PQRI Workshop:
Managing Excipient and API Impact on Continuous Manufacturing
May 17 – 18, 2022

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The Need for Novel, Coprocessed or Modified Excipients Designed for Purpose in CM Processes

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Agenda

1. Survey: CM Technologies and Excipients
2. Coprocessed Excipients
   - Versus Individual Blends
   - Performance in CM
3. Summary

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1 Survey: CM Technologies and Excipients

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Thirty-seven industry practitioners were interviewed.

The survey included drug manufacturers, equipment vendors and excipient suppliers.

Pharmaceutical drug manufacturers / Excipient customers	29	Examples: VERTEX (US), NOVARTIS (US), JINA Pharmaceuticals Inc. (US), SUN PHARMA (IN), Paraza Pharma, Inc. (US), mundipharma (Singapore), PURDUE (US), CONTINUUS pharmaceuticals (US), Lilly (US), Bristol-Myers Squibb (US), Patheon (US), janssen (BE), CutisPharma (US), GILEAD (US), APOTEX (US), MERCK (US)
Pharmaceutical equipment manufacturers	5	Examples: coperion (DE), Glatt (DE), IMA Sustain Ability (IT), KORSCH The Specialist. (DE), Leistritz (DE)
Others (pharmaceutical consultants, excipients manufacturers etc.)	3	Examples: JRS PHARMA The Global Excipient Maker (US), Ingredion (IN), avantor (TW)

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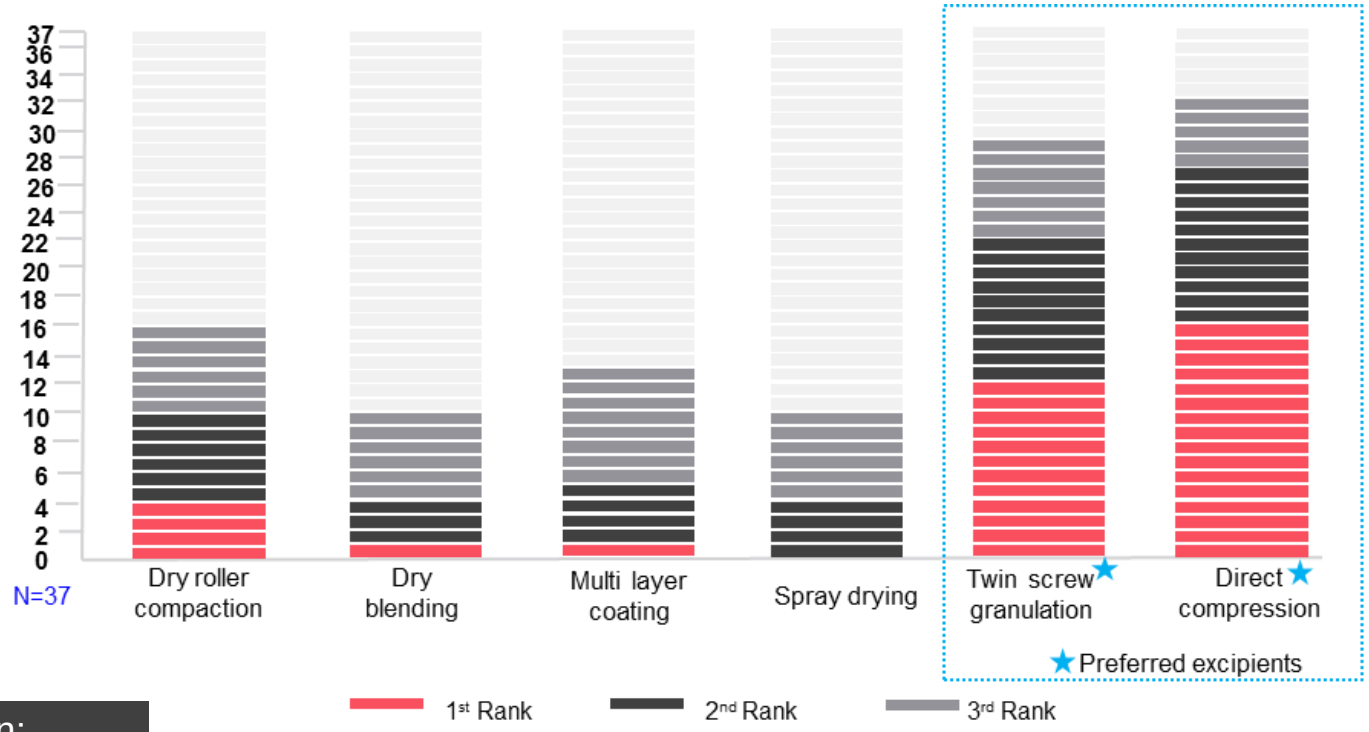
Direct compression, twin screw granulation and roller compaction are the preferred technologies for CM.



Observation:

• Out of different technologies such as dry roller compaction, dry blending, multi layer coating, spray drying, twin screw granulation and direct compression, **32 respondents (86%)** out of **37 respondents** have suggested to use direct compression for continuous manufacturing.

Source (s): Primary interviews with Vertex (US), Eli Lilly (US), Janssen (BE), CONTINUUS Pharma (US), etc., secondary sources such as company websites and

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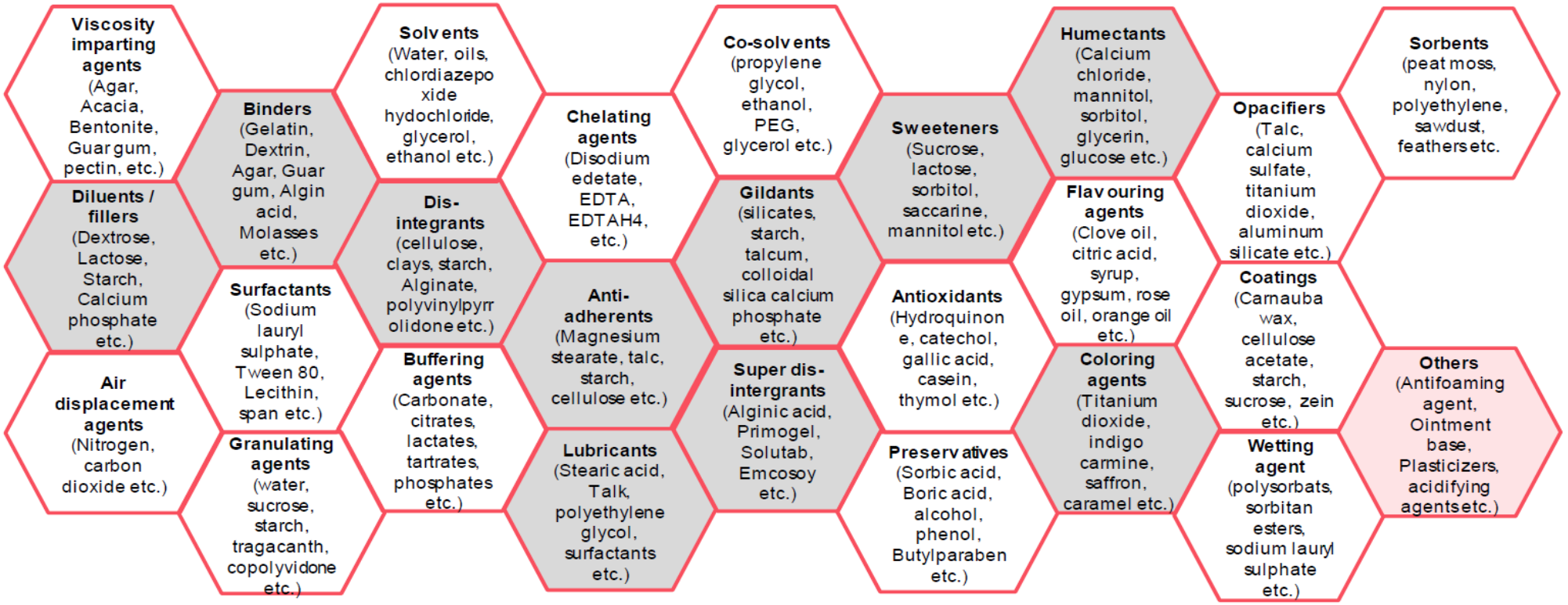
The most important excipient types were aligned with the formulation needs for the preferred technologies.



Important excipient types

Other excipients

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Excipient types are similar for both batch and CM, the only difference lies in selection of the physical properties and grades of the excipients, when they are to be used for CM

Modification required in excipients properties / types when they are used in continuous manufacturing compared to batch manufacturing process ▶ ☐ YES ☑ NO

Although no modification / alteration is required in the excipient types / properties, but selecting the appropriate type / grade and properties of excipients for CM are highly important. Some grade of excipients offer better properties and are highly suitable for continuous process, again there is a common class of excipients that can be used for both batch and continuous process. So, it totally depends upon the drug to be manufactured and process conditions.

Most preferred excipient properties for CM

High priority	• Flowability • Compressibility • Compactibility
Medium priority	• Stability • Binding ability • Mixing potential
Low priority	• Disintegration • Anti-adhesion

Most preferred excipient types for CM

• MCC	• Mannitol
• Lactose	• PVP
• Silica	• Magnesium stearate
• Starch	• Calcium carbonate
• Sorbitol	• Calcium phosphate

Note: These excipients contain majority of the preferred properties, but not all

Source (s): Primary interviews with Vertex (US), Eli Lilly (US), Janssen (BE), CONTINUUS Pharma (US), etc., secondary sources such as company websites and

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No excipient met the Top 3 criteria for Flowability, Compressibility & Compactability.

Excipients preferred for both batch and continuous process	Major properties preferred for continuous manufacturing of drugs (*highlighted in green colour*)							
	Flowability	Compressibility	Compactibility	Mixing potential	Binding ability	Quick disintegration	Stability	Anti-adhesion
MCC		■			■	■	■	■
Lactose	■			■	■			
Silica	■					■		
Starch				■	■	■		
Sorbitol		■		■			■	
Mannitol			■	■				
PVP			■		■		■	
Magnesium stearate	■							■
Calcium carbonate		■		■			■	
Calcium phosphate	■		■	■				

Note: ■ *indicates major properties of the excipients preferred for continuous manufacturing of drugs.*

□ *indicates properties that have negligible / no importance for excipients preferred for continuous manufacturing of drugs.*

- Excipient types are similar for batch and continuous – the selection process is not

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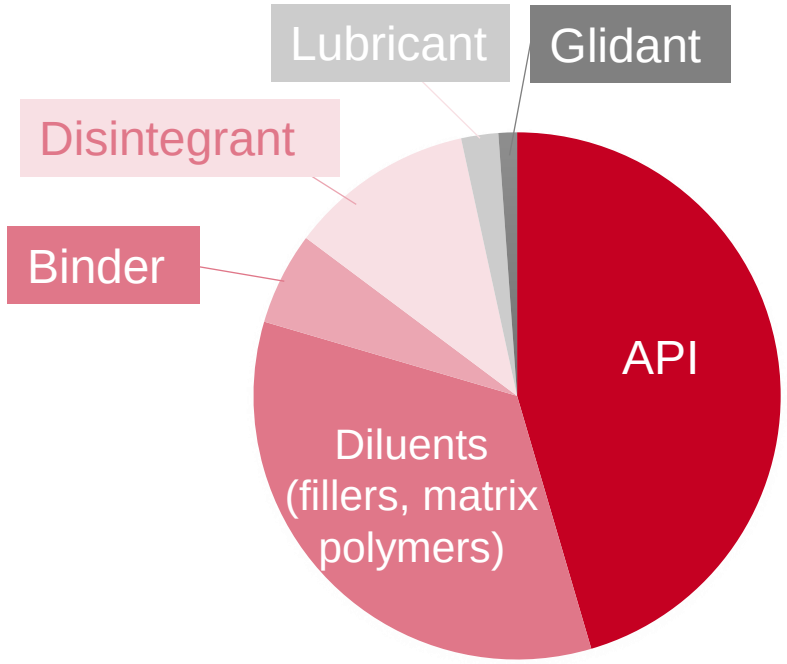
We set out to create a novel excipient that met the Top 3 criteria for flowability, compressibility and compactability.

There are five excipient types in a typical IR tablet.
Diluents, binders and disintegrants are the most common types for both batch and CM.



Typical excipient types in an IR tablet

Should we develop:

a diluent?
a binder?
an all-in-one?

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We defined a Quality Target Product Profile (QTPP) to drive R&D activities and meet the needs of CM formulators.

	Parameter	Values	Method
Physicochemical	Particle size (distribution)	>6.0	ZoomLab™
	Powder density	>6.0	ZoomLab™
	Powder flow	>6.0	ZoomLab™
	Flowability	≤32° (excellent)	Angle of repose (Ph.Eur. 2.9.36)
Performance	Tablettability	>6.0	ZoomLab™
	Compression pressure	~180 MPa [max. 300 MPa]	USP 1062
	(Ejected) solid fraction	~0.85 [range 0.80 to 0.90]	USP 1062
	Ejection force [stress]	<200 N [<3.0 MPa]	USP 1062
	Tablet strength (tensile strength)	>2.0 MPa [min. >1.7 MPa]	USP 1062
	Friability of tablets	<1.0%	Friability (Ph.Eur. 2.9.7)
	Disintegration time	1 to 5 (15) minutes	Disintegration (Ph.Eur. 2.9.1)
	Dissolution	>85% in 15 minutes	Dissolution (Ph.Eur. 2.9.3)

Source: T. Cech, European Pharma Application Lab, Pharma Solutions, BASF SE, Ludwigshafen, Germany

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What are Coprocessed Excipients?

Coprocessed excipients are composed of different functional ingredients combined into a single product

Aiming to:

- Enhance functional material properties
- Optimize performance
- Overcome API's blending and processing challenges.

Resulting in:

- Cost savings
- Faster drug development, and
- Reduced time-to-market

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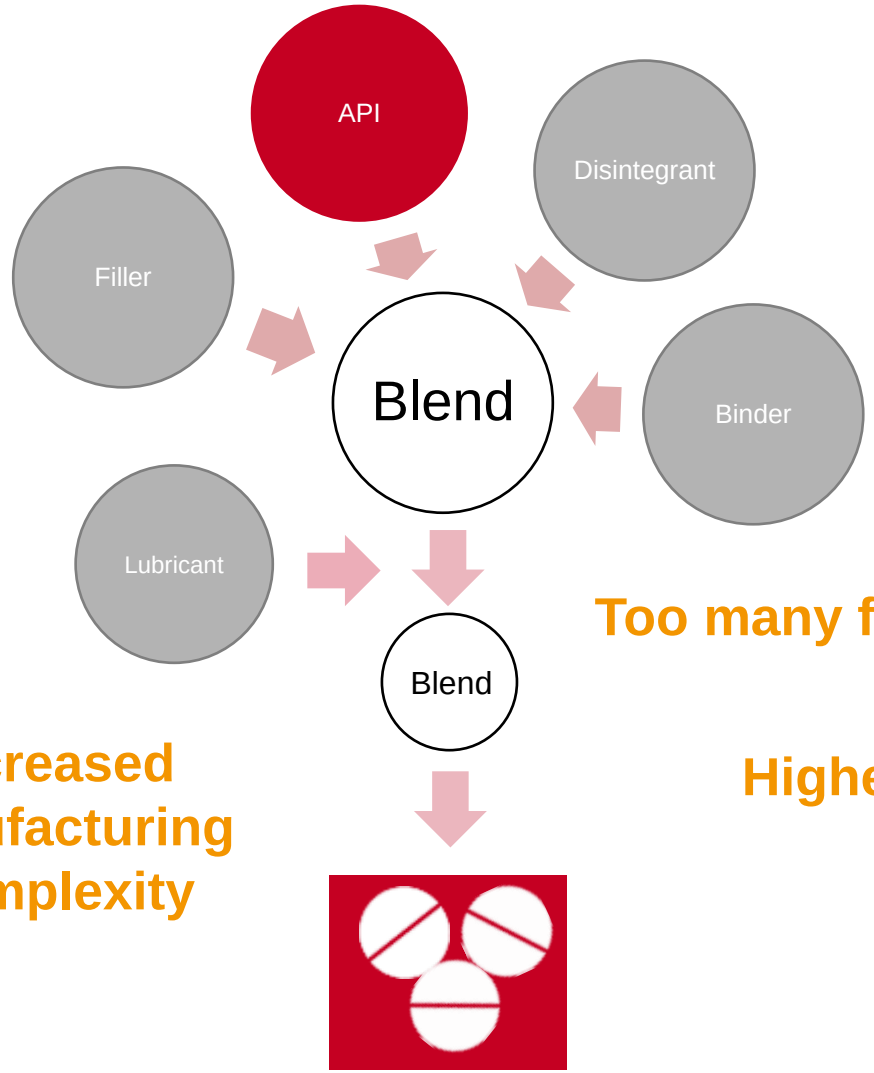
Coprocessed excipients allow for a simpler feeding process & control strategy.

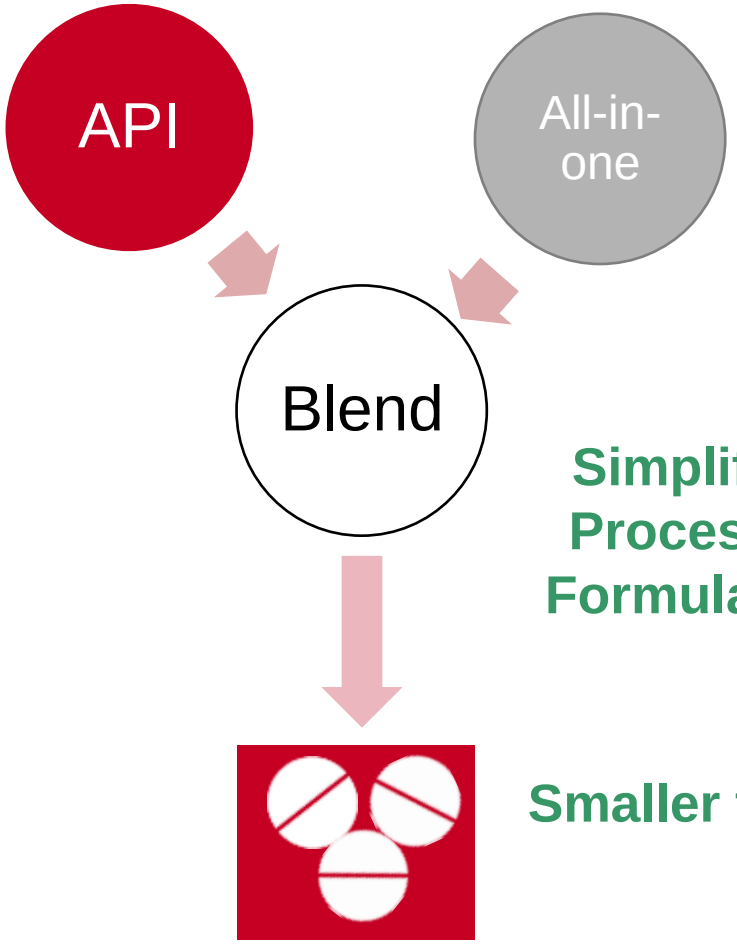


Increased Manufacturing Complexity

Too many feeders /excipients

=

Higher variability!



Simplified Process & Formulation

Smaller footprint

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We created Kollitab™ DC 87 L as an *all-in-one* tableting solution for batch and CM processes.

Composition

Filler: Lactose monohydrate
MDE: 4384 mg for Tablets*
*(Ph.Eur., USP/NF, JP**), (~87%)*

Disintegrant: Crospovidone
MDE: 1680 mg for Tablets*
(Ph.Eur., USP/NF, JP), (~9%)

Binder: PVA-PEG copolymer (Kollicoat® IR)
MDE: 76 mg for Tablets*
(Ph.Eur., USP/NF, JPE), (~3%)

Lubricant: Sodium stearyl fumarate, SSF
MDE: 85 mg for Tablets*
(Ph.Eur., USP/NF, JPE), (~1%)

*MDE: Maximum Daily Exposition – IID List
**Lactose hydrate

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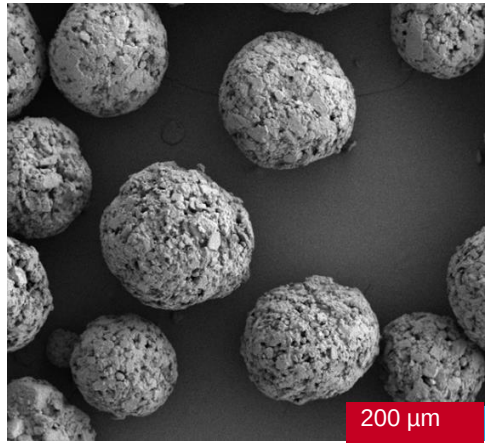
We optimized Kollitab's composition to have optimal Flowability, Compressibility and Compactability (measured in tablets).



Flowability

Bulk [g cm^{-3}]	**0.56**
Tapped [g cm^{-3}]	**0.61**
Hausner Ratio	1.09 (Excellent)
Angle of Repose [°]	27 (Excellent)
Compressibility Index [%]	8 (Excellent)

Particle size (Malvern):

d_{10} [µm]	**76**
d_{50} [µm]	**158**
d_{90} [µm]	**275**

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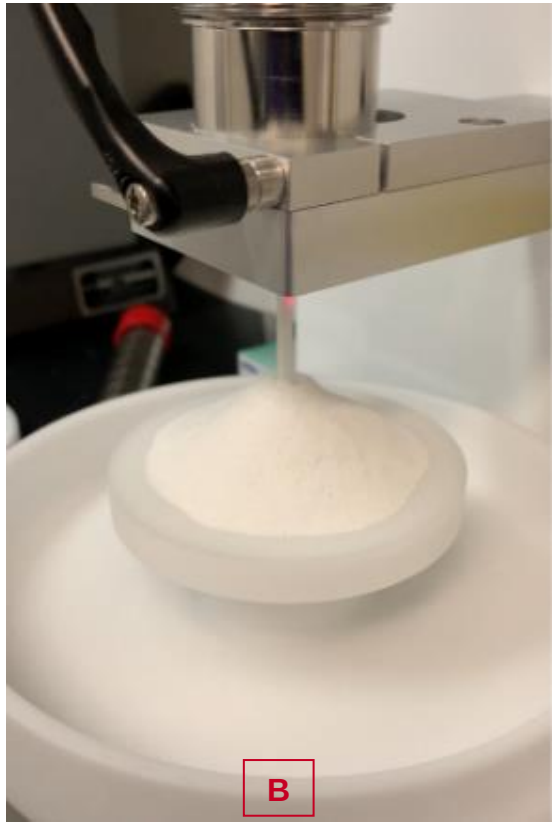
Coprocessed excipient flowability was significantly better than a comparable blend of its individual components.



A. Kollitab™ DC 87 L (6 mm nozzle)
B. Kollitab™ DC 87 L + 10% vardenafil HCl (6 mm nozzle)
C. Lactose blend* (10 mm nozzle)
D. Lactose blend* + 10% vardenafil HCl (25 mm nozzle)

***Lactose Blend:**
87% Lactose, spray dried
9% crospovidone (Kollidon® CL F),
3% copovidone (Kollidon® VA 64)
1% SSF

Equipment Erweka GTB

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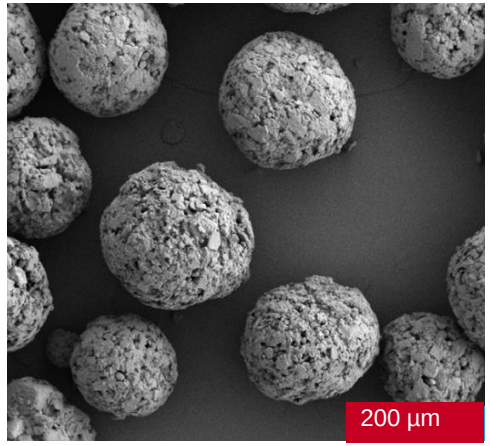
We optimized Kollitab's composition to have optimal Flowability, Compressibility and Compactability (measured in tablets).



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Compressibility

Material @ 15.0 kPa in FT4	**Compressibility** (%)	**Bulk** (g/mL)	**Cohesion** (kPa)
Kollitab™ DC 87 L	4	0.56	0.21
Lactose Blend*	10	0.53	0.46
(API) Vardenafil HCl	26	0.42	1.46
90% Kollitab™ DC 87 L+ 10% vardenafil HCl	6	0.58	0.22
90% Lactose Blend* + 10% vardenafil HCl	11	0.54	0.47

*** Individual Excipients / Lactose Blend:**
87% Lactose, spray dried
9% crospovidone (Kollidon® CL-F,
3% copovidone (Kollidon® VA 64)
1% Sodium Stearyl Fumarate

Compressibility is a measure of the % change in volume to an applied normal force.

- Affected by moisture content, temperature, particle size and cohesivity.
- During feeding and refills, head pressure will compress powder on the screws and changes in feed factor / PERT and variability can be seen.

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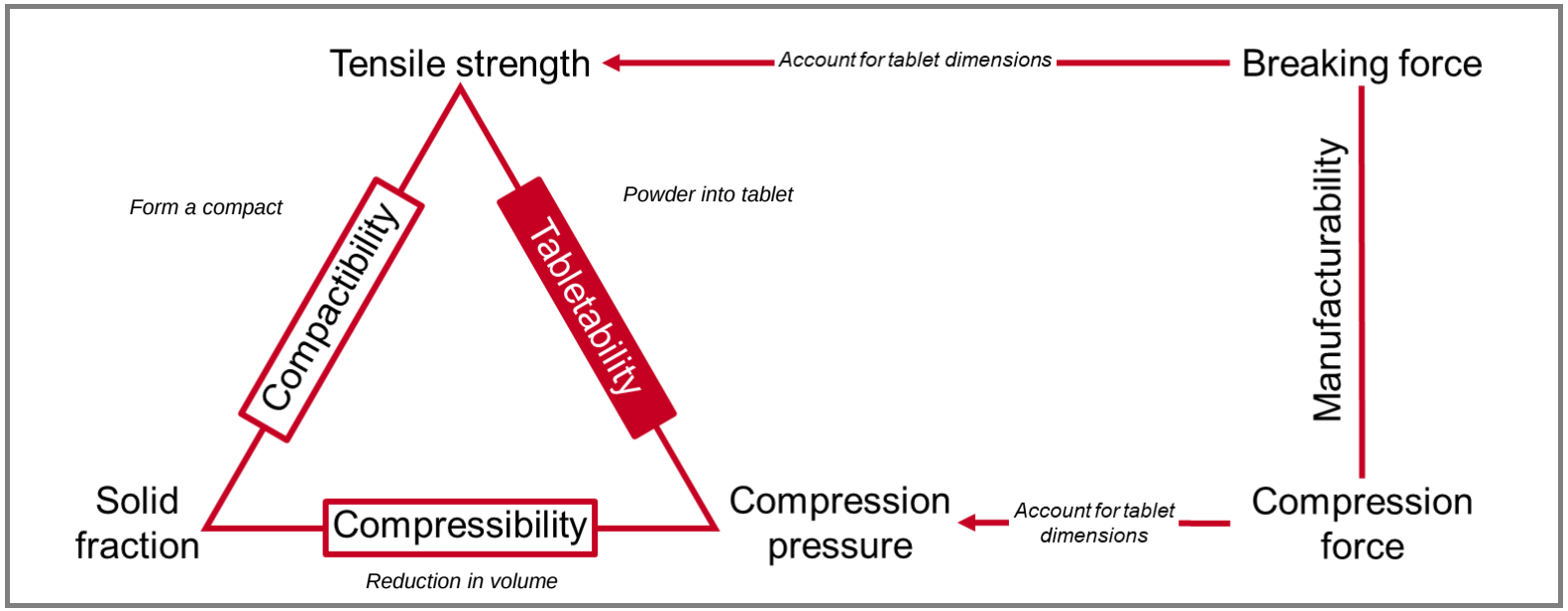
The relationship between compression pressure, tensile strength and (ejected) solid fraction is critical to understanding the tabletting process.



Source: ***Evaluation of the effects of tableting speed on the relationship between compaction pressure, tensile strength, and …***
C. K. Tye, C. Sun, G. E. Amidon; J. Pharm. Sci. Vol 94, No 3, March 2005, pp 465 – 472

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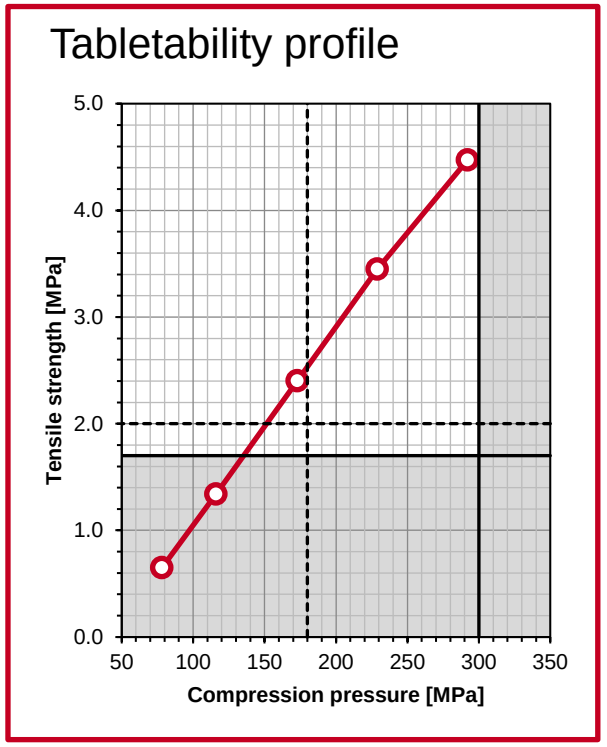
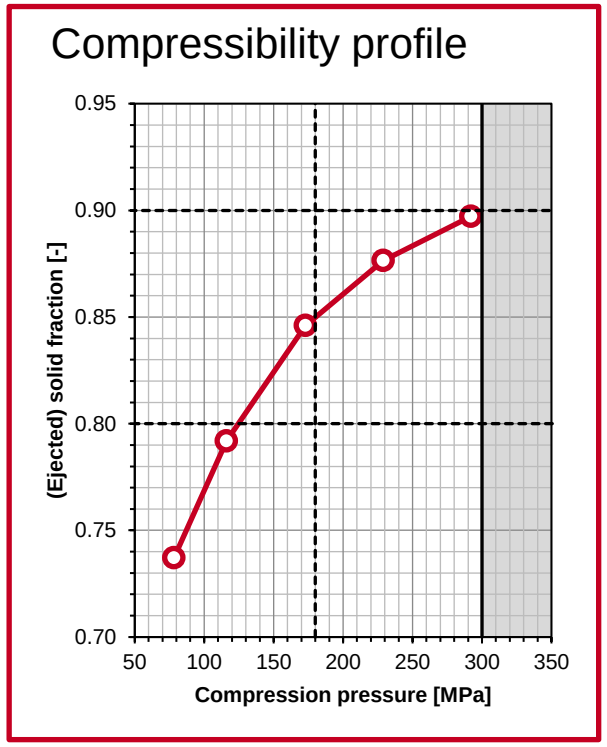
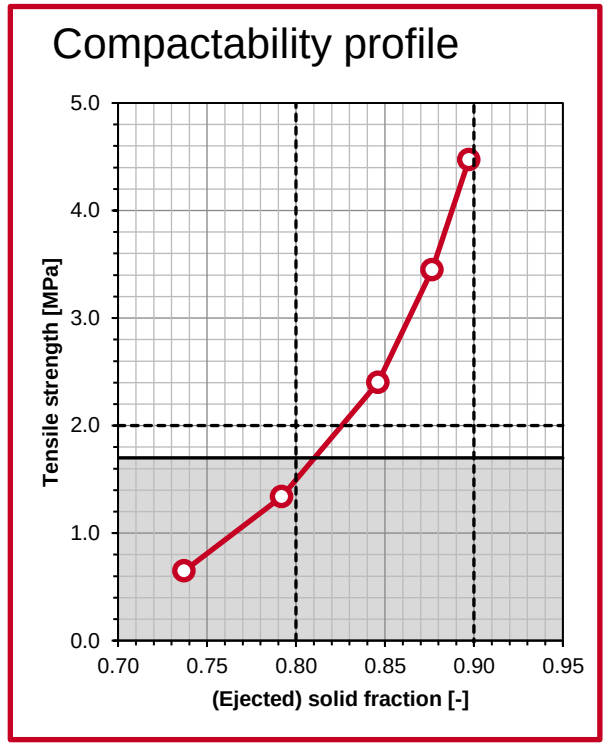
Kollitab showed optimal compressibility and compactability, which led to stronger tablets at lower compression forces.







Tensile strength:	1.7 MPa	min. required for tablet handling
	2.0 MPa	min. required for film-coating
Compression pressure:	180 MPa	generally accepted as low
	300 MPa	max generally accepted
Ejected solid fraction:	0.8 to 0.9	targeted value to avoid over-compression

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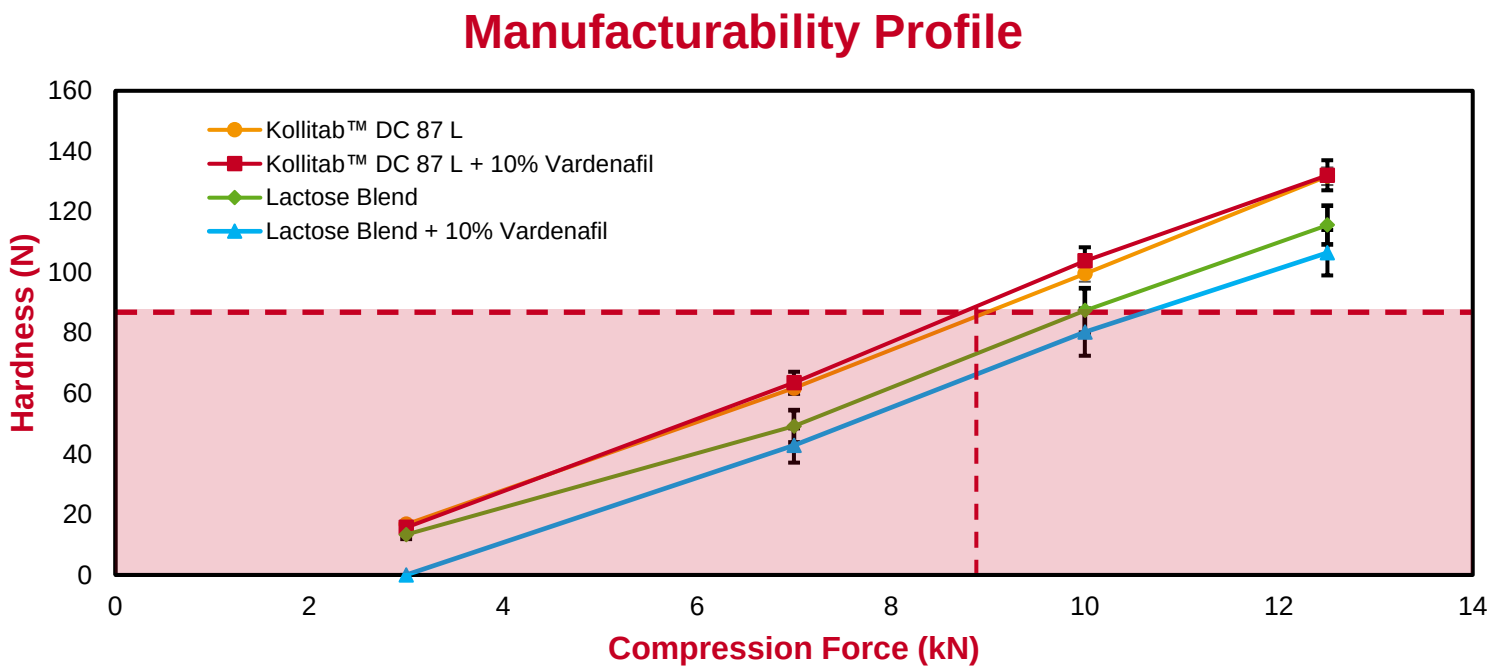
Compressibility and process robustness with the coprocessed blend was higher vs. the individual blend.



Vardenafil HCl: 10%
Kollitab™ DC 87 L: 90% or
Lactose Blend: 90%
Punch: 9.0 mm
Tablet mass: 250 mg

(Lactose Blend: 87% Lactose spray dried, 9% crospovidone (Kollidon® CL F) , 3% copovidone (Kollidon® VA 64) and 1% SSF

- Manufacturability profile does not include Ejection Force or (ejected) solid fraction.
- Lubricant distribution will affect this parameter. It needs to be considered!
- This was not identified as a key property in materials or blends.

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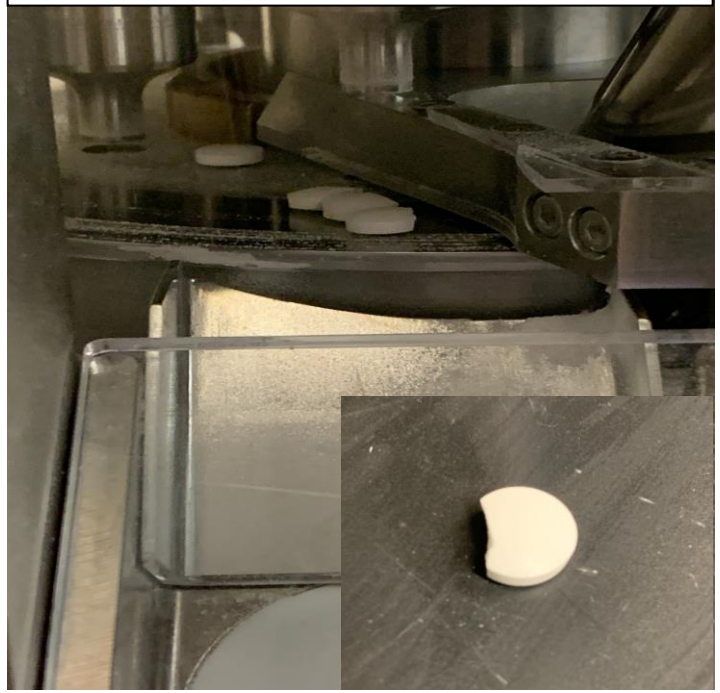
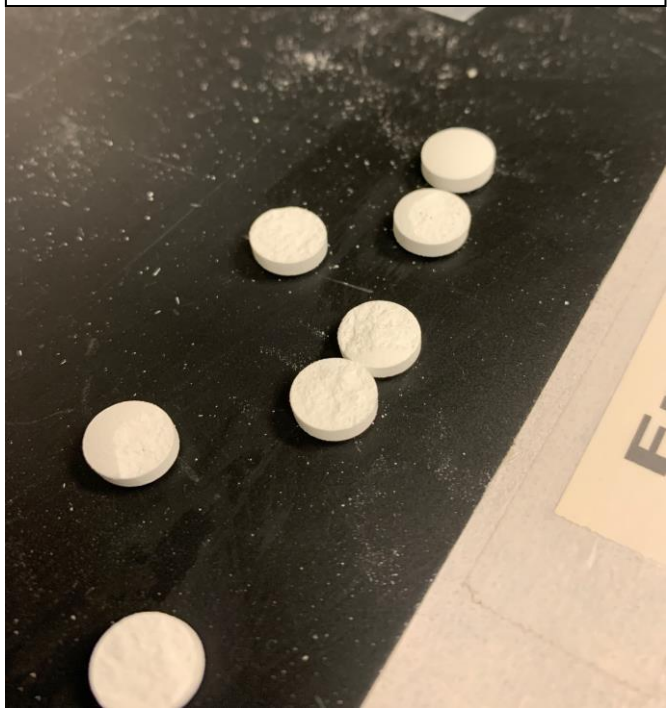
Individual excipient blend led to tablet defects at low and high compression forces. Lubricant distribution was key.

Lactose Blend + 10% vardenafil:
Breakage at 7-10 kN



Lactose Blend + 10% vardenafil:
Delaminated at 3 kN



Lactose Blend + 10% Vardenafil:
Punch Sticking

- Lactose blend led to **delamination and punch sticking.**
- Coprocessed blend allowed for DC of fine cohesive vardenafil

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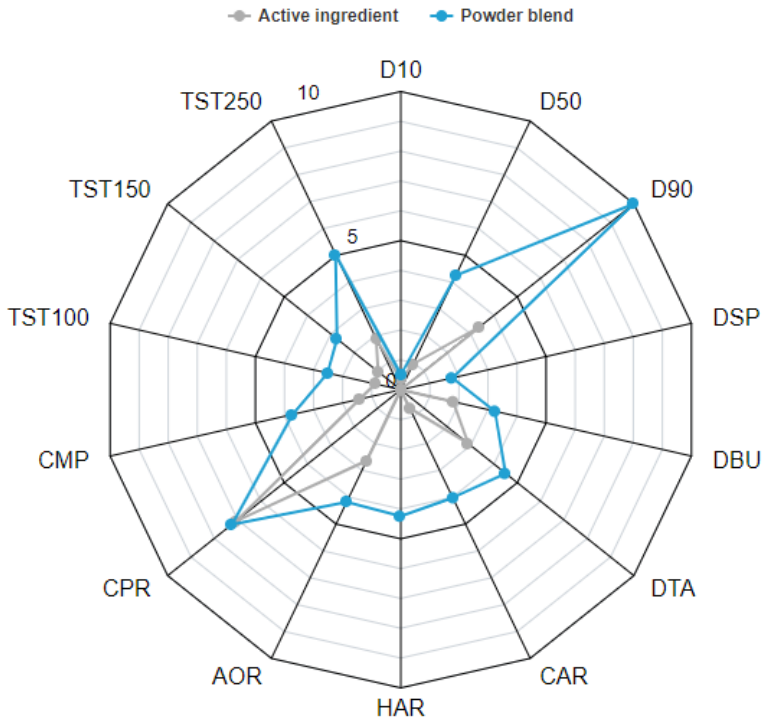
We can control excipient selection but we can‘t easily control API

- 50% fine APAP

Direct compression is not possible

Dry granulation (roller compaction) is not possible

Wet granulation (fluid-bed or high-shear granulation) is possible

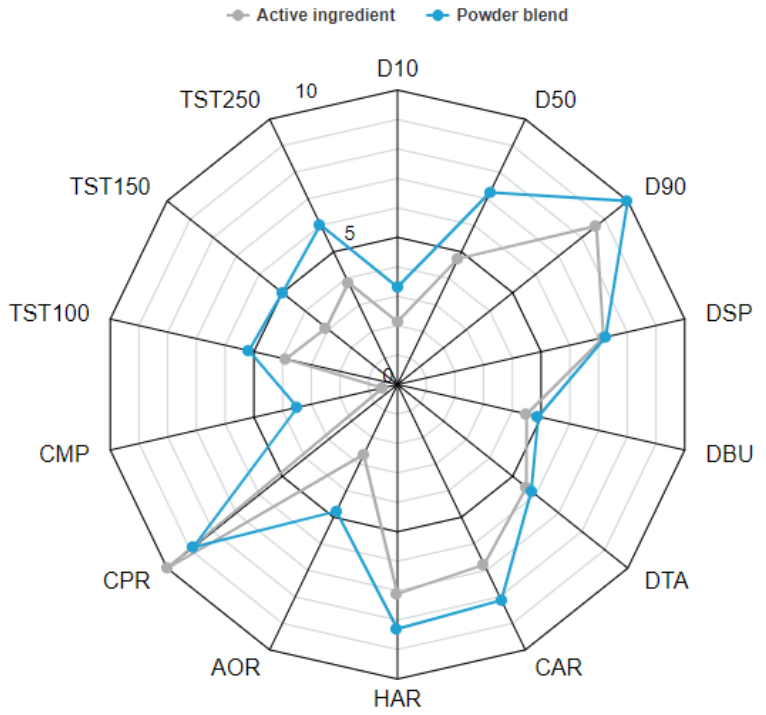


- 50% Ibuprofen 70

Direct compression may be possible

Dry granulation (roller compaction) may be possible

Wet granulation (fluid-bed or high-shear granulation) is possible



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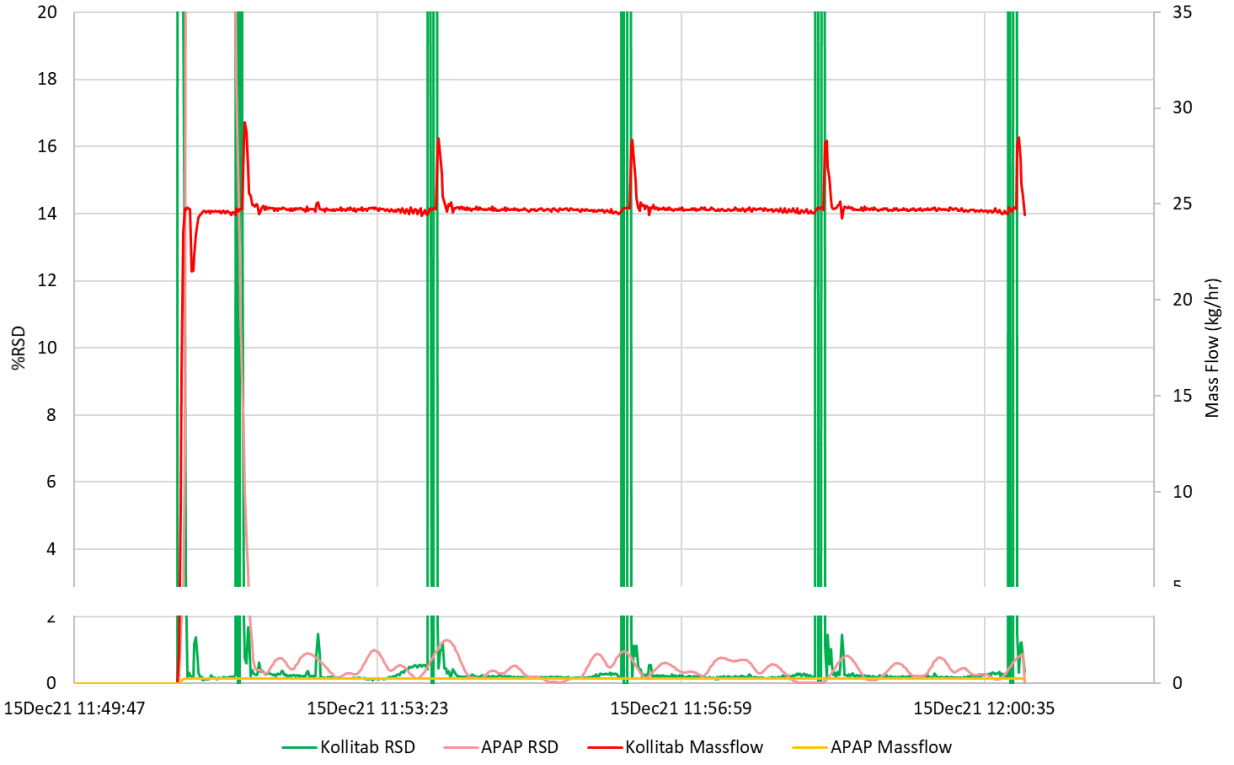
Continuous manufacturing of fine APAP at 1% with an all-in-one coprocessed led to high drug uniformity

Wt% APAP	Throughput (kg/hr)	Blender Speed (RPM)	Screw configuration
1	25	400	Low Shear

Tablet No.	APAP %
1	1.07
2	1.05
3	1.08
4	1.06
5	1.06
6	1.04
7	1.06
8	1.06
9	1.04
10	1.06
Avg	1.06
STDev	0.012
% RSD	1.16



Parameter	Value
Kollitab™ DC 87 L	24.75 kg/hr
APAP	0.25 kg/hr

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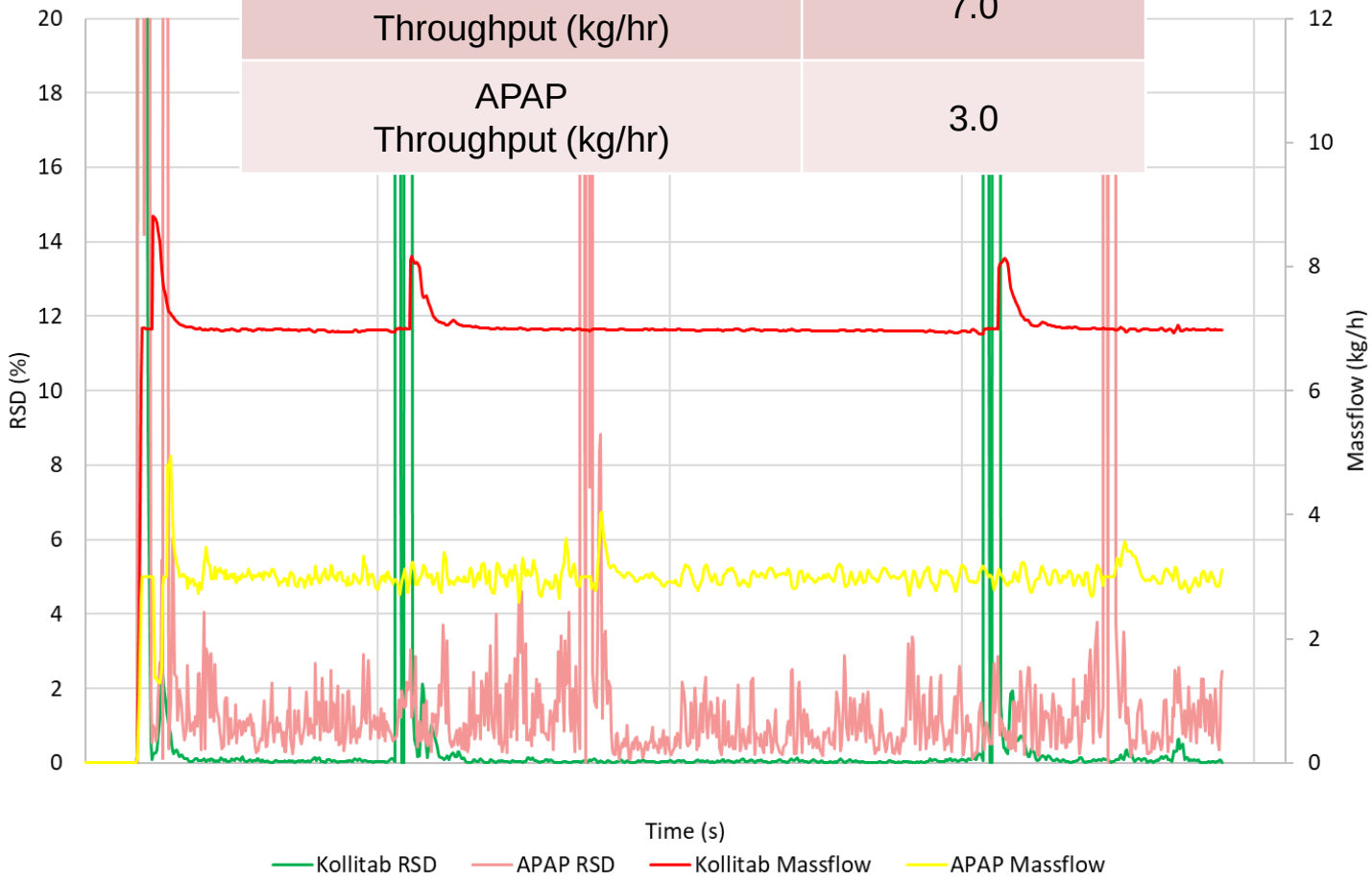
Kollitab™ DC 87 L and APAP - Feeding Properties

GEA Engineering for a better world.

Parameter	Value
Kollitab™ DC 87 L Throughput (kg/hr)	7.0
APAP Throughput (kg/hr)	3.0



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The impact of shear cannot be negated on CM blends as it impacts content uniformity. Should it be included in the Top Criteria?

Tablet	APAP 30% Low Shear	APAP 30% High Shear
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
Average		
STDev	1.21	0.18
% RSD	4.6	0.7

High shear

Wt% APAP	Throughput (kg/hr)	Blender Speed (RPM)	Screw configuration
10 / 30	10	300	Low Shear

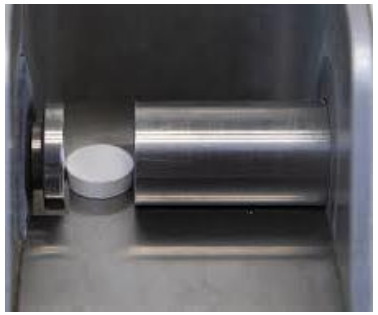
Wt% APAP	Throughput (kg/hr)	Blender Speed (RPM)	Screw configuration
10 / 30	10	275	High Shear

We innovated and accomplished: Kollitab™ DC 87 L

Your new *all-in-one* tableting solution

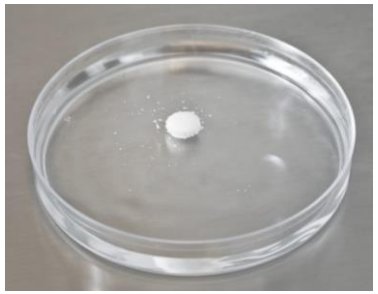
Superior flowability

- ▶ **High process consistency**
- ▶ **Reduced weight variability**



High Hardness Tablet at low compression force

- ▶ **Minimize tablet defects**
- ▶ **Improve process robustness**
- ▶ **Reduce machines stress and punch damage**



Fast Disintegration time

- ▶ **Minimize impact on drug dissolution**

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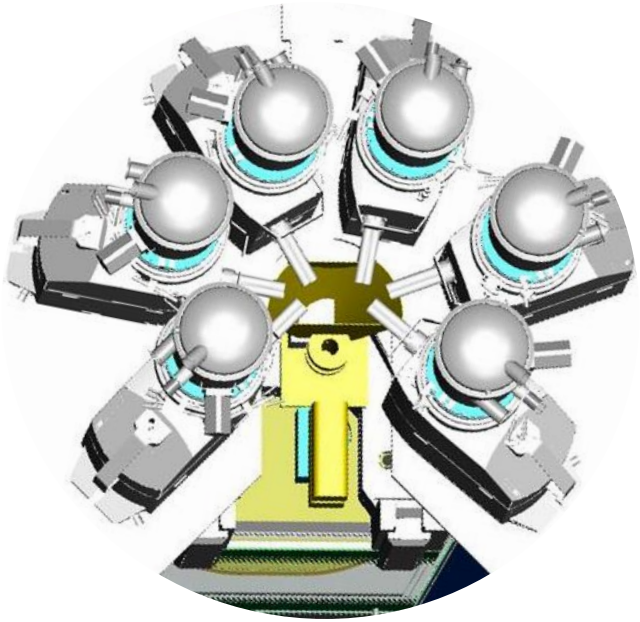

- Direct compression, twin screw granulation and dry granulation are the preferred CM processes
- **No excipient has all the desired criteria**
  - Consider fit-for purpose novel coprocessed excipients
- Designing robust formulations require a **systematic understanding** of the effect of material attributes on process dynamics and tablettability.
- **All-in-one coprocessed excipients can improve feeding and blending** processing due its low compressibility and cohesion, as well as, streamline feeder configuration.
- Kollitab™ DC 87 L provides high flowability, compressibility and fast tablet disintegration. **Consider involving us in your next trial!**

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Contact us to learn more!

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