrast, reached the target level of homogeneity much more rapidly, thus creating a larger "safety margin" around the standard blending time.

In a production environment, such findings may support a reduction of blending time, and therefore an increase in effectiveness.

It is important to bear in mind that blending curves as recorded for **VIVAPUR® 302** are specific to certain API / excipient combinations. If there is intent to minimize the blending time, a careful evaluation of the best suited combination of a given API quality and excipient(s) must be carried out.

JRS Pharma offers a wide range of excipients and high functionality excipients which can optimize the blending process in regards to the blending time, particle size density, or particle size. Our excipients can be adapted to your API size and quality.

Literature:

Mischen von Feststoffen, Ralf Weinekötter, Herman Gericke,
Springer Verlag, 1995

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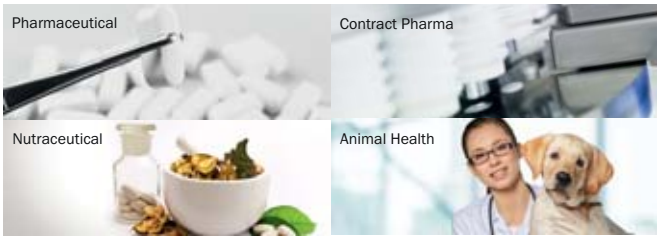

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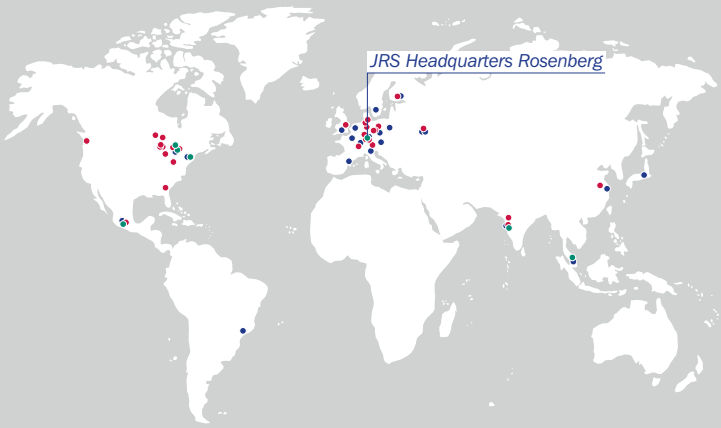

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