Glatt CPS® Technology: Case study

Monika Wentzlaff [1]; Annette Grave [1]; Norbert Pöllinger [1]
monika.wentzlaff@glatt.com
[1] Glatt GmbH, Pharmaceutical Services; Werner-Glatt-Str.1, 79589 Binzen, Germany

INTRODUCTION

The Glatt CPS® Technology (Complex Perfect Spheres) is a fluid bed rotor technology for producing spherical matrix pellets with a smooth surface and high density. Typically, microcrystalline cellulose is used as a basic excipient for pelletization using the CPS® Technology [1].

In the past extensive studies using soluble APIs (active pharmaceutical ingredient) as Metoprolol succinate [2] and Propranolol hydrochloride [3] were performed.

During this study matrix pellets containing an insoluble API shall be developed whereby a high drug load was envisaged (not less than 50 %). Furthermore, the particles shall be as spherical as possible, and the D90 value of the particle size distribution should not exceed 400 µm.

MATERIAL AND METHODS

Materials and formulation

Besides the water-insoluble API microcrystalline cellulose (Avicel® PH 105; FMC Internation Helath and Nutrition; Ireland) was used to build the matrix pellets. Purified water was used as spraying liquid. The respective formulations are given in Table 1.

Process No	1	2	3	4	5**
Material	Quantity				
	g	g	g	g	g
Solid starting material					
API	240	400	480	480	480
Avicel® PH 105	560	400	320	320	320
Spraying liquid					
Purified water *	960	960	768	700	700
Total solids	800	800	800	800	800

*volatile components were removed during the process
**reproduction of batch No 4

Table 1. API-Pellet formulations

Methods

Drug milling

The API was first milled by passing through a rotor sieve (Glatt GSF 180, screen 1 mm round hole). Afterwards, the pre-milled API was passed through a 200 µm sieve to ensure the absence of particles > 200 µm. The milled API was used for the CPS® direct pelletization process.

Direct pelletization

In comparison to previous studies [2, 3] the entire manufacturing (blending of API / excipient, pelletization and drying) was performed using the Glatt GPCG 2 fluid bed unit equipped with a CPS 3 insert. The process parameters are reflected in Table 2. The spraying rate was adapted during process development.

		Blending / Spheronization	Drying
$T_{Inlet\ air}$	°C	20 ± 5	45 - 100
$T_{Product}$	°C	20 ± 5	30 - 40
$V_{Inlet\ air}$	m³/h	45 ± 5	45 - 80
$DP_{Product}$	kPa	1.5 ± 0.5	1.5 ± 0.5
Rotation speed Rotor	rpm	1200	800 - 1200
Rotation speed Atomization air	rpm	6000 - 10000	--

Table 2. Pelletization process parameters, T = Temperature, DP = differential pressure.

Characterization of pellets

The API was characterized concerning the particle size distribution (sieve analysis, Retsch AS200 control g, laser diffraction, Malvern Mastersizer 2000). The pellets obtained were characterized with regard to aspect, particle size distribution (sieve analysis, Retsch AS200 control g), residual moisture (Karl Fischer), assay / purity and dissolution behaviour (phosphate buffer pH 6.8, n=3).

RESULTS AND DISCUSSION

Particle size distribution of API

Since a small particle size is mandatory for success of CPS processes the API was manipulated via milling and sieving. After manipulation the D90 value of the API was 170 µm.

Particle size distribution and aspect of pellets

By increasing the amount of API respectively decreasing the amount of Avicel PH 105 (batches No 1 and 2) the particle size increased) although the spraying rates (minimum: 14 g/min; maximum: 21 g/min; mean: 19 g/min) and total amount of water were kept constant (figure 1).

Aside from the inappropriate particle size distribution it was possible to build spherical pellets with smooth surface incorporating 30 % of API as well as 50 % API (figure 2).

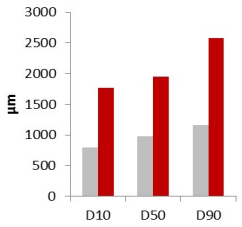

Figure 1. Particle size distribution of Batch No 1 (red) and 2 (grey)

Figure 2. Image of pellets containing 50 % of API (Batch No 2)

For incorporation of 60 % of API (batch No 3) the total amount of water was reduced, since it was seen in batches 1 and 2 that less water is needed to produce pellets with the same size while in the same time reducing the amount of binder. Furthermore, the spraying rates were decreased (minimum: 5 g/min; maximum: 12 g/min; mean: 10 g/min) to build up strong pellets The spraying rates are on the one hand influencing the particle size. On the other hand, reduced spraying rates lead to more stable pellets.

The pellets obtained were nearby the targeted particle size distribution (D10: 220 µm; D50: 310 µm; D90: 430 µm). Nonetheless, the pellets with a particle size > 315 µm clearly started to build agglomerates

Therefore, the total amount of water was reduced slightly whereby the spraying rates were kept constant (batches No 4 and 5). The pellets were dried for 30 min using the CPS®, to residual moisture of 2.5 %. The total process duration was 120 min.

As shown in figure 3 the pellets showed the targeted particle size distribution (D10: 200; D50: 290; D90: 400) although the D90 value of the API itself was 170 µm.

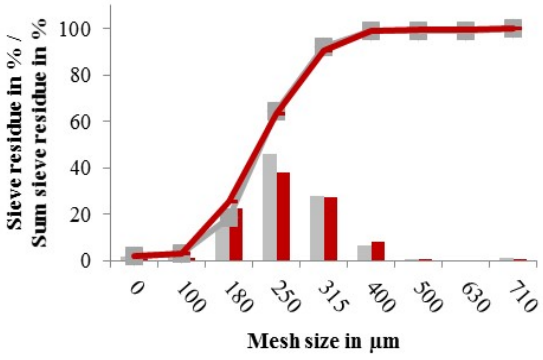

Figure 3. Particle size distribution of pellets containing 60 % of API; Batch No 4 (grey) and 5 (red).

The pellets showed a smooth surface and spherical shape (figure 4).

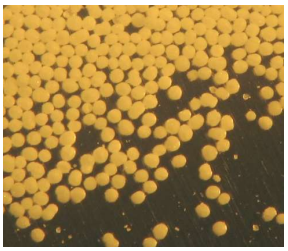

Figure 3. Image of pellets containing 60 % of API (Batch No 4).

The assay relative to theory was 97 % (batch No 4) The dissolution profile of batch No 4 is given in figure 4.

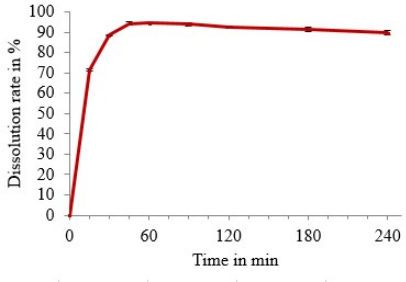

Figure 4. Dissolution profile of Batch No 4 (n=3 ± SD, phosphate buffer pH 6.8)

The pellets showed an immediate release profile.

CONCLUSION

By using the Glatt CPS®-Technology it was possible to develop spherical pellets using a water-insoluble API with a high drug load and the targeted particle size distribution. The pellets showed a spherical shape and smooth surface and the reproducibility of the process was demonstrated. Contrary to former studies [2, 3] the CPS® Technology was used as a stand-alone unit without pre-mixing of the powders in a high-shear granulator and drying using a fluid-bed unit. Nonetheless, the pellets were built and dried within short process times.

Data obtained are a profound basis for further studies using APIs with different physicochemical characteristics such as solubility and particle size distribution.

REFERENCES

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