



Role of Excipients in Development of Continuous Dry and Wet Granulation Processes for Tablets by Applying Twin-Screw Melt Extruders

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PQRI Workshop:

***Managing Excipient and API Impact on
Continuous Manufacturing***

May 17 – 18, 2022

State of Pharmaceutical Manufacturing: FDA Perspective

A conceptual integrated continuous manufacturing process

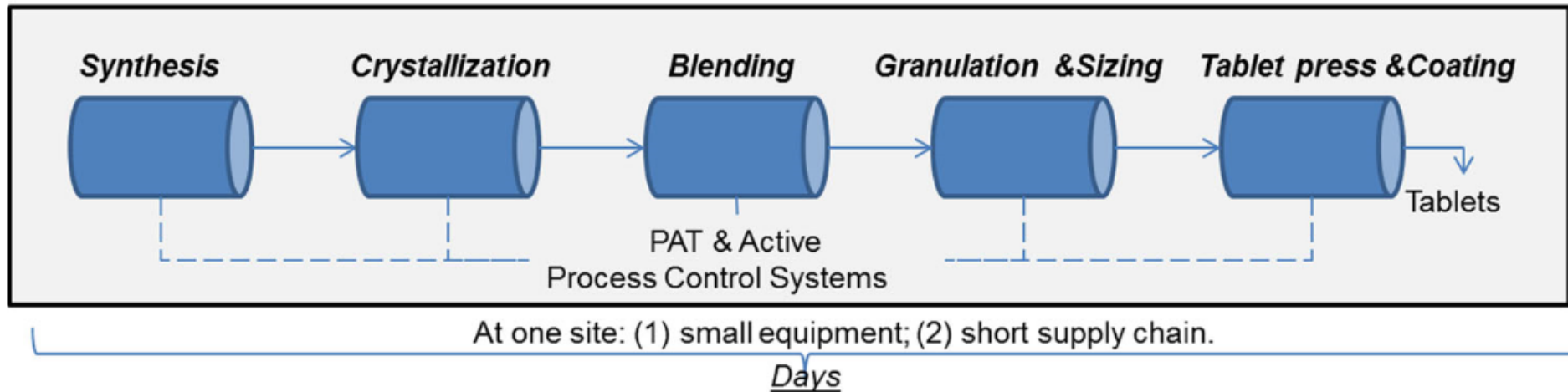
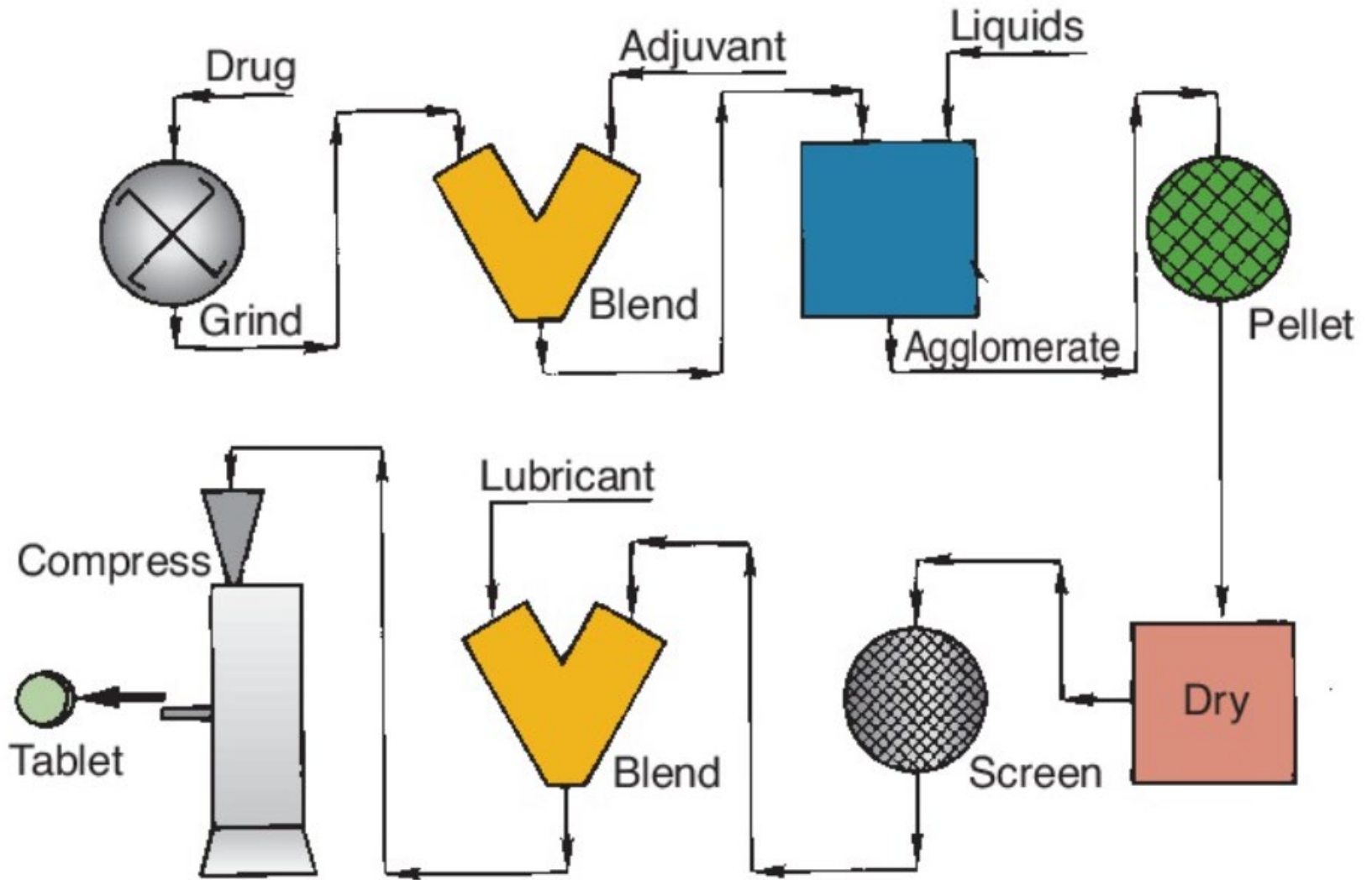


Image courtesy of Sau Lee, J Pharm Innov (2015) 10:191-199.

Ref: Lee SL, O'Connor T, Yang X, Cruz CN, Chatterjee S, Madurawe RD, Moore CMV, Lawrence XY, Woodcock J.
Modernizing pharmaceutical manufacturing: from batch to continuous production. J Pharma Innov. 2015;10(3):191-199.

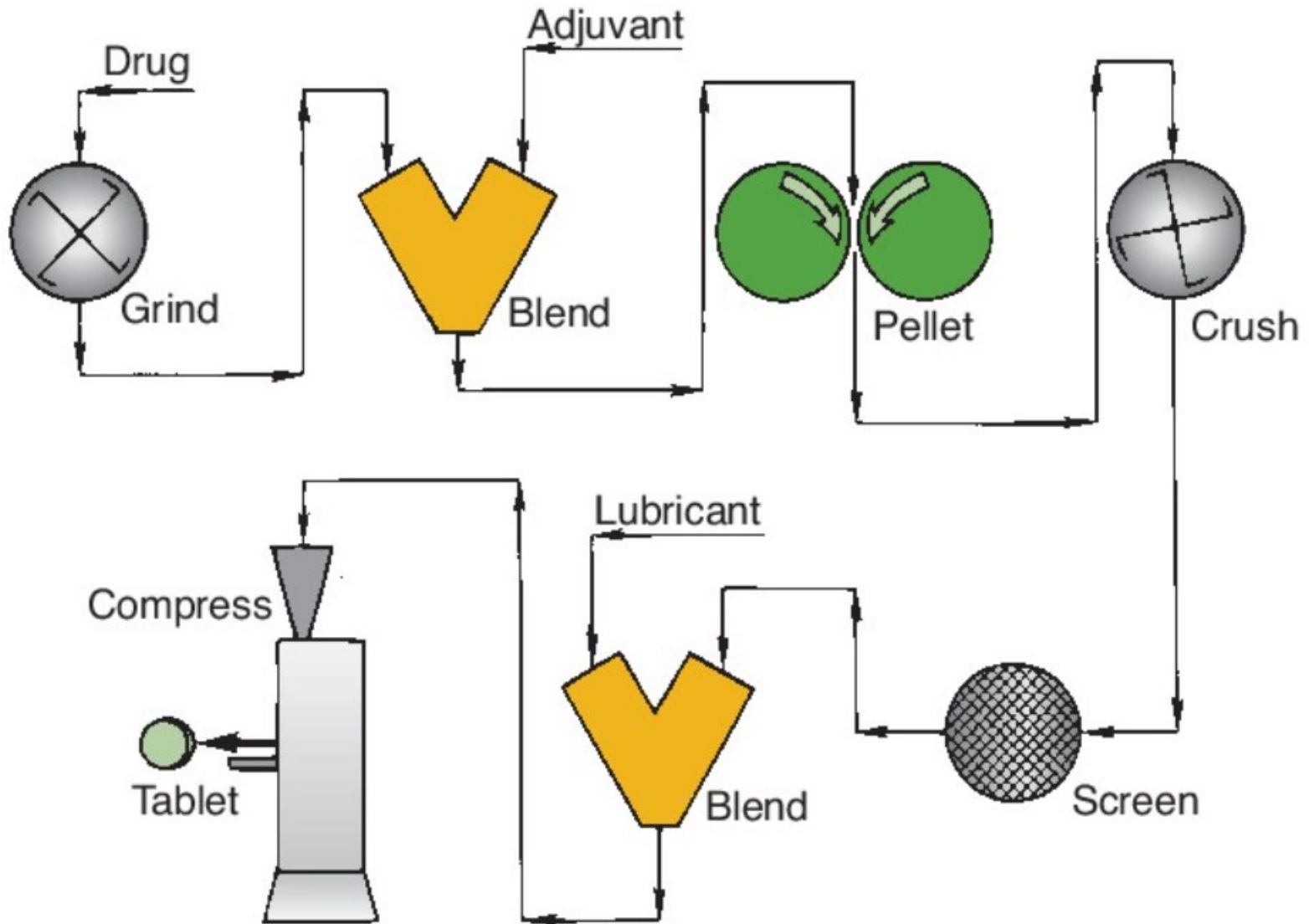
Current State of the Manufacture of Solid Dosage Forms

Wet Granulation



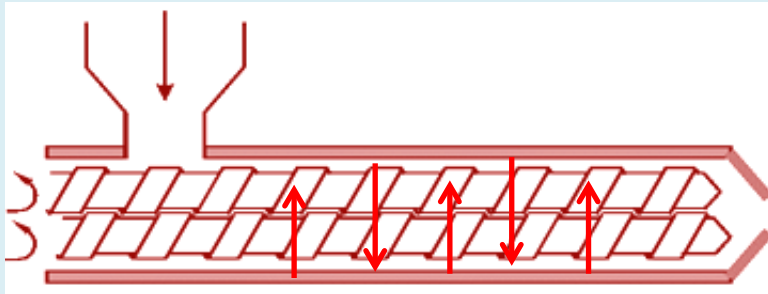
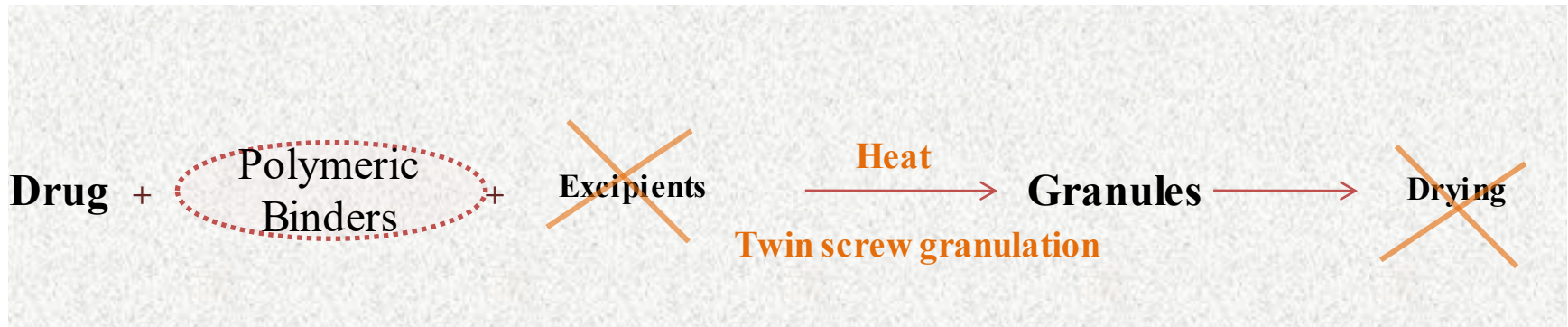
Ref: Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, 12th ed., 2021

Dry Granulation



Twin Screw Extrusion Technology for Continuous Manufacturing

Dry Melt Granulation using Twin Screw Extruder



Pharma 16 Extruder, Thermo Fisher Scientific

- Uniform heat distribution
- Design suited to melt granulation
- Die of extruder removed to enable granule formation
- Better control over granule size distribution
- Temperature range = 40°C- 200 °C

Case Study 1:

Development of Metformin HCl Fixed Combination Immediate Release Tablet

Lakshman, J.P., Kowalski, J., Vasanthavada, M., Tong, W.Q., Joshi, Y.M. and Serajuddin, A.T., 2011. **Application of melt granulation technology to enhance tableting properties of poorly compactible high-dose drugs.** Journal of pharmaceutical sciences, 100(4), pp.1553-1565.

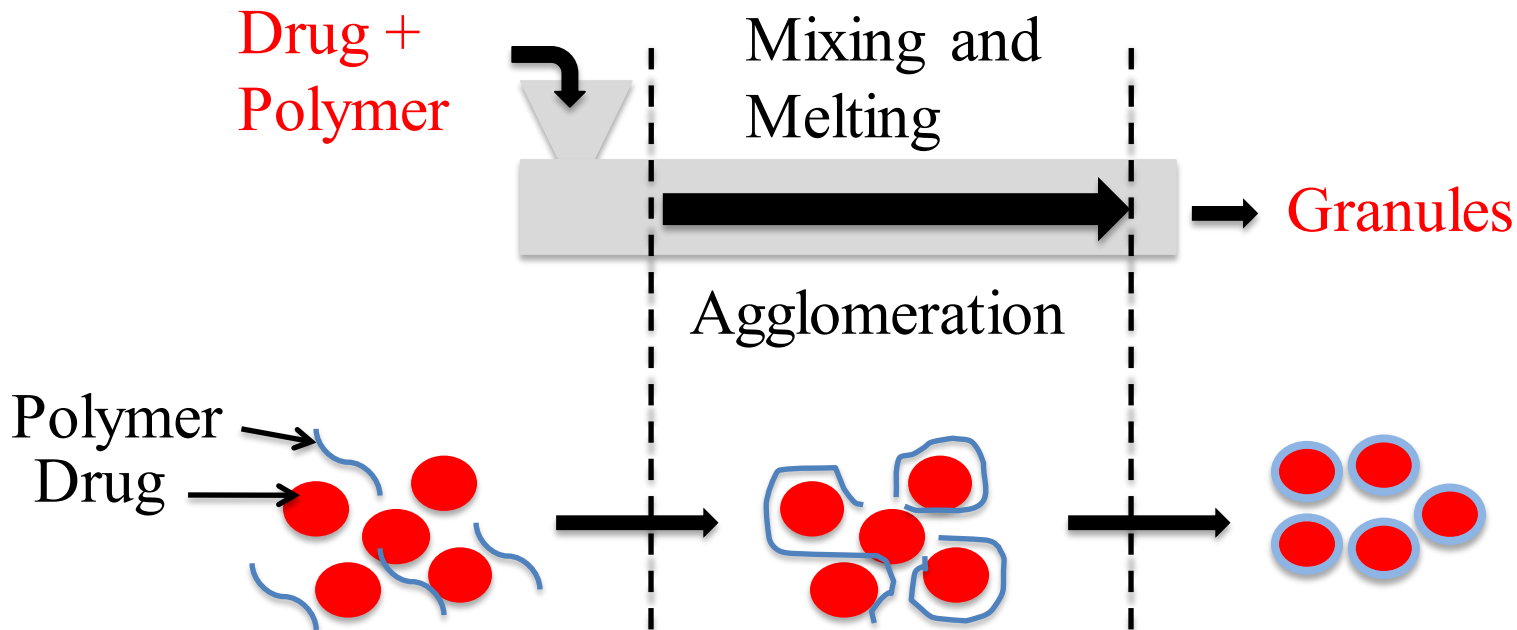
Composition of Metformin HCl Tablet

| Ingredients | Amount/ tablet (mg) | %w/w |
|--------------------|------------------------|--------|
| Metformin HCl | 1000.0 | 91%* |
| HPC | 98.9 | 9%* |
| Second API | 25.0 | 2.2%** |
| Magnesium stearate | 10.2 | 0.9%** |
| Total weight | 1134 | |

* Melt granulated

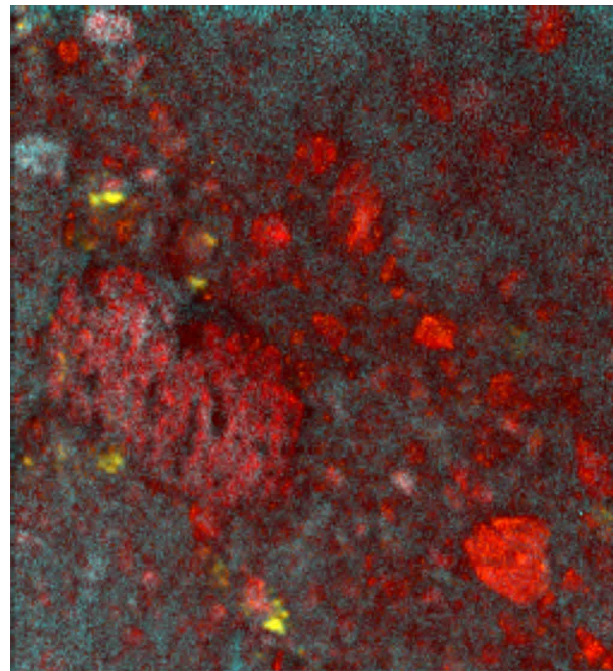
** Added extra-granularly for a combination tablet

Twin Screw Melt Granulation: Principle



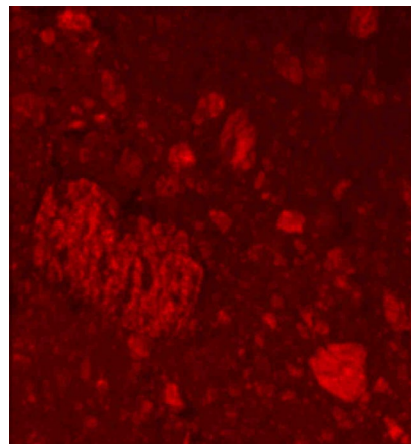
T_g of polymer $<$ **Processing temperature** $<$ Melting point of drug

Confocal Raman Microscopic Study – Hydroxypropyl Cellulose Polymer



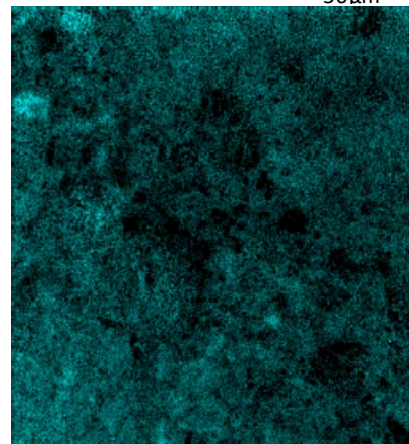
overlay

50µm



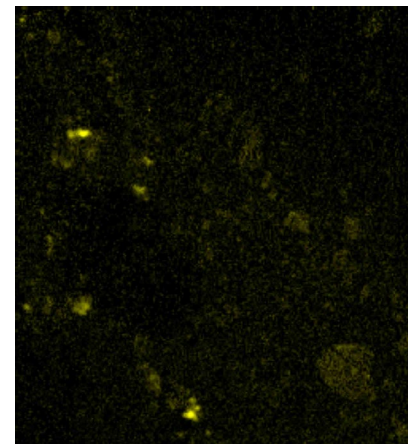
STI571

50µm



HPC

50µm



Mg Stearate

50µm

Case Study 2:

Development of Gleevec (Imatinib Mesylate) Modified Release Tablet

M. Vasanthavada, Y. Wang, J. P. Lakshman, W. Tong, Y. M. Joshi, A. T. M. Serajuddin. **Application of Melt Granulation Technology Using Twin-screw Extruder in the Development of Modified-release Oral Formulation for a High-dose Drug Product.** J. Pharm. Sci. 100, 1923–1934 (2011)

Development of Imatinib Mesylate 800 mg Modified Release Tablet



- Immediate release Gleevec 400-mg marketed tablet weighs ~775 mg
- 800 mg drug substance by itself weighs ~960 mg
- What will be the weight of a 800-mg tablet?
- MRformulation was needed to reduce peak plasma concentration
- Is the development of a single-unit tablet formulation feasible?

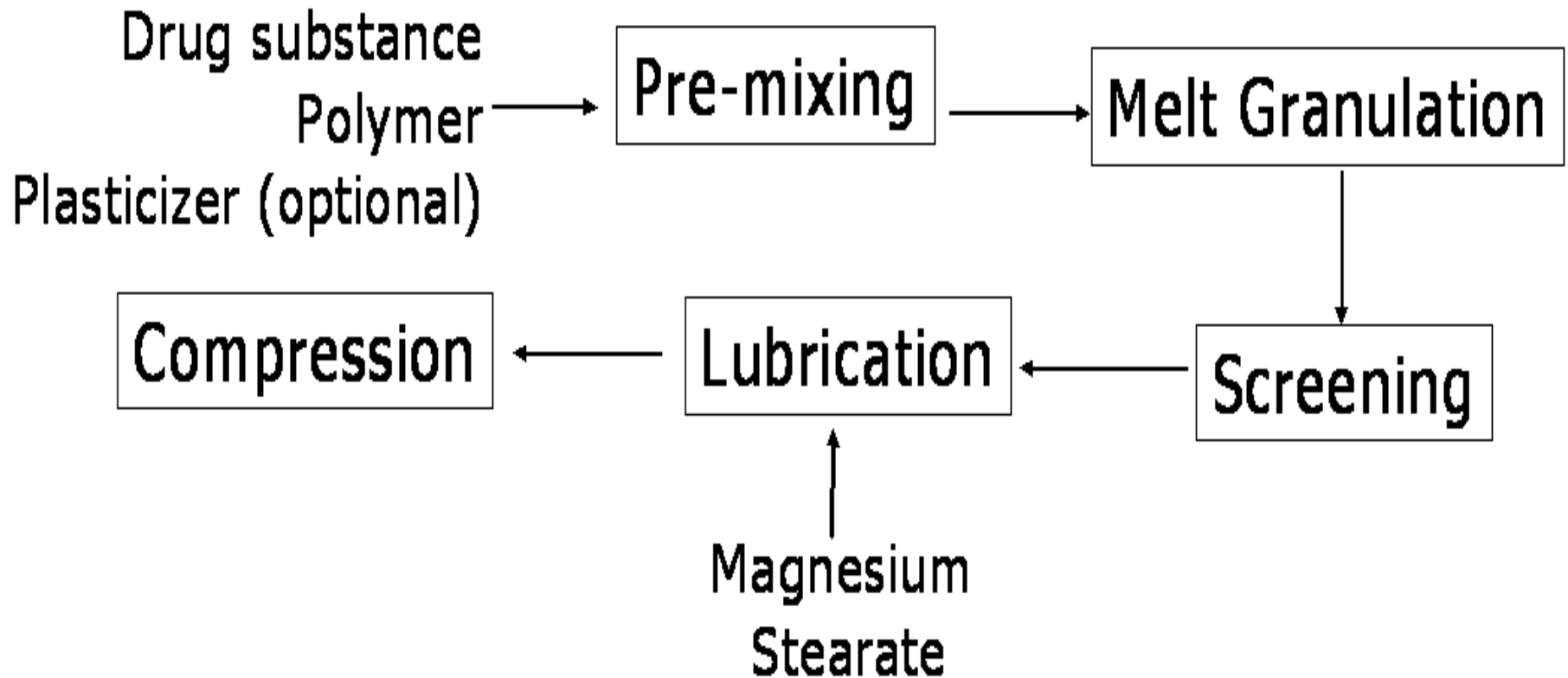


Imatinib Mesylate 800 mg Tablets (960 mg API per Tablet)

| Formula | API* [%w/w] | Process above glass transition temperature of polymer, but below the melting point of drug | | Tablet weight [mg] |
|---------|----------------|--|----------------|--------------------|
| | | Polymer | Polymer [%w/w] | |
| MR1 | 94 | Hydroxypropyl cellulose (Klucel HF) | 5 | 1017 |
| MR2 | 89 | Hydroxypropyl cellulose (Klucel HF) | 10 | 1074 |
| MR3 | 89 | Ethyl cellulose 100cP | 10 | 1074 |
| MR4 | 89 | Hydroxypropylmethyl cellulose K100M + Ethyl cellulose 100cP | 5 + 5 | 1074 |

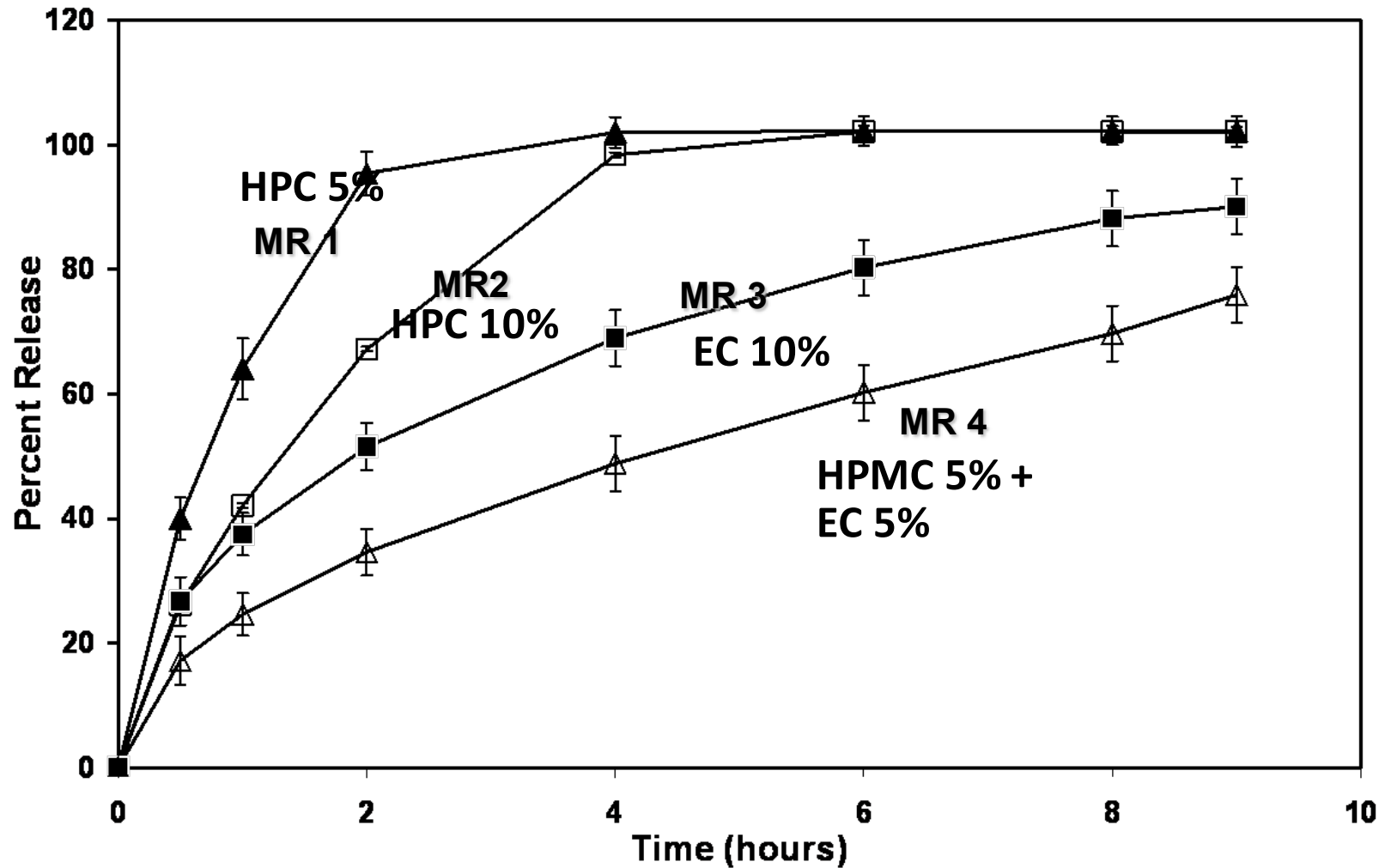
* Drug load in the final tablet, since all formulations contained 1% w/w magnesium stearate as lubricant to aid in tableting.

Processing of Imatinib Mesylate 800 mg Tablet



Pharma 16 Extruder (Thermo Fisher Scientific) was used.

Imatinib Mesylate 800 mg Tablet



Continuous Processing

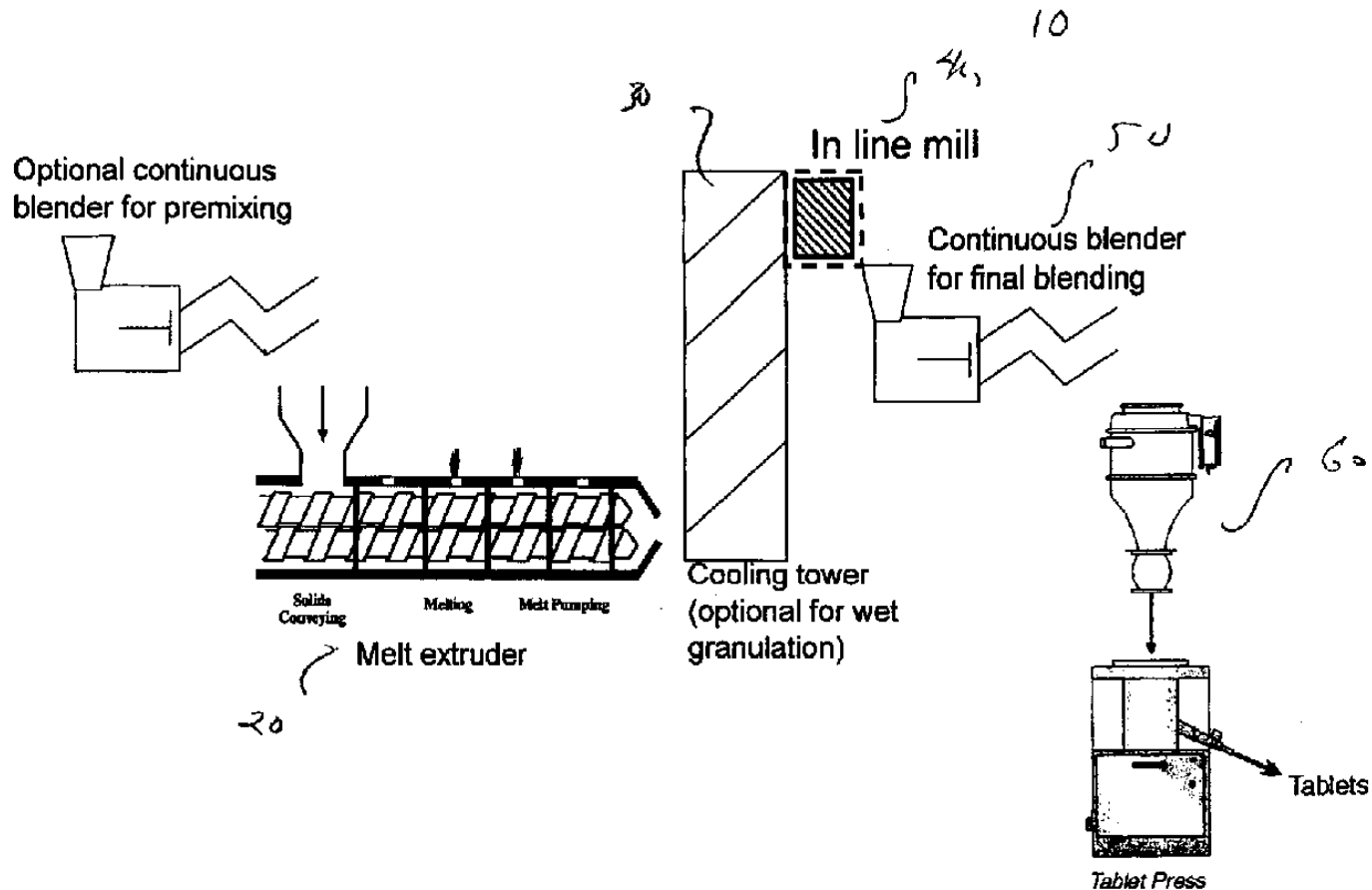


Fig. 1

Continuous processing for making pharmaceutical compositions.

Ref: Kowalski, J., Lakshman, J. P., Serajuddin, A. T., Tong, W. Q., & Vasanthavada, M. (2011). U.S. Patent Application No. 12/990,151.

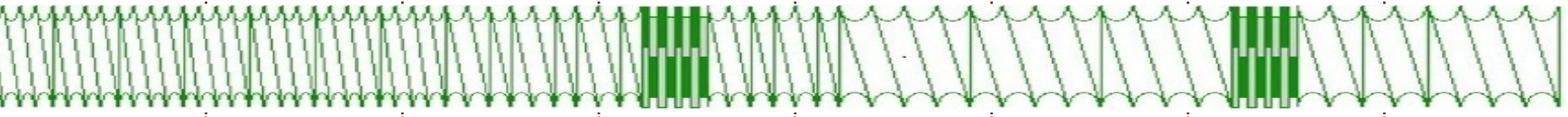
Case Study 3:

Screening of Polymeric Binders for Twin Screw (Dry) Melt Granulation

Batra, A., Desai, D. and Serajuddin, A.T., 2017. **Investigating the use of polymeric binders in twin screw melt granulation process for improving compactibility of drugs.** Journal of pharmaceutical sciences, 106(1), pp.140-150.

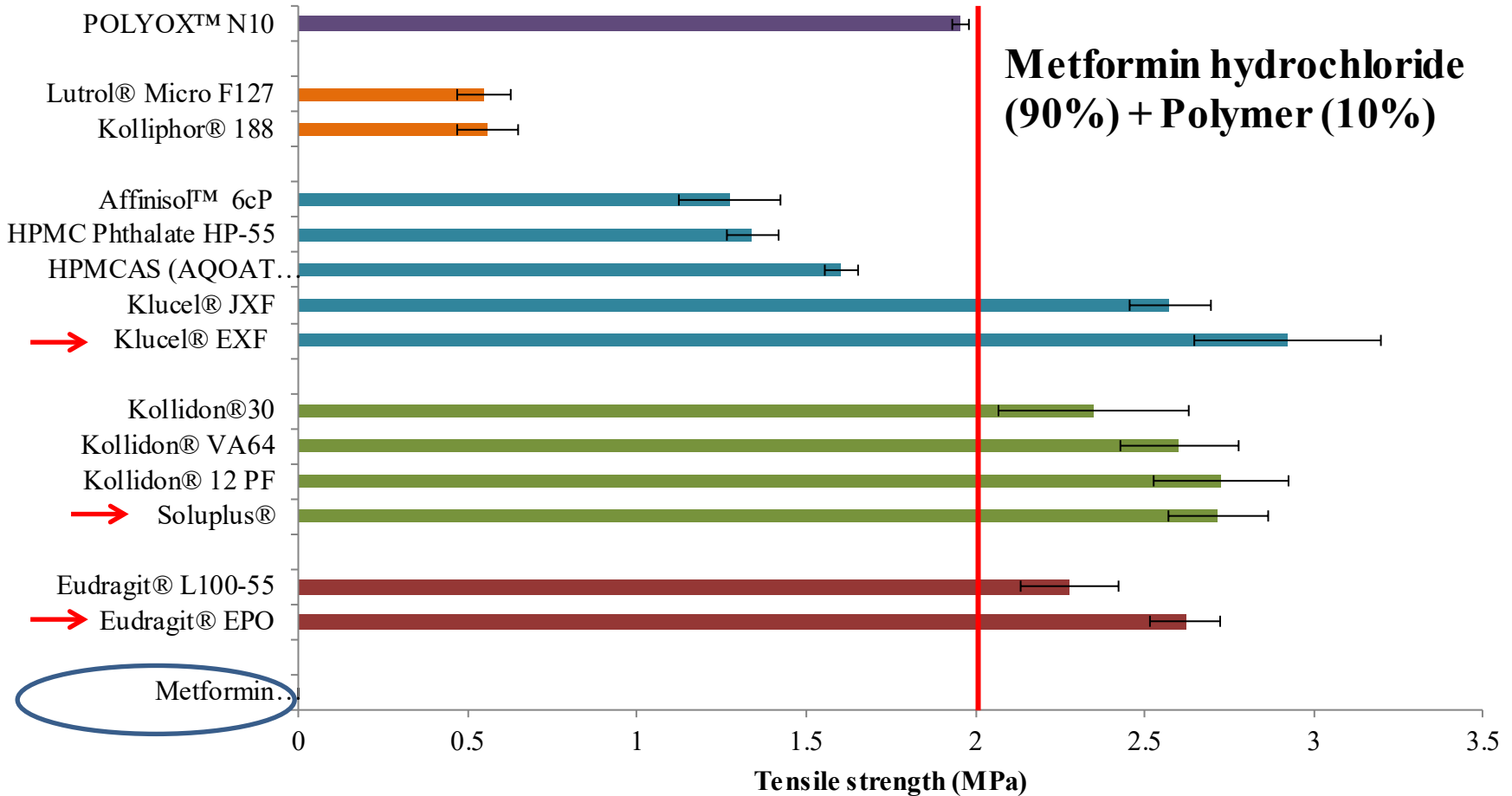
Melt granulation Experimental Conditions for Polymer Screening

Twin Screw 18 mm Leistritz Extruder Used

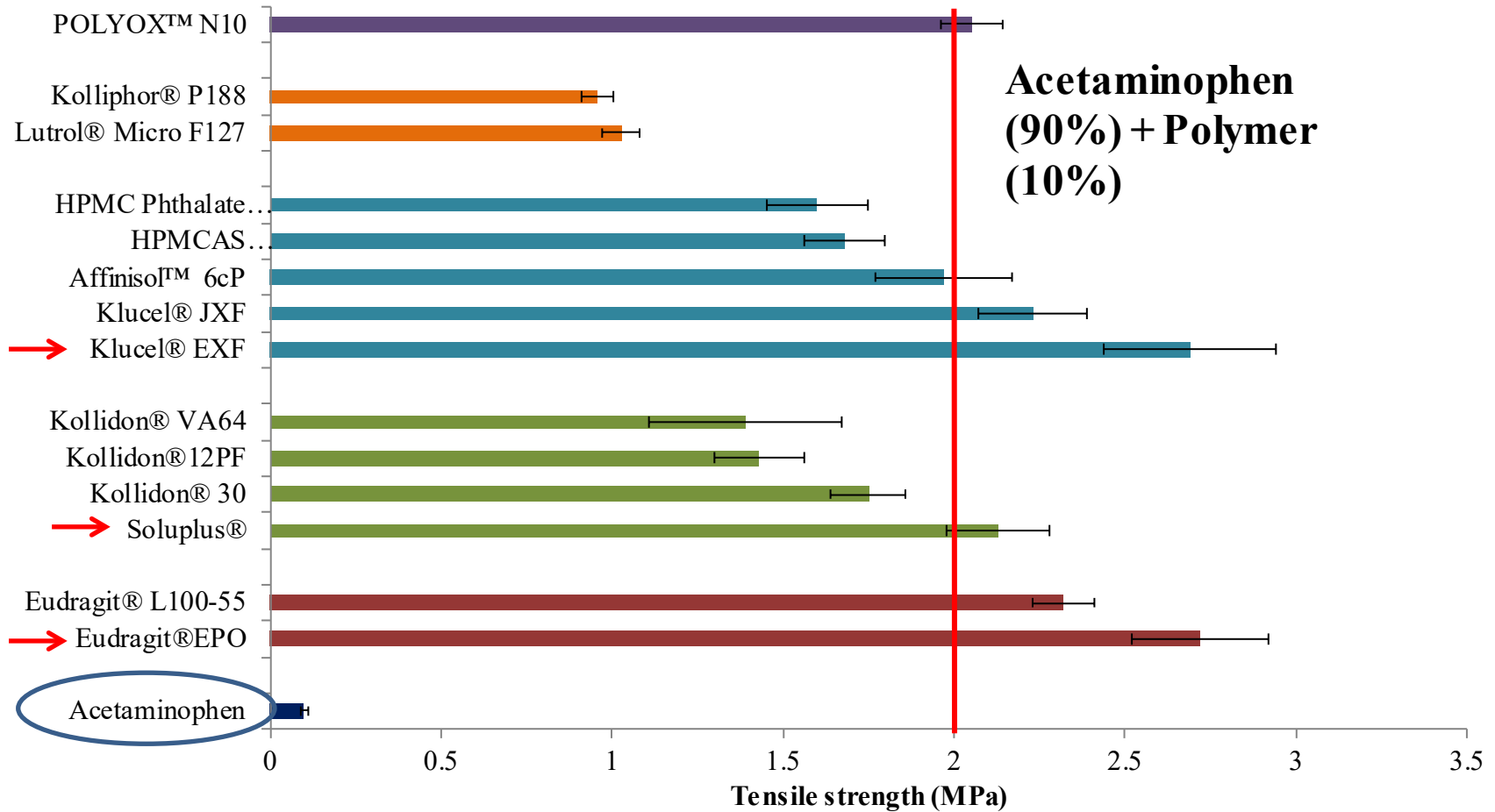
| Zone 8 | Zone 7 | Zone 6 | Zone 5 | Zone 4 | Zone 3 | Zone 2 | Zone 1 |
|--|--------|--------|----------|--------|--------|----------|--------|
| Metformin hydrochloride | | | | | | | |
| 20 °C | 180 °C | 180 °C | 180 °C | 180 °C | 180 °C | 100 °C | 20 °C |
| Acetaminophen | | | | | | | |
| 20 °C | 130 °C | 130 °C | 130 °C | 130 °C | 130 °C | 100 °C | 20 °C |
| | | | 60°, 30° | | | 60°, 60° | |
|  | | | | | | | |

FEED RATE= 60 g/min SCREW SPEED= 100 RPM

Polymer Screening: Metformin hydrochloride

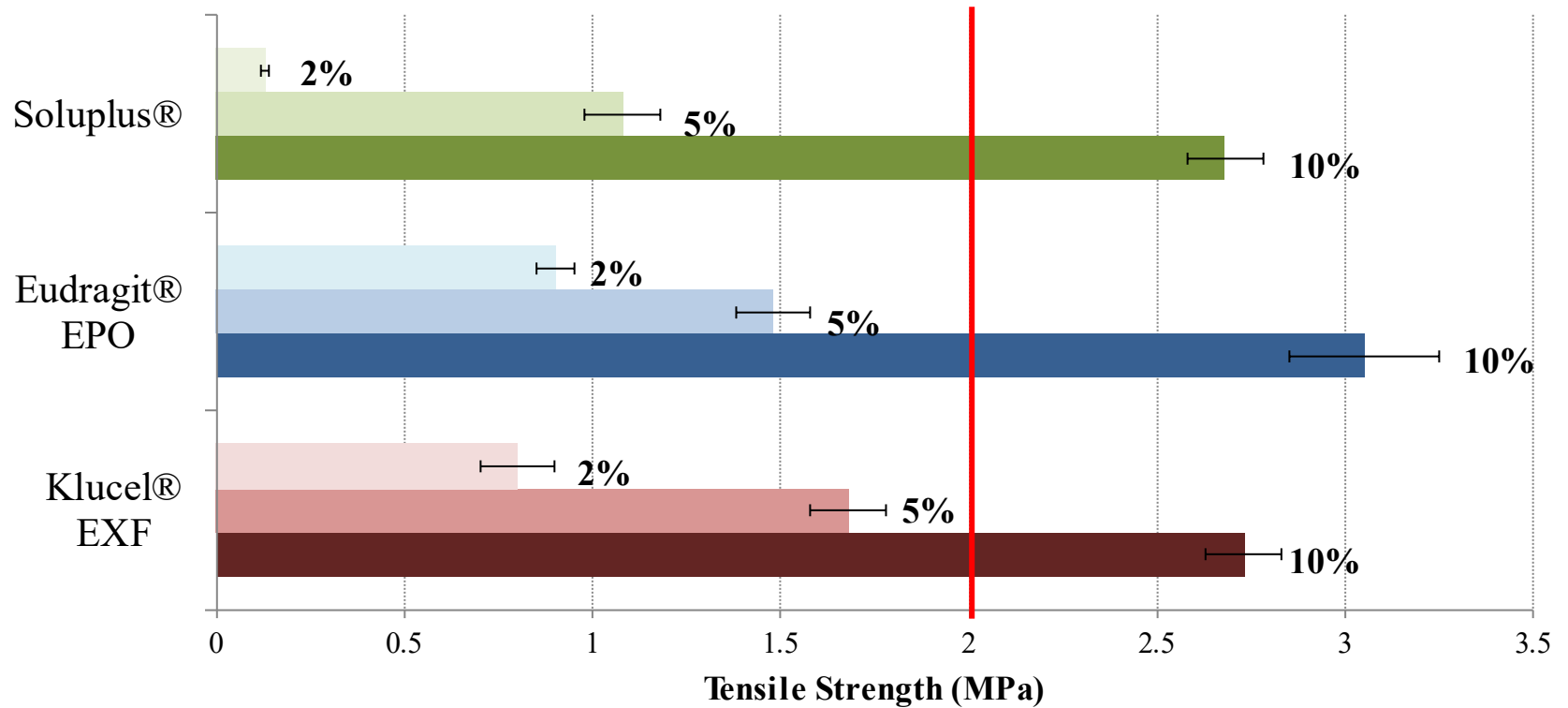


Polymer Screening: Acetaminophen



Effect of Polymer Concentration: Metformin hydrochloride

180 °C, 60 g/min, 100 RPM



Case Study 4:

Twin Screw **Wet Granulation**: A Case Study of Acetaminophen

Meena, A.K., Desai, D. and Serajuddin, A.T., 2017.
Development and optimization of a wet granulation process at elevated temperature for a poorly compactible drug using twin screw extruder for continuous manufacturing. *Journal of Pharmaceutical Sciences*, 106(2), pp.589-600.

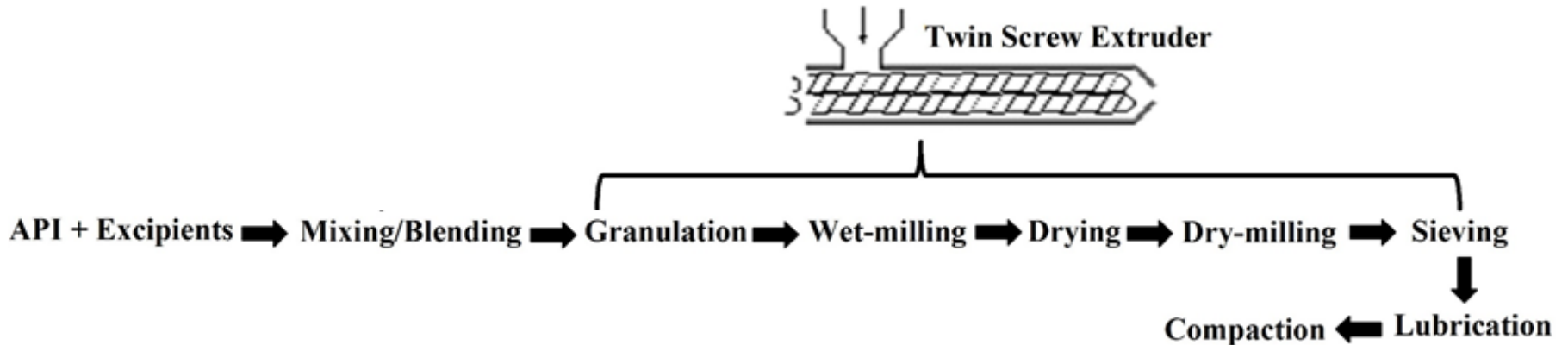
Melt Granulation (Wet) using Twin Screw Extruder



**Process 11 Co-rotating Twin Screw Extruder
Thermo Fisher Scientific**



**Pharma 16 Extruder
Thermo Fisher Scientific**



Materials

Poorly compactible model drug

- Acetaminophen

Binders

- PVP- polyvinylpyrrolidone (Kollidon[®] 30)
- PGS- partially pregelatinized starch (Starch 1500[®])

Granulating liquid

- Purified water

Process and Formulation Variables

API+ Binder

Powder Feed Rate

Feeder

Water Concentration (%)

Water

Granule
characterization

Granules

Screw Speed (RPM)

Barrel Temperature/
Granulation temperature

- Size distribution
- Moisture content



Tablets

- Hardness test
- Disintegration test

Mixing/kneading zone

Conveying zone

Powder feed

Water addition

Die is removed to get granular product

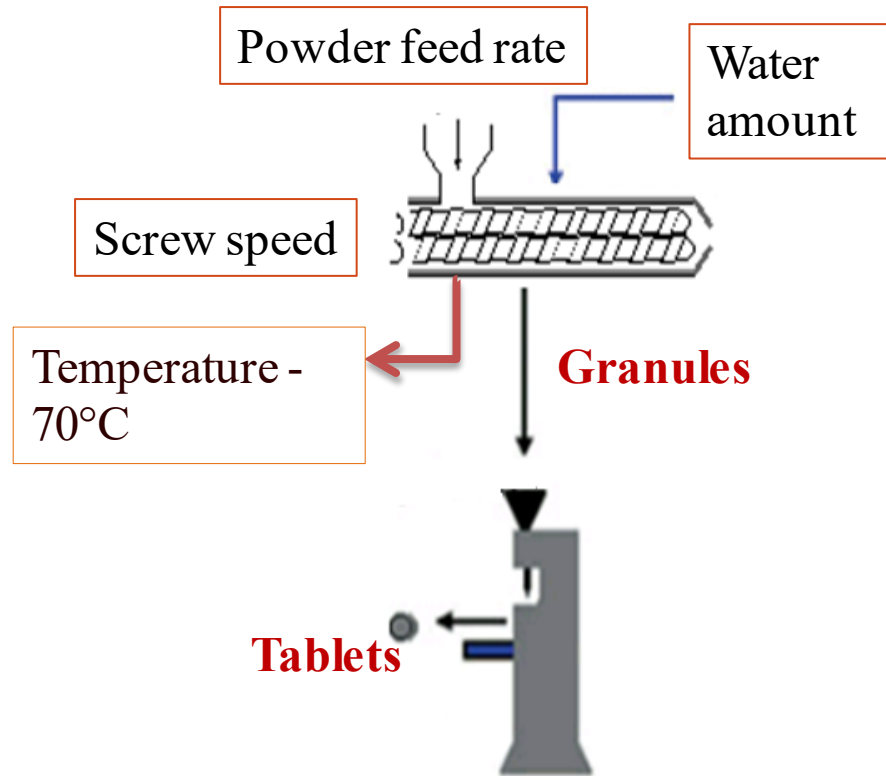
Dried granules



Formulation parameters:

- Binder concentration
2.5 and 5% w/w

Granulation and Tableting of Poorly Compactible Drug - Acetaminophen



Model drug:

Acetaminophen

Binders:

Povidone (PVP) 5%

Pregelatinized starch (PGS) 5%

Target:

Granules: 125 μm – 1 mm

< 5% oversized granules (> 1 mm)

< 10% fines (< 125 μm)

Water content < 1%

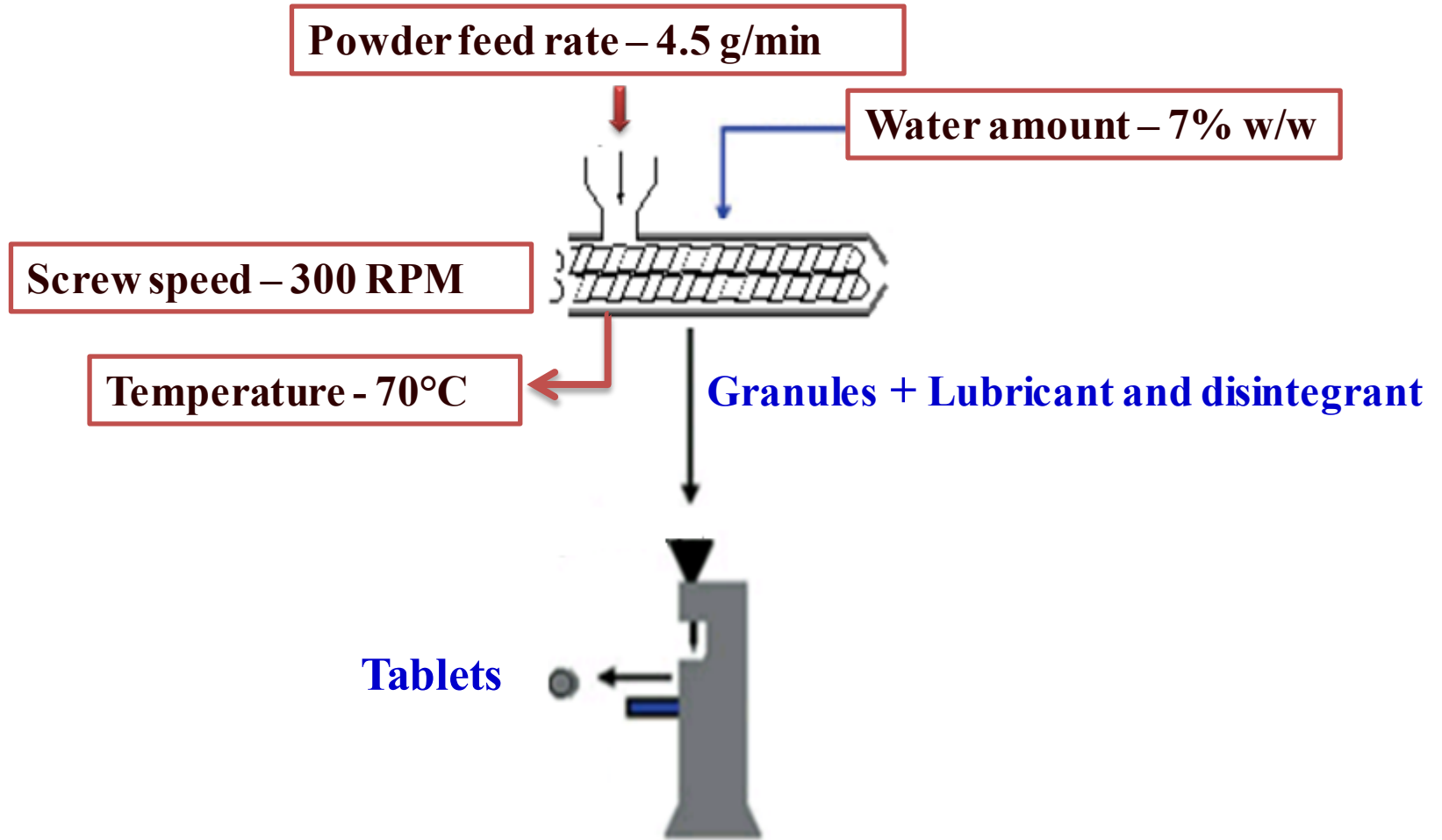
Tablet:

Tablet tensile strength (hardness)

> 1.7 MPa

Process 11 Co-rotating Twin Screw Extruder (Thermo Fisher Scientific) was used

Optimized Acetaminophen Granulation Parameters



Acetaminophen Formulation Composition

Granules produced at 300 RPM, 4.5 g/min and 7% water

| Formulation | Weight per tablet (mg) | Weight per tablet (%) |
|---------------------|---------------------------|--------------------------|
| Acetaminophen | 500.0 | 93.6 |
| Binder (PVP or PGS) | 26.3 | 4.9 |
| Disintegrant | 5.3 | 1.0 |
| Lubricant | 2.7 | 0.5 |
| Total | 534.3 | 100.0 |

- Disintegrant - Croscarmellose sodium
- Lubricant - Magnesium stearate

Acetaminophen Tablet Properties Produced by Twin Screw Granulation

Continuous processing for making pharmaceutical compositions.

| Binder type | Tablet hardness (MPa) | Friability (% w/w) | Disintegration time (min) |
|-----------------------------|------------------------------|---------------------------|----------------------------------|
| Povidone (PVP) | 2.5 | 1.0 | 5.0 |
| Pregelatinized starch (PGS) | 3.5 | 0.8 | 1.5 |

▪ **500 mg acetaminophen tablet (93.6 % drug load) + only 6.4% excipients (5% binder, 1% croscarmellose sodium and 1% magnesium stearate)**

▪ **No diluents required to improve granule and tablet quality**

Case Study 5:

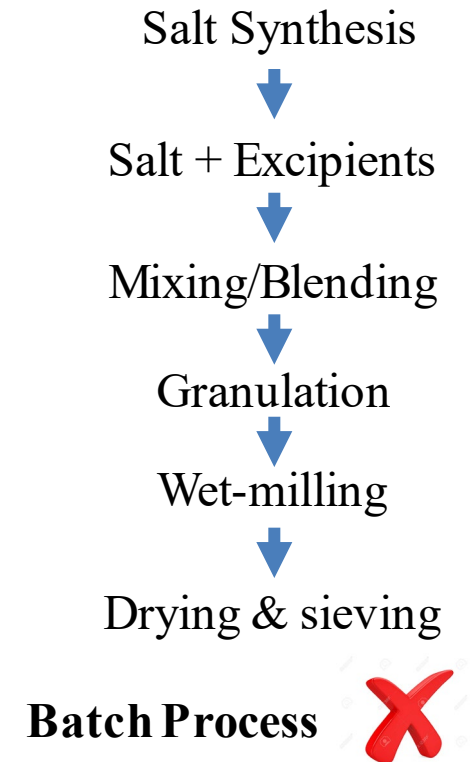
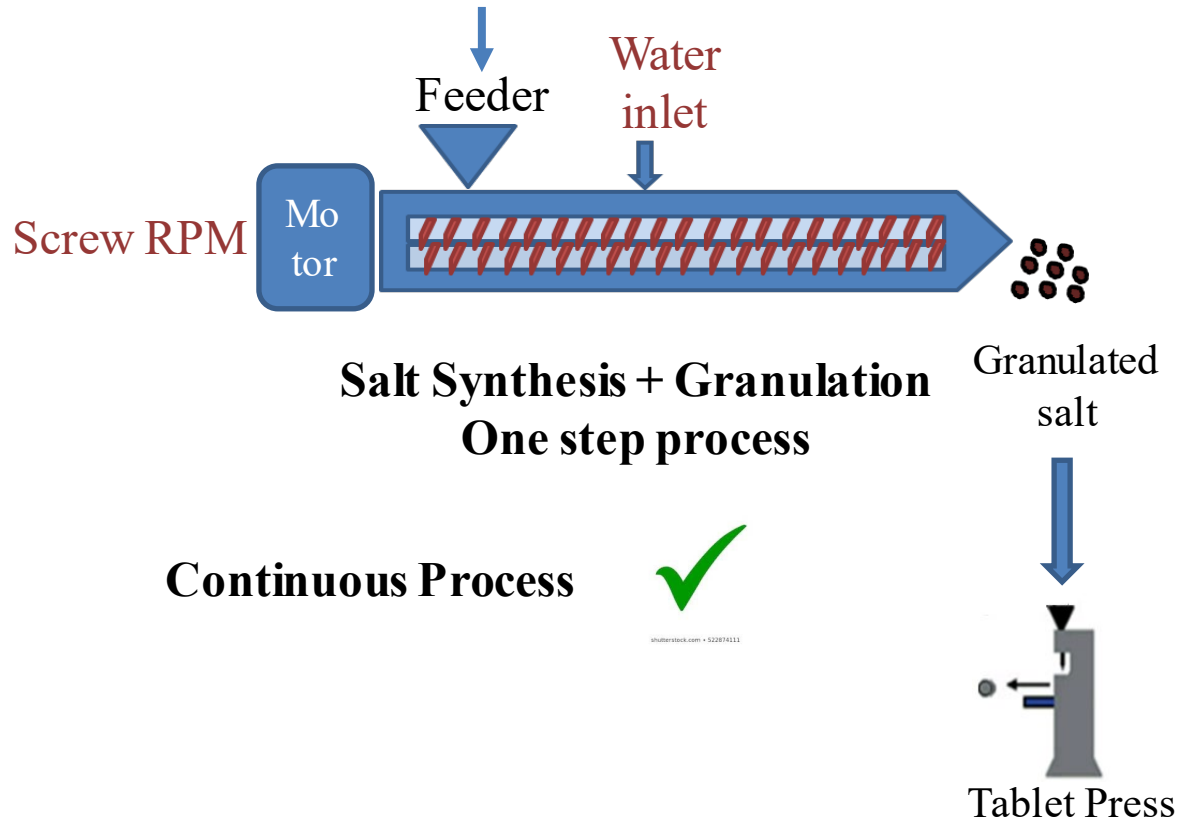
Continuous Salt Synthesis and Melt Granulation

Lee, H.L., Vasoya, J.M., Cirqueira, M.D.L., Yeh, K.L., Lee, T. and Serajuddin, A.T., 2017. **Continuous Preparation of 1: 1 Haloperidol–Maleic Acid Salt by a Novel Solvent-Free Method Using a Twin Screw Melt Extruder.** *Molecular pharmaceuticals*, 14(4), pp.1278-1291.

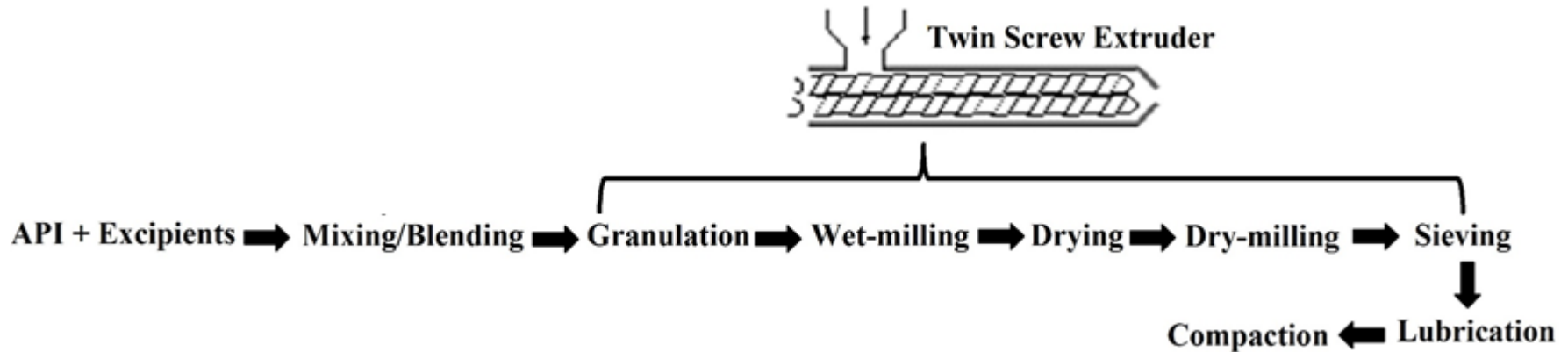
Vasoya, J.M., Lee, H.L., Lee, T. and Serajuddin, A.T., 2022. **Continuous Salt Synthesis and Melt Granulation.** *Manuscript under preparation.*

Continuous Salt Synthesis and Granulation

Cinnarizine + malic acid (1:1 molar mixture)
+ binder + disintegrant + glidant

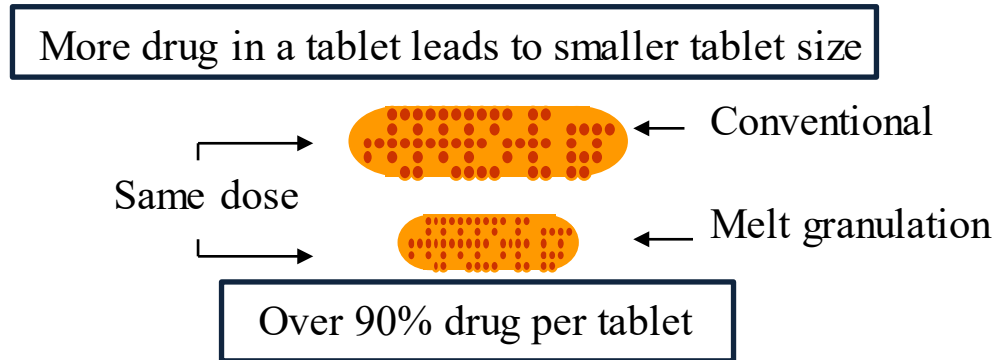


Conclusions -1



- One step granulation process
- In case of wet granulation, no drying and milling needed
- Higher effectiveness compared to low shear and high shear granulation
- Continuous API (salt) synthesis and granulation feasible
- Twin screw granulation at elevated temperature has potential to emerge as powerful technology for continuous tablet production

Conclusions -2



- Smaller tablet
- Cost savings
- Higher productivity
- Process scaled up to 1000 kg batch