

Soft-pelletization of micronized substances: Development of a novel, continuous production process

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Summary

A novel continuous production technique for micronized soft pellets has been developed and it was shown that the new method is a promising approach for the production of soft pellets. The described method leads to soft pellets of almost identical morphological and aerodynamic characteristics compared to the common way of soft pellet production. Most notably the production can be carried out in a significantly lower amount of time, and a vast increase in soft pellet yield can be achieved. The main advantage of the novel approach is the facilitation of the production process itself by enabling a continuous soft pellet production, therefore leading to lower batch-to-batch variation. Due to its construction the machinery may also be equipped with PAT systems, e.g. online size and shape control by image analysis. Experiments have shown that the new process is applicable to any kind of micronized actives, excipients and mixtures thereof.

Introduction

As an alternative to interactive mixtures, soft pellets of micronized actives delivered by a dry powder inhaler represent an alternative formulation approach to pulmonary delivery of APIs, while their established method of production, i.e. spheronization of the micronized substances in a tilted vessel, entails several disadvantages. Therefore, a novel production method has been developed to avoid the considerable time consumption of the standard process, the constraint to batch-wise manufacturing in small scale and unsatisfying yields.

Materials and Methods

To compare both methods of production, cromolyn sodium (DSCG) was used as a model drug in 'bulk-condition' to avoid uncontrollable influence of agglomeration and dispersion caused by jet-milling (tribo-electrical charge). DSCG was forced through a 355 μm -sieve to form morphologically irregular 'starter-pellets' and applied to the novel apparatus. A sketch of the experimental setup showing this table-top sized device is presented in **Figure 1**.

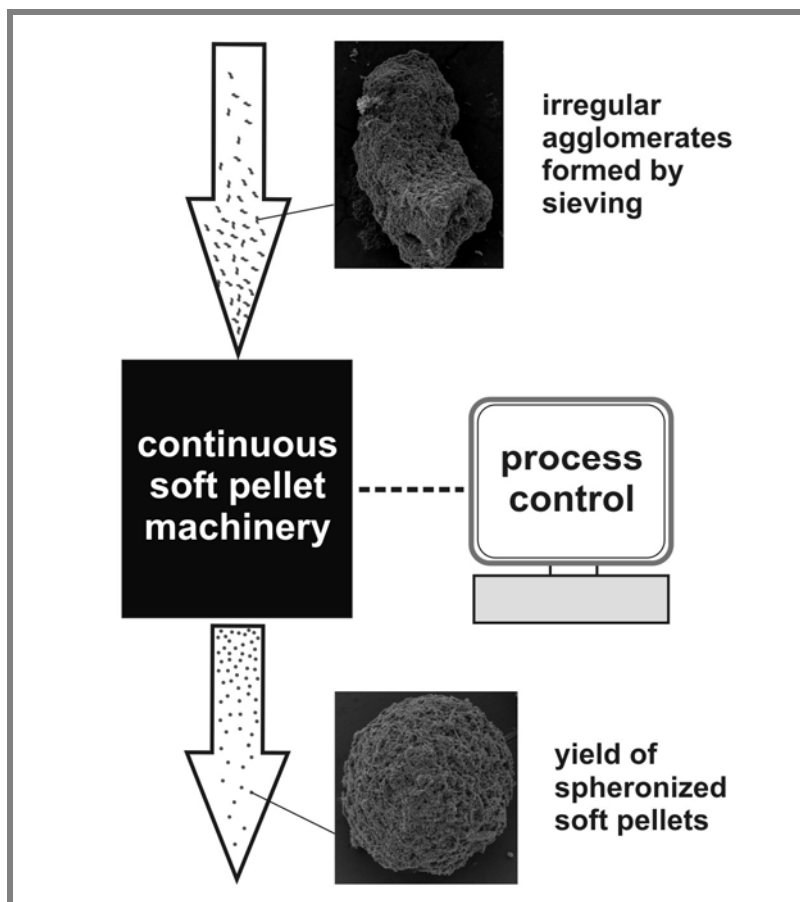


Figure 1: sketch of experimental setup

During the production process the starter-pellets were continuously rounded and finally attained almost ideal spherical shape. The SEM images inserted in **Figure 1** present actual results of the produced DSCG-softpellets. A following classification step by screening the obtained spheres through a 200 μm -sieve was added. The resulting soft pellet batch (**A**) was compared to a batch produced using the disclosed process of Trofast et al. ¹ in a tilted, rotating vessel (**B**), while this vessel-batch resulted from optimising vessel-production-parameters and, therefore, showed the best morphological characteristics of 9 batches produced under different conditions (time= 30 min, rotation speed= 15 U/min and sieve-size when applied to vessel= 355 μm in case of batch **B**).

Examination of morphological characteristics by image analysis (L2001, Leco GmbH, Kirchheim, Germany) led to resulting values for roundness ($RN = (4\pi \cdot \text{area}) / (\text{perimeter})^2$; ideal case = 95 due to pixel-matrix) and roughness (RG = ratio of real perimeter/convex perimeter; ideal case = 1). In addition, SEM-images (XL20, Philips, Eindhoven, Netherlands) of both batches were prepared. In order to investigate the aerodynamic dispersion properties and the extent of similarity between **A** and **B**, both batches were individually filled into the reservoir of an Oxis[®]-Turbuhaler device and analysed with a Next Generation Pharmaceutical Impactor (NGI, MSP Corp., Shoreview, MN, USA) at a flow rate of 60 l/min (pressure drop 4 kPa). NGI runs were carried out in triplicate with 10 Turbuhaler actuations per run. The deposition on each stage of the NGI was assessed using an established HPLC-method (Waters Corp., Milford, MA, USA), enabling determination of the fine particle fraction (particles < 5 μm) as percentage of the delivered dose. Assuming full dispersion into individual particles, the calculated ideal-FPF of the 'bulk-DSCG' (with a x50 of 5.9 μm) would be approximately 45 %, determined by laser diffraction in aqueous dispersion (HELOS-CUVETTE-system, Sympatec GmbH, Clausthal-Zellerfeld, Germany) as presented in **Figure 2**.

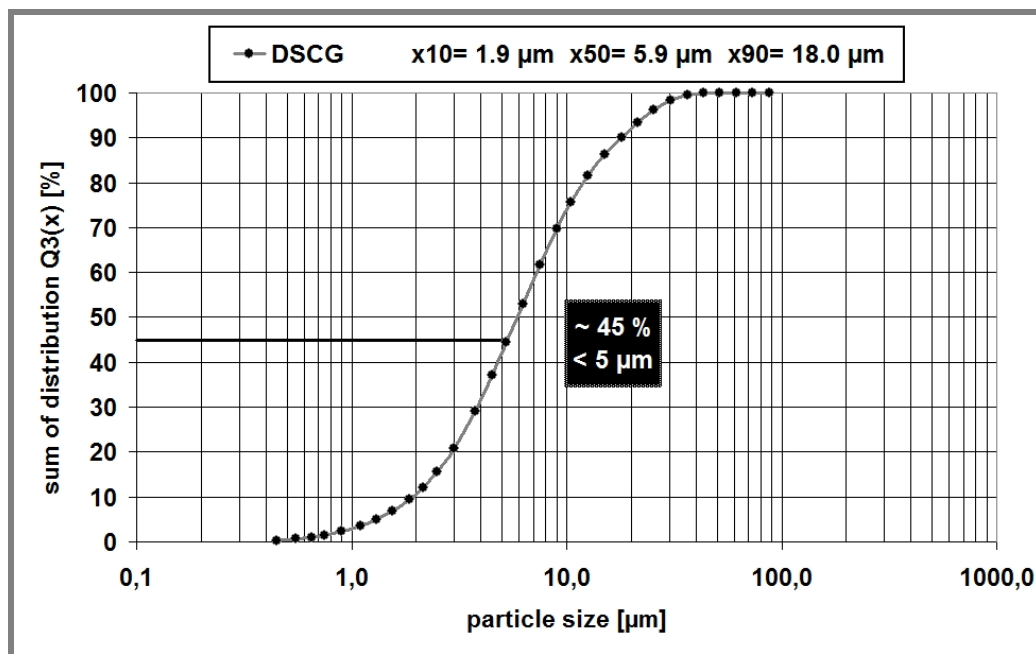


Figure 2: DSCG, sum of distribution determined by laser diffraction in miglyol 812 dispersion (HELOS-CUVETTE)

Results and Discussion

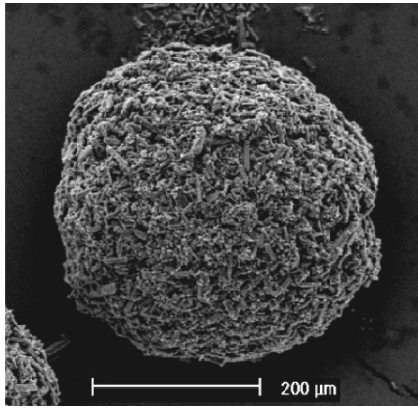
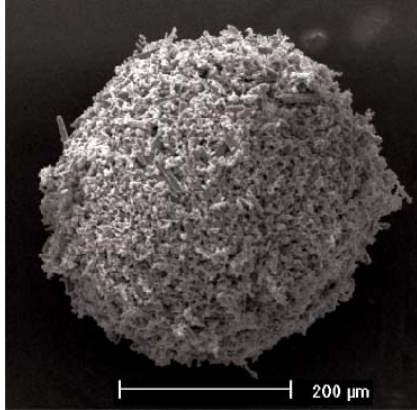
The image analysis results revealed direct morphological comparability between processes **A** and **B**, as process **A** showed a value for roundness of 87.7 (± 0.5) and roughness of 1.02 (± 0.001), with values of 85.8 (± 0.6) and 1.02 (± 0.002) for vessel-process **B** respectively. The SEM-images of both processes at a magnification of 150x visually underlined the equivalence of the two processes in terms of shape and surface properties.

Total time needed for production is significantly decreased in case of the novel method of production. Batch **A** was produced within 2 minutes using the novel soft pellet machinery, while the rotation during vessel-production had to be applied for 30 minutes in case of batch **B**.

Eliminating a marginal amount of fines by screening the spheres of batch **A** through a 200 μm -sieve after production led to a yield of more than 90 %. For batch **B** merely an amount of 33 % was obtainable, relating to the examined soft pellet fraction 200 μm <x<355 μm .

With respect to the results for morphology and production parameters, process **A** can be considered superior to process **B** regarding all aspects. Results of the image analysis, production time and achieved yield for both processes are presented in **Table 1**, along with a comparison of SEM-images.

Table 1: production results and image analysis values of process A compared to process B

Batch	A (novel method)	B (common method)
roundness	87.7 (± 0.5)	85.8 (± 0.6)
roughness	1.019 (± 0.001)	1.023 (± 0.002)
SEM-images (magnification = 150x)		
production time	< 2 min	30 min
yield (200 μm <x<355 μm)	> 90 %	33 %

The NGI deposition results of processes A and B, obtained by Turbuhaler dispersion, are presented in **Figure 3** along with the FPF achieved for each batch.

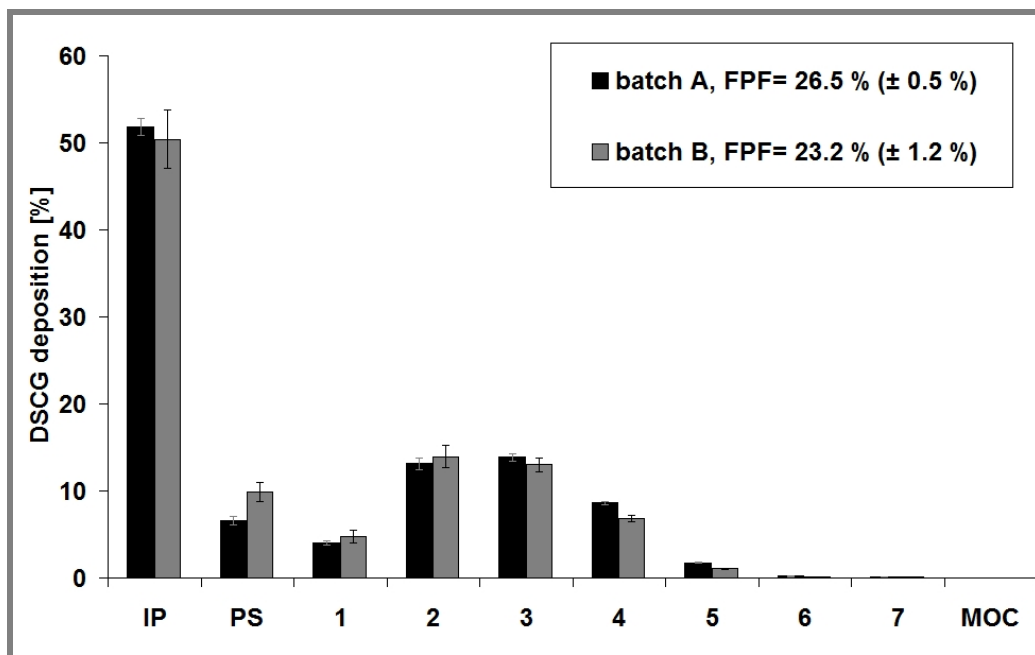


Figure 3: NGI per stage deposition and FPF results for process A and B (Oxis® Turbuhaler, flow rate 60 l/min, n=3)

Both batches show a relatively high throat deposition, with 52 % for batch **A** and 50 % for batch **B**, respectively. The pre-separator deposition decreases about 3 % in case of batch **A** indicating increased re-dispersibility, i.e. a lesser amount of remaining soft pellet fragments. On the following NGI stages both deposition profiles reveal a similar aerodynamic behaviour for batches **A** and **B**, while the three runs of batch **A** show a lower variation in deposition and therefore FPF.

Conclusion

Several disadvantages of the common soft pellet production technique can be eliminated with the novel approach to production. Besides higher obtainable yield and decreased production time, resulting soft pellets reveal similar to superior characteristics in morphology compared to soft pellets produced by classical means. The re-dispersibility during aerodynamic impactor analysis can also be considered as almost identical. Particularly with regard to a modern and controllable production process, the new method overall represents a faster and, in conclusion, less expensive way of soft-pelletization.

¹ Trofast, Eva A. C., Falk, Erik. J., Astra Aktiebolag Sweden, Agglomeration of finely divided powders, United States Patent, US 5,551,489, 1996