

Introduction

- ProCell® Technology is a continuous spouted bed pelletization process [1,2] which 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.
- 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

Objectives

- Highly drug loaded matrix pellets were produced using the Glatt proprietary ProCell® lab system technology
- The target pellet size was between 315 µm and 500 µm
- In addition to a standard polymer (Hydroxypropyl methylcellulose, Pharmacoat 603), a polyacrylic acid-based polymer (Carbomer, Carbopol 974 P NF) and a polyaminosaccharide (Chitosan) were used as binders

Materials

- For hydroxypropyl methylcellulose (Pharmacoat 603) polymer as binder, the API was diluted in purified water, then the polymer was added and dissolved while stirring. API:polymer ratio was **93:7**
- Carbomer (Carbopol 974 P NF) 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**
- Chitosan was dispersed in purified water. Afterwards acetic acid was added to colloiddally dissolve the polymer and the API was dissolved in purified water. Finally, both liquids were merged and stirring continued. The spraying liquid contained an API:polymer ratio of **99:1** resp. **95:5**

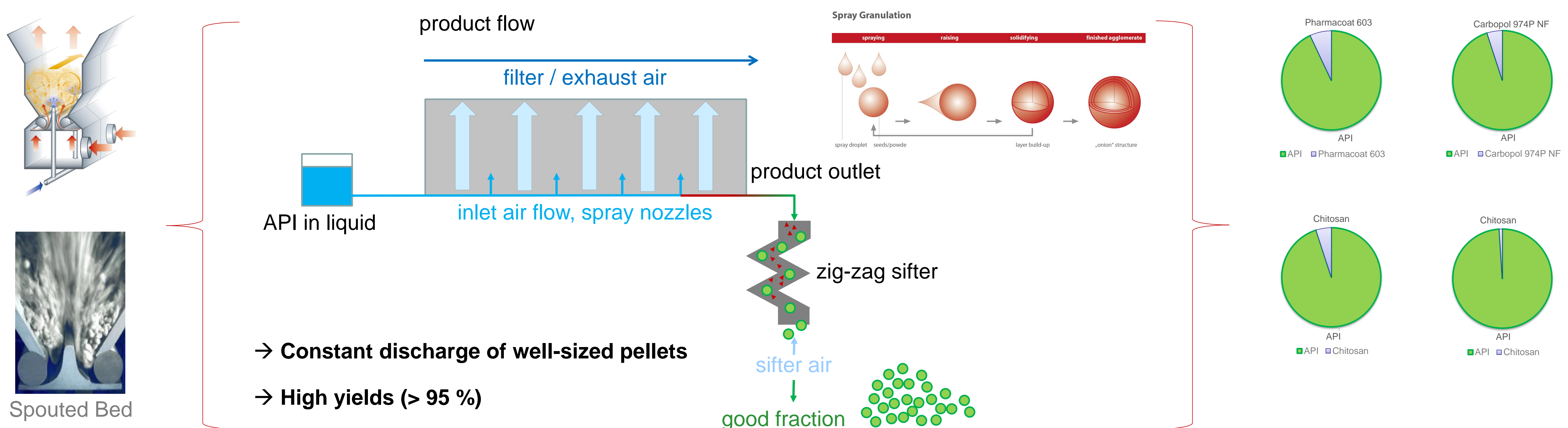


Figure 1: Illustration of the manufacturing process for matrix pellets produced in a direct palletization in the Spouted Bed.

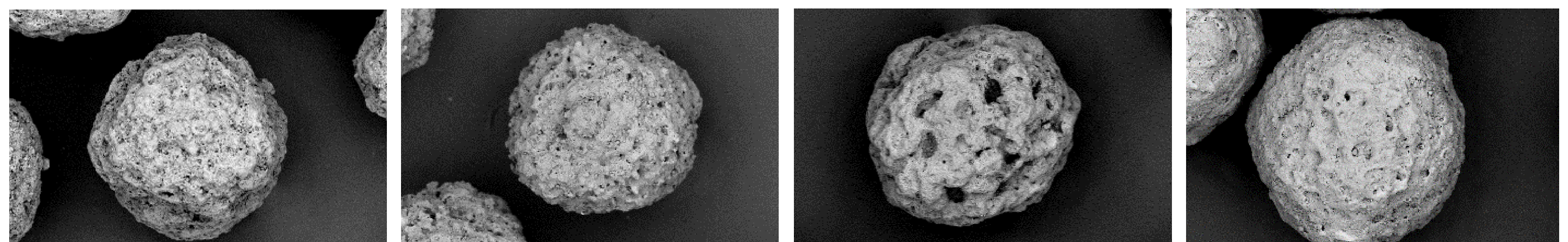
Characterization of matrix pellets

	API:Pharmacoat 603 93:7	API:Carbopol 974P NF 95:5	API:Chitosan 95:5	API:Chitosan 99:1
Sphericity	0.91-0.96	0.80-0.96	0.89-0.96	0.87-0.96
Residual moisture [%]	0.32	0.17	0.33	0.17
Mean particle size [µm]	436 ± 57	425 ± 73	434 ± 55	411 ± 59
Eccentricity	0.3449 ± 0.1516	0.4146 ± 0.1582	0.3904 ± 0.1588	0.3252 ± 0.1293
Assay [%] (absolute)	92.06	92.52	93.23	97.79
Assay [%] (rel. to theory)	98.84	97.39	99.24	99.00
Specific surface area [m ² /g]	n.a.	0.01210	0.01170	0.01150

Table 1: Data of IPC analysis as well as quality control for ProCell® matrix pellets. The specific surface area is not available for Hydroxypropyl methylcellulose-based 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.

SEM Images

Figure 2: SEM pictures, from left: API:Pharmacoat 603 (ratio 93:7), API:Carbopol 974P NF (ratio 95:5), API:Chitosan (ratio 95:5), API:Chitosan (ratio 99:1)



Dissolution

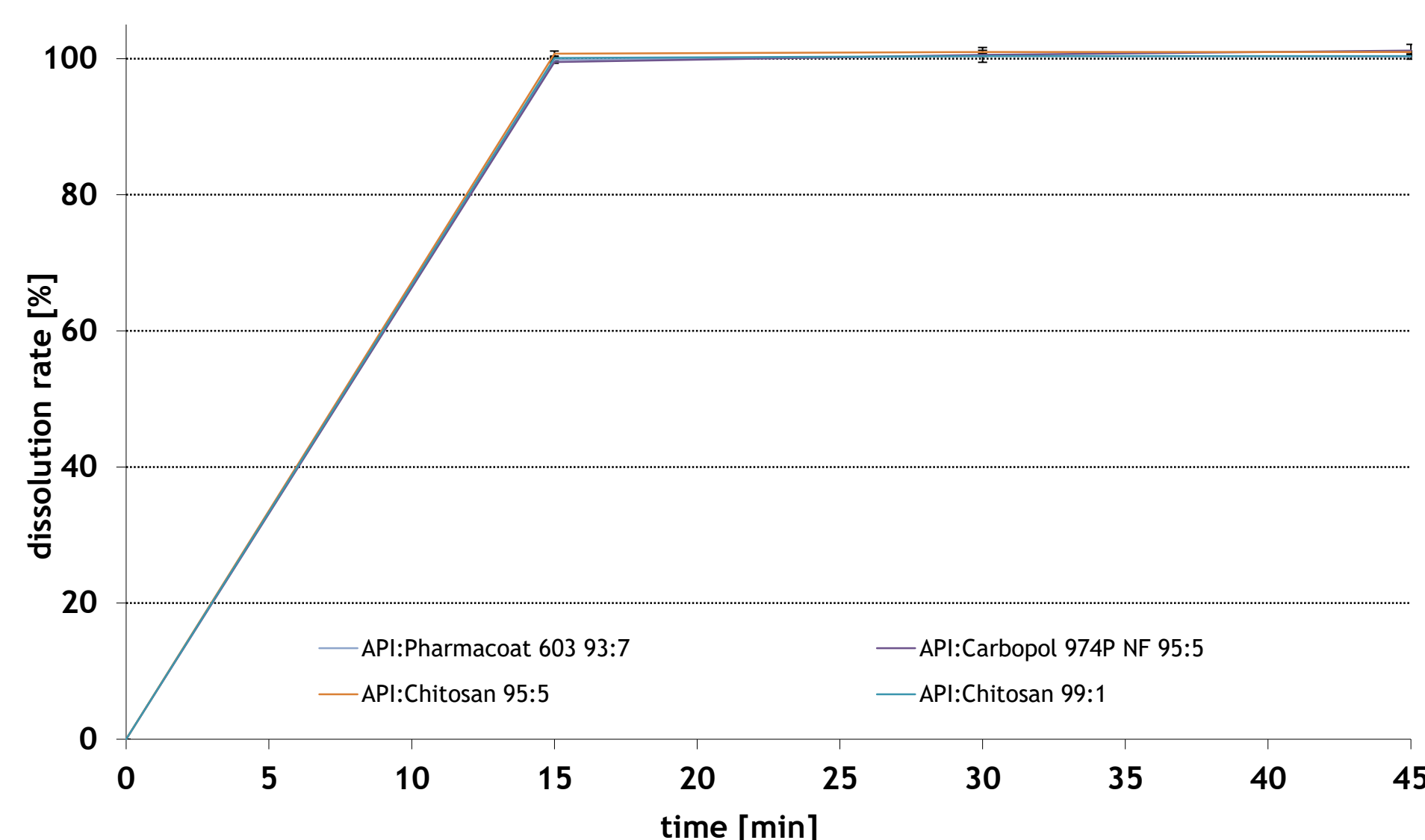


Figure 3: Dissolution in buffer pH 6.8 for 45 minutes by using paddle apparatus with 75 rpm (n = 3)

References

- [1] Uhlemann, H, Moerl, L. Wirbelschicht-Sprühagglomeration, Springer-Verlag, Berlin, Heidelberg (2000)
- [2] Jet apparatuses for batchwise or continuous processing and process using the jet bed apparatus; EP 1622711 (AT, CH, DE, DK); ZL200380101825.2 (CN); 4819365 (JP); 241143 (IN); US7993595 (US)

Acknowledgement

The results were partly obtained during the master's thesis of M. R. Schwander at Glatt Pharmaceutical Services GmbH Co. KG

Results

- Pellets with the target particle size between 315 and 500 µm were produced
- Round pellets with a narrow size distribution were obtained [Fig. 2, Table 1]
- Assay values of up to 98 % were analyzed. All pellet types show fast dissolution in pH 6.8

Conclusion

- The ProCell® Technology is a suitable technology for the development and manufacture of highly drug loaded pellets
- The manufacture of pellets with different polymers and API-to-polymer ratios is possible, resulting in high drug loads and immediate release dissolution profiles for all tested polymers
- Narrow particle size distributions and round pellets can be obtained