Development of High Drug Load Multiparticulate Beads Using an Extrusion-Spheronization Process

Katie Pepper, Alexandra Whiteland, Dolly Jacob, Wu Lin, Peter Scholes

Quotient Sciences Limited, Ruddington, Nottingham, NG11 6JS UK

CONTACT INFORMATION: +44 (0)115 974 9000 (UK) +1-800-769-3518 (USA) info@quotientsciences.com

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PURPOSE

- Drug X is high solubility, high permeability BCS/DCS I small molecule drug.
- High dose and potential pediatric indication required multiparticulate formulation with not less than 80% drug loading to achieve flexible and low quantity dosing with potential for modified release via functional coating.
- Extrusion-spheronization is one of the most common processes to produce multiparticulate formulations, providing numerous advantages such as narrow particle size distribution, smooth coatable surfaces, relatively fast processing times.
- However, for highly soluble drugs, achieving a high drug loading in multiparticulates using extrusion-spheronization can be challenging.
- In this study, the impacts of formulation composition (grade of Avicel and Syloid content), processing parameters for wet massing and extrusion-spheronization on multiparticulate formation were investigated. An optimized composition and manufacturing process were identified.

METHODS

High Shear Wet Massing (Diosna high shear mixer)

- A dry blend containing Drug X, microcrystalline cellulose (Avicel) and up to 5% w/w mesoporous silicon dioxide (Syloid 244FP) was prepared.
- Wet granulation was carried out by drip feeding into the mixing bowl at 8g/min.

Extrusion (Caleva Extruder 20)

- Wet mass transferred to extruder using slow feeding speed.
- Extrusion performed through 1mm screen at 25 rpm.

Spheronization (Caleva Spheronizer 250)

- Extrudates transferred to Spheronizer fitted with 3x3mm cross hatch pattern plate.
- Spheronization performed at up to 1000rpm for maximum of 10 minutes
- Tray dried in hot air oven at 45°C

Characterization

- Yield
- Size distribution (sieve stack)
- Appearance (microscopy)
- Surface morphology (SEM)

Coating (Procept Fluid Bed)

- Selected formulations coated with Opadry as a seal coat

RESULT(S)

Wet Massing

During high shear wet massing, changes in impellor torque occur as a result of changes in cohesive forces in the wet powder bed, and can be used to assess end points. However, for these formulations the change in torque was not sensitive enough for end point identification. Optimal end point for extrusion-spheronization reached just before the traditional wet granulation end point.

Figure 1: *Wet mass end point (LHS), extrudate (RHS)*

Spheronization: Avicel PH 301 vs Avicel PH 101

Higher density Avicel PH 301 showed better results in terms of yield and particle size distribution compared to Avicel PH 101 which produced more fines (***Figure 2***). Smaller unwanted beads were also observed to be sticking to the larger beads in the product containing Avicel PH 101 (***Figure 3***).

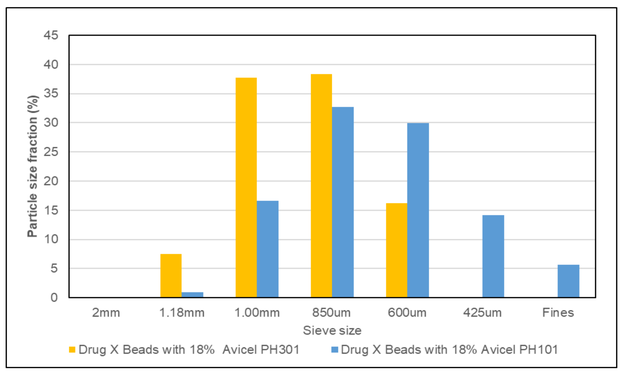

Figure 2: *Particle size distribution comparison of formulation with Avicel PH101 and Avicel PH301*

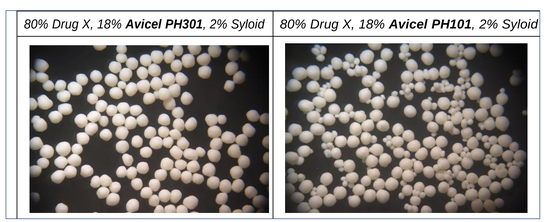

Figure 3: *Microscopy images of core beads with different grades of Avicel.*

Spheronization: Syloid Content and Spheronization Time

As Drug X is highly soluble, the inclusion of Syloid as a water absorbent can provide additional moisture balance and provide a more robust extrusion-spheronization process.

Sieve size	% particle size distribution		
	Bx001 (80% API + 20% MCC PH301)	Bx002 (80% API + 18% MCC PH301+ 2% Syloid)	Bx003 (80% API + 15% MCC PH301 + 5% Syloid)
2mm	0.6	0.1	1.9
1.18mm	22.2	9.6	28.6
1.00mm	46.3	39.8	38.4
850um	26.3	35.0	23.6
600um	4.4	14.1	6.1
425um	0	0.1	0
Fines	0	0.0	0
Total % of dried cores within collectable range	**77.1%**	**88.9%**	**68.0%**

- The composition containing 2% w/w Syloid achieved the highest yield of beads in the 600-1000 µm size range.
- No difference in shape was observed between 0-5% w/w Syloid, but a higher content did appear to have a slightly rougher surface area (Figure 4)
- Increased spheronization time from 2 to 10 minutes resulted in a smoother surface texture, but particle morphology did not change after 5 minutes.

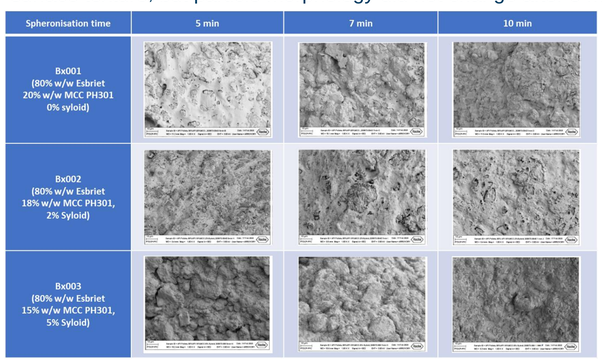

Figure 4: *SEM images of the multiparticulates with increasing Syloid content from Top to Bottom and increasing spheronization time from Left to Right.*

Coating

It was possible to successfully coat the beads with a Opadry seal coat (5% weight gain) resulting in a smooth shiny surface for moisture barrier or ready for further functional coating (Figure 5).

Figure 5: *Microscopy image of 5% Opadry QX seal coated beads..*

CONCLUSIONS

- Extrusion-spheronization is one of the most common processes for producing multiparticulate formulations.
- Achieving high drug loading for highly water soluble drugs can be challenging.
- In this study, a multiparticulate formulation with size range between 600 - 1000 µm and drug loading of 80% w/w was achieved for a BCS / DCS I drug.
- High density filler Avicel PH301 MCC was found to be a better excipient for high drug loading compared with the more conventional PH101 grade.
- Introducing small amounts of mesoporous silicon dioxide provided a positive impact to the manufacturing process.
- Process optimization especially during wet massing stage was also critical to the success of the final product.

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