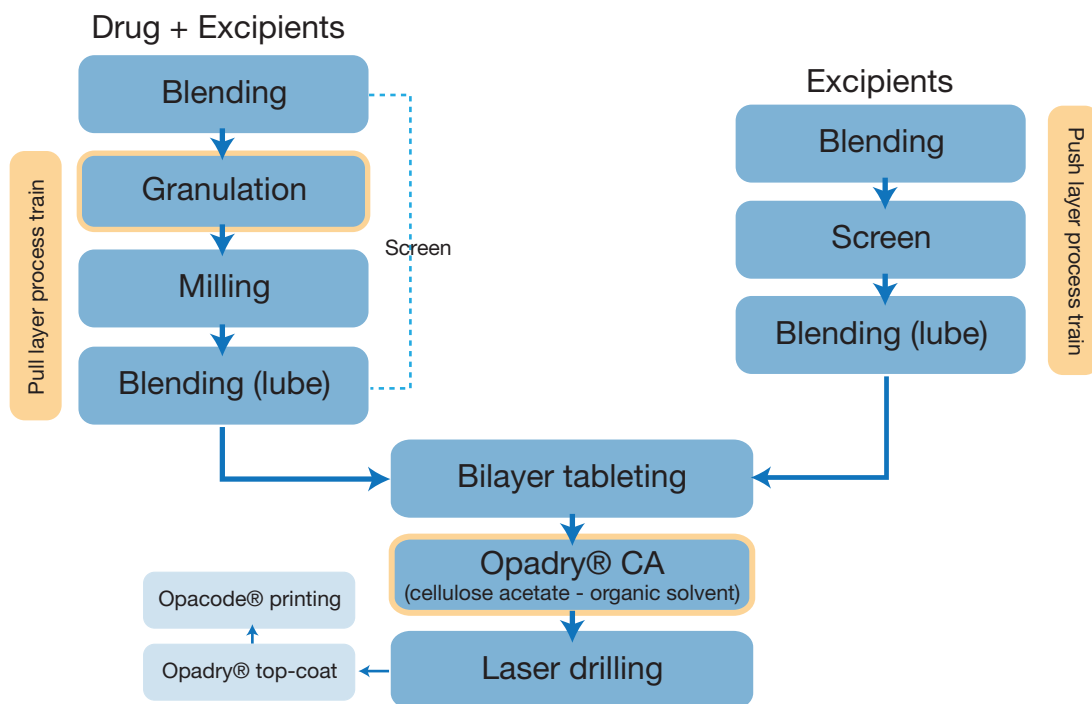


Push-Pull Osmotic Pump (PPOP) Manufacturing and Processing

Manufacturing Steps: Multi-Unit Operations



Granulation

Granulation processing variable	Recommended starting point
Percentage intra-granular POLYOX™	50-100%
Granulation fluid	Ethanol (or IPA) : water (85:15)
Impeller speed	50-500 rpm (300-500 rpm)*
Chopper speed	1000-3000 rpm (preferably off)*
Percentage granulation fluid/blend (fluid/dry blend* 100)	10-15%
Addition rate (g/min)	20-80 (75-80)*
Post addition mixing time (high-shear)	0.5-2 min
Drying conditions (recommended)	Tray drying 40°C for 16h

Note: wet milling may be required to control particle size distribution
 * shows possible parameter range for larger batch sizes and/or equipment

CA Film coating

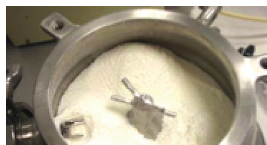
Coating processing variable	Recommended starting point
Inlet temperature (°C)	40-42
Exhaust temperature (°C)	31-33
Product temperature (°C)	30-31
Pan speed (RPM)	15**
Spray rate (g/min)	20**
Gun to bed distance (inch/cm)	2.3/6.35**
Air flow (cfm/CMH)	60/102**
Atomizing air (psi/bar)	13/0.97**
Pattern air (psi/bar)	7.6/0.52**

** parameters are for batch size of 1.5kg

High Shear Granulation: Importance in controlling end point



Dry blend



Under wetted



Granulated mix



Over wetted

Manufacturing: Potential Critical Processing Parameters

Variable	Critical Processing Parameters [CPP]	Potential Impact on QTPP*	Experimental data available from Colorcon
API dispersivity (plume)	Blend uniformity of API (pull layer) Blend uniformity of Osmogen (push layer)	+	✓
Drug (pull) layer compressibility	Granulation method / parameters Wet milling method / parameters Drying method / parameters	++	✓
Push layer compressibility	Granulation method / parameters Wet milling method / parameters Drying method / parameters	++	✓
Bilayer tablet hardness	Compression force during pull layer, then push layer Speed of compression press (dwell time) Scraper and feed-frame setting Hopper auger, force feeder setting (if present) Vacuum setting during compression	++	✓
Semipermeable membrane : thickness, density and clarity (transparency)	Coating parameters	+++	✓
Laser hole size and position	Laser drilling set-up parameters, Blend uniformity of dye	+	✓

**Target dissolution specification available on request

*QTPP - Quality Target Product Profile

Tableting Guidelines - Single Radius Concave or Double Radius Concave

Weight (mg)	Tooling size		Osmotic hardness (kP)
	(mm)	(inch)	
111	5.5	7/32"	3-5
323	8.5	11/32"	5-7
442	9.5	3/8"	5-7
617	11.0	7/16"	8-10
650	12.5	1/2"	9-11

- Typical target hardness for osmotic tablet ~ 20-30% less than IR tablets
- Friability not compromised by decreasing tablet hardness for osmotic tablets

POLYOX™

For more information, contact your Colorcon representative or call:

North America
+1-215-699-7733

Europe/Middle East/Africa
+44-(0)-1322-293000

Asia Pacific
+65-6438-0318

Latin America
+54-11-5556-7700

You can also visit our website at www.colorcon.com



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