High Drug Loaded Pellets produced by ProCell® Technology

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INTRODUCTION

- Drug loaded pellets were produced by using the **ProCell®** lab system technology
- The aim was to produce highly drug loaded matrix pellets with an API-polymer ratio of approximately 95:5 by using different polymers, with the target pellet size between 315 µm and 500 µm
- The ProCell® Technology is a **continuous spouted bed pelletization process** [1, 2] which especially allows the manufacture of pellets with very high active drug loadings (> 95 %) and narrow particle size distributions
- The production of very small pellets (100 – 400 µm) is possible
- The process is characterized by a permanently balanced ratio of spray drying, agglomeration and layering of already existing seeds. Well sized pellets are continuously classified through a zig-zag sifter or a sieve-mill-circuit and discharged out of the process. Too small pellets are transported back into the process for further growth

MATERIAL AND METHODS

Materials

- Water soluble model API
- Polyacrylic acid-based polymer was purchased from Lubrizol
- Polysaccharide based polymer from Sigma-Aldrich
- Cellulose based polymer from Shin-Etsu
- Acetic acid from Sasol, Merck
- Purified water was used for the preparation of the spraying liquids.

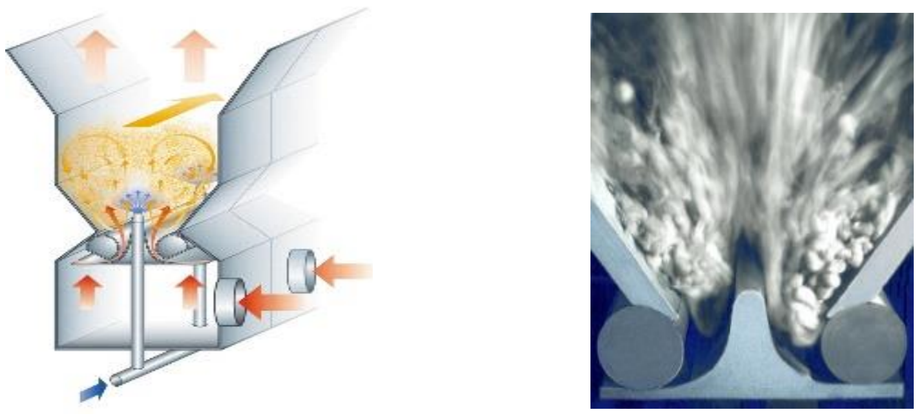


Figure 1. Schematic view of ProCell® unit (left), flow gradient of a spouted bed (right)

Equipment

The continuous pelletization trials were performed in the lab scale using a ProCell® lab system (Glatt GmbH, Germany) [Fig. 1]. Well sized pellets were continuously discharged via an air sifter system [schematic view in Fig. 2].

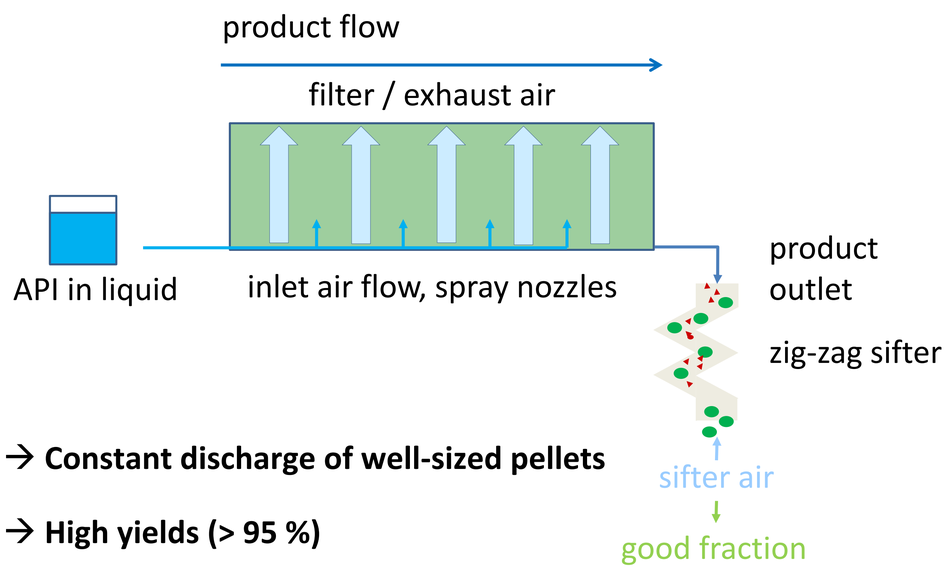


Figure 2. Principle of ProCell® process with zig-zag sifter

In case of cellulose-based polymer as binder the API was diluted in purified water, then the polymer was added while stirring and dissolved. The API:polymer ratio was 93:7.

The polyacrylic acid-based polymer was dispersed in purified water and let swell by gently stirring for at least one hour; the API was added and dissolved while stirring, resulting in an API-polymer ratio of 95:5.

For the polysaccharide-based polymer containing spraying liquids the polymer was dispersed in purified water, acetic acid was added to colloidally dissolve the polymer; API was dissolved in purified water, both liquids were merged and stirring continued. The spraying liquid contained an API:polymer ratio of 99:1.

Characterization of pellets

The obtained pellets were characterized and compared concerning particle size, sphericity, eccentricity (sieve analysis, RETSCH, and Camsizer® XT, Eyecon$_2$™, Horiba), porosity (gas pycnometry, AccuPyc 1330, Micromeritics), residual moisture (loss on drying, Halogen Moisture Analyzer HB 43, Mettler Toledo), specific surface area (AccuPyc 1330, and Mastersizer 2000, Malvern Panalytical).

Assay was tested with an internal test procedure, which was modified for analysis of pellets.

RESULTS AND DISCUSSION

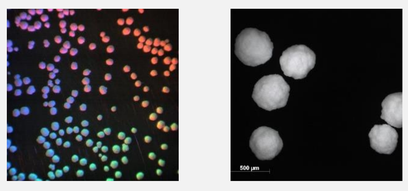
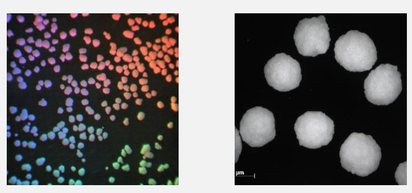
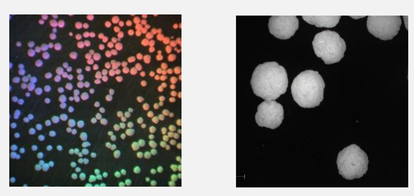
	Cellulose-based polymer	Polyacrylic acid-based polymer	Polysaccharide-based polymer
API-polymer ratio	93:7	95:5	99:1
Sphericity	0.91-0.96	0.80-0.96	0.87-0.96
Residual moisture [%]	0.32	0.17	0.17
Mean particle size [µm]	436 ± 57	425 ± 73	411 ± 59
Eccentricity	0.3449 ± 0.1516	0.4146 ± 0.1582	0.3252 ± 0.1293
Assay [%] (absolute)	92.06	92.52	97.79
Assay [%] (rel. to theory)	98.84	97.39	99.00
Specific surface area [m²/g]	n.a.	0.01210	0.01150
Microscopic pictures			

Table 1. Data of in process controls analysis as well as quality control for ProCell® matrix pellets. The specific surface area is not available for cellulose based polymer pellets as no end-point detection was possible for the true density. The mean particle size and the eccentricity are listed with their mean ± SD

Pellets with the target particle size between 315 µm and 500 µm were produced. Round pellets with a narrow size distribution were obtained [Table 1]. Assay values of up to 98 % (99 % related to theory) were analyzed.

CONCLUSION

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The ProCell® Technology is an adequate technology for the development and manufacture of highly drug loaded pellets. The manufacture of pellets with different polymers and API-to-polymers ratios is possible. Narrow particle size distributions and smooth pellets surfaces can be obtained.

ACKNOWLEDGEMENT

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