The influence of binder addition techniques on continuous twin-screw melt granulation

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PURPOSE

As a solvent-free continuous process, twin-screw melt granulation (TSMG) is becoming an emerging processing method for improving the flowability and tabletability of powder blends. The intensive mechanical forces during TSMG enables effective binder distribution but jeopardizes API stability. Binder addition methods have shown to significantly impact granule growth and granule properties in batch melt granulation processes. However, the influence of binder addition methods on granule properties and API stability in TSMG has not been investigated.

This study compares three binder addition methods in TSMG: (1) pre-mixing API and binder (pre-mixing), (2) feeding drug at the main port and liquid inject molten binder (liquid injection), and (3) feeding binder at the main port and side stuffing API (side stuffing).

The objective is to investigate the effect of binder addition methods on

(1) granule formation

(2) stability of primary solid particles.

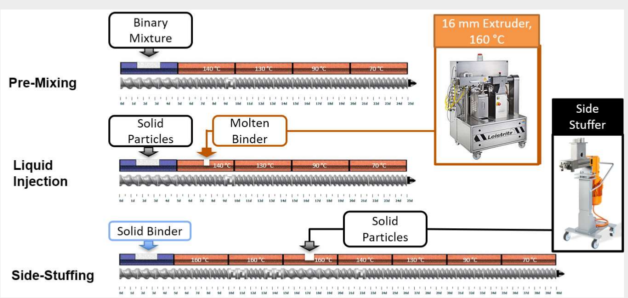
METHOD(S)

Leistritz ZSE 18 mm corotating twin-screw extruder was used as the main extruder to prepare granules containing 80% lactose monohydrate (LAC, solid particles) and 20% hydroxypropyl cellulose (HPC, Klucel™ ELF grade, binder).

In the pre-mixing method, LAC and HPC were pre-mixed in plastic bag and then feeded into the 18 mm extruder.

In the liquid injection method, LAC was feeded into the main port of 18 mm extruder. HPC was melted in a Leistritz Nano 16 mm twin screw extruder and injected through the liquid injection port to the main extruder.

In the side-stuffing method, HPC was feeded and melted in the main extruder. Lactose monohydrate was feeded downstream through a side stuffer.



RESULT(S)

Run #	Operational Parameters			Pre-Mixing			Liquid Injection			Side-Stuffing		
	Screw Speed (RPM)	Feed Rate (kg/h)	Specific Rate (g/revolution)	Granule temperature (°C)	Residence Time (s)	% Torque	Granule temperature (°C)	Residence Time (s)	% Torque	Granule temperature (°C)	Residence Time (s)	% Torque
1	100	1.0	0.167	57	26	6	56	47	8	55	36	7
2	300	1.0	0.056	59	10	8	60	11	11	61	13	11
3	200	2.0	0.167	61	12	7	58	18	9	67	21	13
4	100	3.0	0.500	74	29	10	63	34	8	68	30	12
5	300	3.0	0.167	67	8	9	60	11	12	65	15	13

Table 1. Process conditions of TSMGs with three binder addition methods.

- Pre-mixing, liquid injection, and side-stuffing methods had similar trend of granule temperature, but the pre-mixing caused the highest granule temperature due to the deficient lubrication of molten binder.
- The three binder addition methods had similar range of residence time. Short residence time was achieved at high screw speed and high feed rate.
- Side-stuffing caused the highest torque among three methods, because of the resistance of the compacted solid particles at side-stuffing port.

Granule Size Distribution

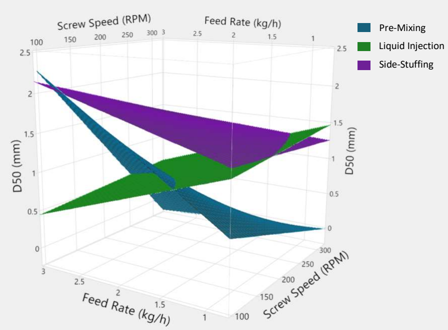


Figure 1. D50 of granule size distribution

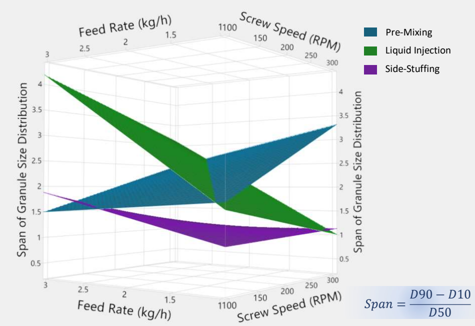


Figure 2. Span of granule size distribution

- Large granule and uniform size distribution of pre-mixing method were obtained at high specific rate (high feed rate and low screw speed). Granule formation in pre-mixing method was dependent on high shear stress and efficient heat transfer at high specific rate.
- Large granule and uniform size distribution of liquid injection was achieved at low specific rate (low feed rate and high screw speed). Granule formation in liquid injection method was based on intensive dispersing of molten binder from injection nozzle at low specific rate.
- Granule size of side-stuffing was the largest and most uniform among those of three methods. Coating of molten binder on screw elements in main extruder caused large surface area of binder and facilitated binder distribution in granules.

Primary Solid Particle Size

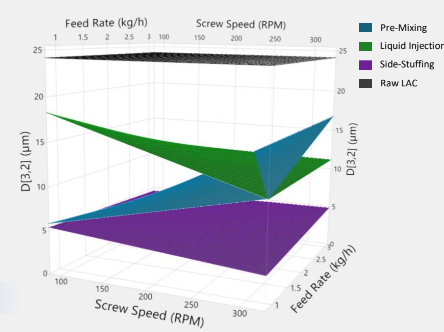


Figure 3. Sauter mean diameter of LAC after leaching HPC in ethanol

- Compared to pre-mixing method, Liquid injection method reduced size reduction of LAC, due to the lubrication effect of molten binder.
- Side-stuffing caused significant size reduction of LAC, because of the strong shear stress at side-stuffing port.

CONCLUSION(S)

1. The binder addition methods influenced the TSMG mechanism and the stability of primary solid particles.
2. Liquid injection method maintained the stability of solid particles better but required stronger mechanical force for binder distribution.
3. The side stuffing method achieved more uniform granule size distribution but caused severe size reduction of solid particle.

ACKNOWLEDGEMENT

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Methods

Leistritz ZSE 18 mm corotating twin-screw extruder was used as the main extruder to prepare granules containing 80% lactose monohydrate (LAC) and 20% hydroxypropyl cellulose (HPC, Klucel™ ELF grade). In the pre-mixing method, LAC and HPC were mixed in plastic bag and feeded into the 18 mm extruder. In the liquid injection method, LAC was feeded into the main port of 18 mm extruder. HPC was melted in a Leistritz Nano 16 mm twin screw extruder and injected through the liquid injection port to the main extruder. In the side-stuffing method, HPC was feeded and melted in the main extruder. Lactose monohydrate was feeded downstream through a side stuffer.

DOE was used to examine the effect of screw speed and feed rate in each binder addtion method. The responses of DOE include residence time, granule temperature, granule size distriubtion and size distribution of LAC. Granule size distribution was measured using Camsizer®. Particle size of LAC in the granules was characterized using Sympatec® cuvette.

Results

The screw profiles for the three binder addtion methods were designed to have the same transport distance. The residence time of material was not significantly affected by different binder addtion method. The liquid injection method significanlty reduced granule temperauture by 5 °C, compared to the other two methods.

The size of granules changed considerablely with different binder addition methods. In the pre-mixing method, granule size was positively related to the degree of fill. High degree of fill caused strong consolidation in granule growth and faciliated the granule growth. In the liquid injection method, granule size was positively related to the specific mechanical energy input. Because the molten binder contacted with solid particles through the narrow injection nozzle, the liquid injection method required strong mechanical force to distribute molten binder. In the side-stuffing method, HPC granules size was not sensitive to the operation parameters. Molten binder was coated on the surface of screw element in the main extruder. The contact area between molten binder and solid particles was large and led to uniform binder distribution.

The primary particle size of LAC (22.3 µm) was reduced in all three binder addtion methods. The Sauter mean diameters of LAC were 10.0 µm in pre-mixing method, 12.3 µm in liquid injection method, and 4.5 µm in side stuffing method. The molten binder lubracated the solid particles and reduced the breakage of solid particle in liquid injection method. However, the side stuffer strongly pressurized LAC and caused severe size reduction.

Conclusion

The binder addition methods influenced the TSMG mechanism and the stability of primary solid particles. Liquid injection method maintained the stability of solid particles better but required stronger mechanical force for binder distribution. The side stuffing method achieved more uniform granule size distribution but caused severe size reduction of solid particle.

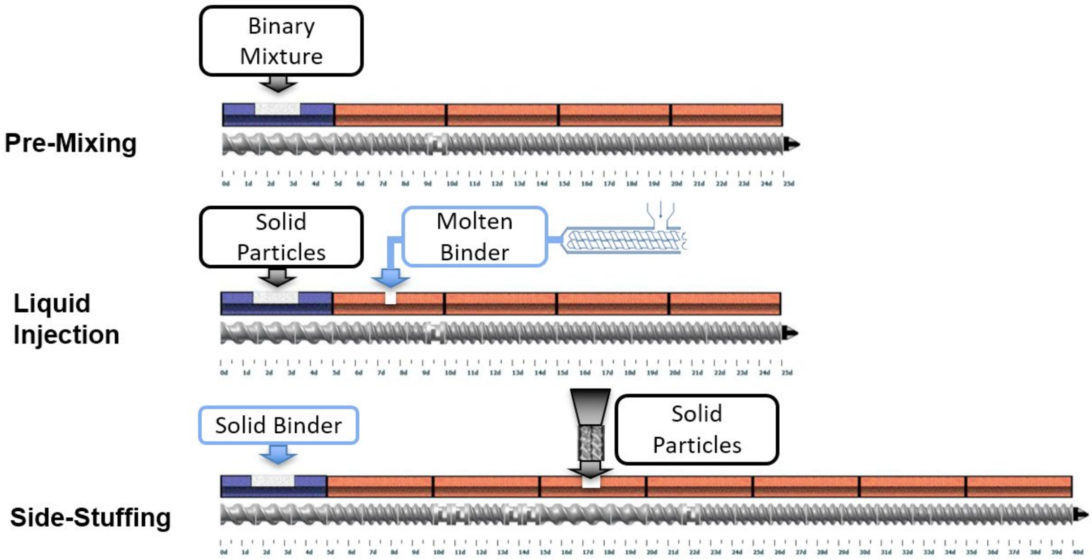
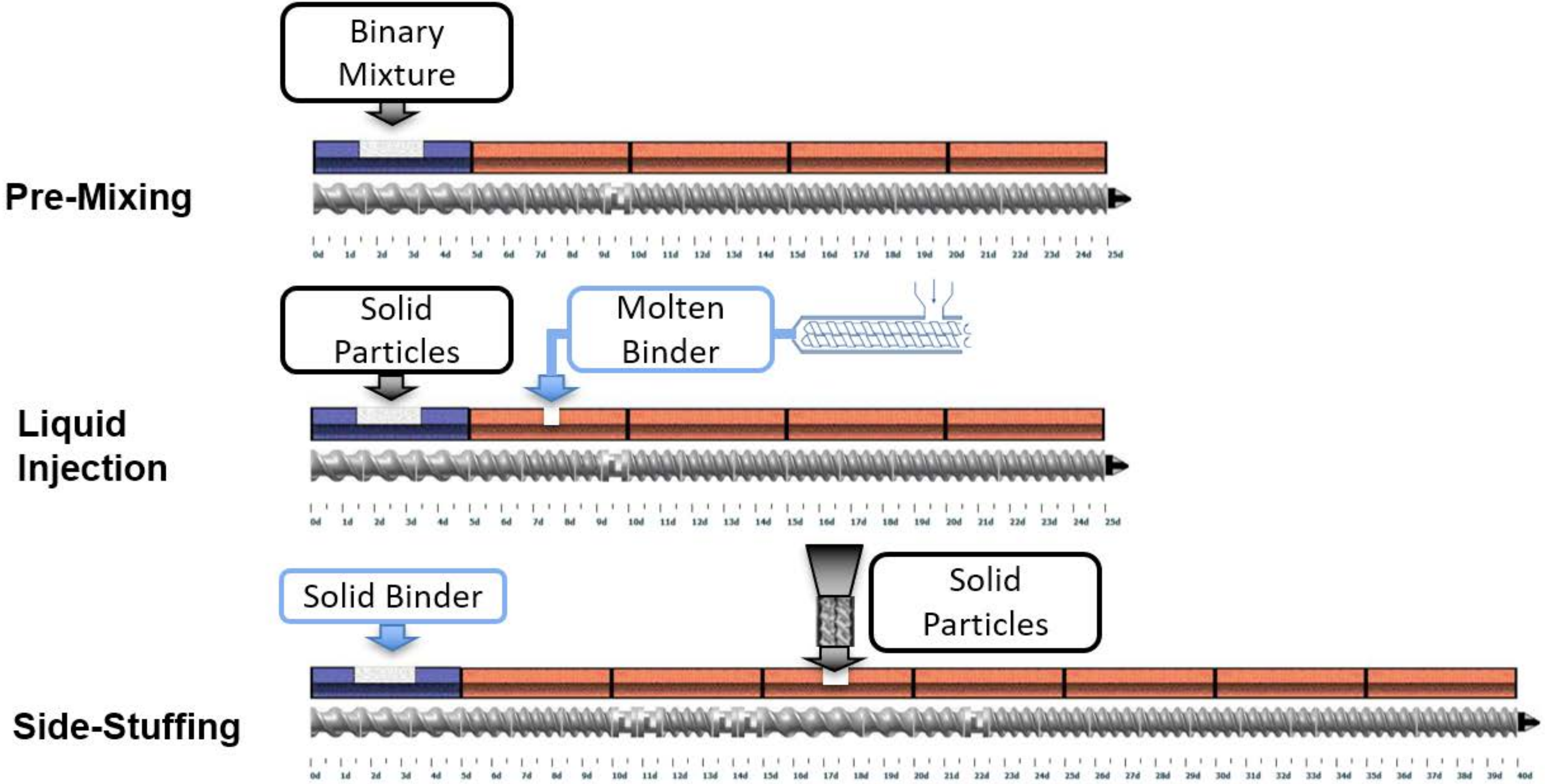


Figure 1. Graphic scheme of binder addition methods, e.g. pre-mixing, liquid injection, and side-stuffing.



Binary Mixture
Pre-Mixing
Solid Particles
Molten Binder
Liquid Injection
Solid Binder
Solid Particles
Side-Stuffing