M5095

Comparison Of Various Operating Conditions And Formulations On A Counter-rotating, Intermeshing Twin Screw Extruder

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PURPOSE

To compare various extrusion operating conditions and formulations to enhance solubility and recovery of Meloxicam (MLX) in Copovidone on a counter-rotating, intermeshing twin screw extruder (TSE). (Counter-rotating TSE's have different pumping and mixing mechanisms as compared to co-rotating TSE's) (1, 2).

OBJECTIVES

1) Determine processing parameters & formulations necessary to achieve near 100% recovery of MLX.
2) Analyse viability of counter-rotating TSE's in pharmaceutical processing.

METHODS

Based on the initial development work on a co-rotating TSE, where Meloxicam in Copovidone was successfully solubilized and recovered using a Leistritz model nano 16 mm corotating TSE (3) and Leistritz co-rotating ZSE 18 mm. Further analysis was performed using a Leistritz Micro-27 mm counter-rotating TSE at 28:1 L/D. The goal was to increase the residence time (RT) while managing shear and energy input from the screws, using distributive mixing elements (Figure 1). Conditions (Table 1) of 2 kg/hr, 75-150 rpm, and zone temperatures between 122-155 °C were used. Formulations varied between 10-20% Meloxicam, 0-11% Meglumine (MEG) as a stabilizer, and 69-90% Copovidone. The Copovidone was dried at 65 °C for two hours before processing and vacuum was used in the final vent. Extrudate clarity and percent recovery were used to determine solubility and degradation (Table 2). Percent recovery was measured using high performance liquid chromatography with a retention time of 12.6 min.

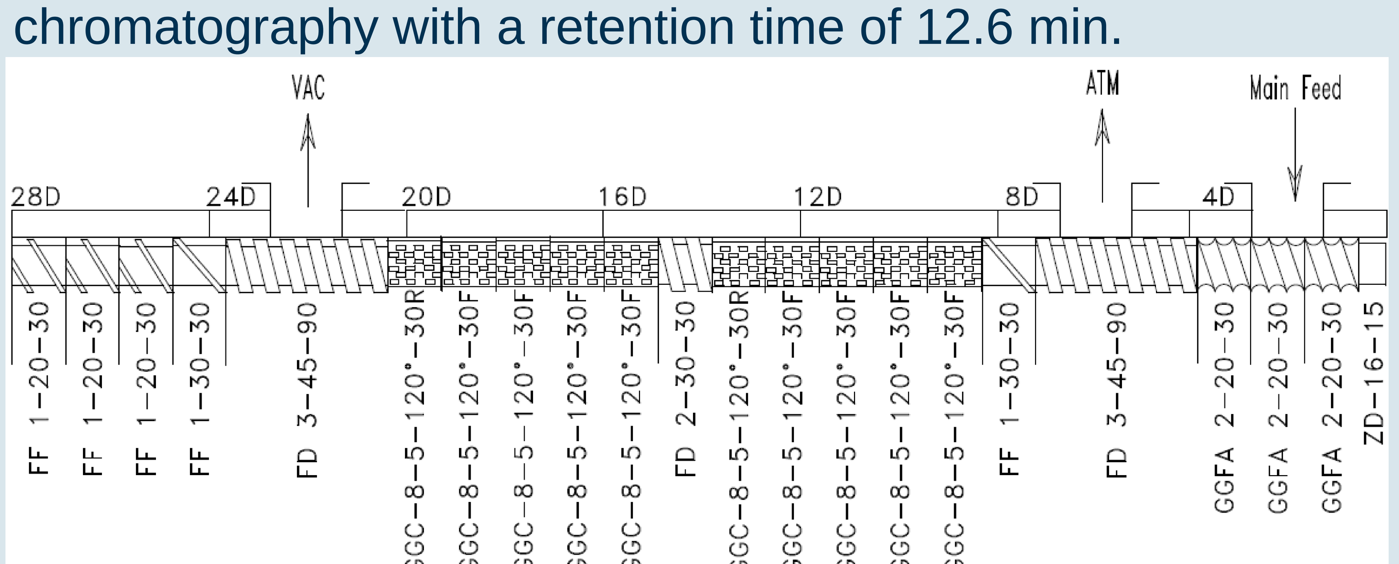

Figure 1: Leistritz Micro 27mm counter-rotating, intermeshing 28:1 L/D screw design.

RESULTS

Several operating conditions produced degradation: high screw rpm, high operating temperatures, low feed rates, and aggressive screw designs with high shear and high energy input to enhance solubility. Several operating conditions produced low solubility of MLX: low rpm, low operating temperatures, high feed rate, particle size, and a weak screw design with low shear and low energy input to prevent degradation.

Formulations of 10, 15, and 20% MLX were used with and without Meglumine. The clarity and amorphous content of the extrudate increased dramatically with lower rpm and tighter residence time distribution (RTD), both with and without the addition of Meglumine. When decreasing the rpm from 150 rpm to 75 rpm, RT was approximately 5 minutes while RTD narrowed and the recovery of MLX increased by 4.2% while remaining amorphous. With the addition of Meglumine at a 1.82:1 ratio, the extrudate became amorphous at higher concentrations, up to 20%, and the recovery further increased to 99.2 - 99.4%.

Table 1: Run conditions from Micro 27 mm counter-rotating trials.

Run #	Formulation (MLX : MEG : Copovidone)	Screw RPM	Rate (kg/hr)	Torque (%)	Melt Pressure (psi)	Melt Temp. (°C)	Barrel Set Points (°C)
1	10:0:90	150	2	43	240	161	122-122-133-144-144-155-155
2	10:0:90	75	2	69	420	152	122-122-133-144-144-155-155
3	15:0:85	75	2	62	380	152	122-122-133-144-144-155-155
4	20:0:80	75	2	62	380	153	122-122-133-144-144-155-155
5	10:5.5:84.5	75	2	50	380	153	144-144-144-144-144-155-155
6	15:8.25:76.75	75	2	49	370	153	144-144-144-144-144-155-155
7	20:11:69	75	2	47	330	152	144-144-144-144-144-155-155

Table 2: Results from Micro 27 mm counter-rotating trials.

Run #	MLX Loading (%)	MEG Loading (%)	Recovery (%)	Std. Dev	Visual Assessment	Sample
1	10	0	92.9	0.158	Semi-Crystalline	
2	10	0	97.1	0.00	Amorphous	
3	15	0	97.9	0.10	Crystalline	
4	20	0	98	0.03	Crystalline	
5	10	5.5	99.2	0.01	Amorphous	
6	15	8.25	99.4	0.01	Amorphous	
7	20	11	99.2	0.45	Amorphous	

CONCLUSION

While the co-rotating, intermeshing, TSE is more commonly used in pharmaceutical R&D and production, the counter-rotating, intermeshing TSE is a viable tool to successfully process these formulations. Energy input must be strategically balanced to perform mixing functions without degradation of API. Changes of screw rpm, temperature, residence time, residence time distribution, and feed rate all played roles in both degradation and solubility. Optimized conditions and formulation development should be defined on a case to case basis to maximize results. In this case, lower temperatures, longer but tighter RTD, and the addition of a stabilizer to the formulation all were factors that helped increase recovery to near 100%.

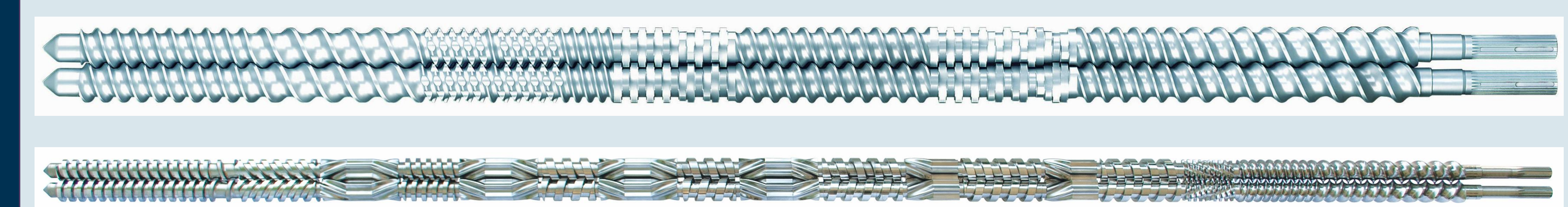

Figure 2: Generic co-rotation vs. generic counter-rotation screw design.

ACKNOWLEDGEMENTS

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