FACULTY OF
PHARMACEUTICAL SCIENCES

DEPARTMENT OF PHARMACEUTICS
LABORATORY OF PHARMACEUTICAL TECHNOLOGY

IDENTIFYING CRITICAL BINDER ATTRIBUTES TO FACILITATE BINDER SELECTION FOR EFFICIENT FORMULATION DEVELOPMENT IN A CONTINUOUS TWIN SCREW WET GRANULATION PROCESS

Lise Vandevivere – ExciPerience 10/03/2020

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INTRODUCTION

Who am I?

- Lise Vandevivere – Pharmacist
- PhD researcher at Ghent University
    - Laboratory of Pharmaceutical Technology
- Research focusing on formulation development using the ConsiGma-25 line
    - In collaboration with Roquette Frères
    - 3 research papers

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INTRODUCTION

- Continuous twin screw wet granulation

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INTRODUCTION

- Continuous twin screw wet granulation

  → Suitability of excipients

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Binders

- Facilitate the granulation process
- Granule quality is affected by the binder type

→ Binder selection for continuous TSG should rely on a <u>scientific approach</u> to obtain efficient formulation development:

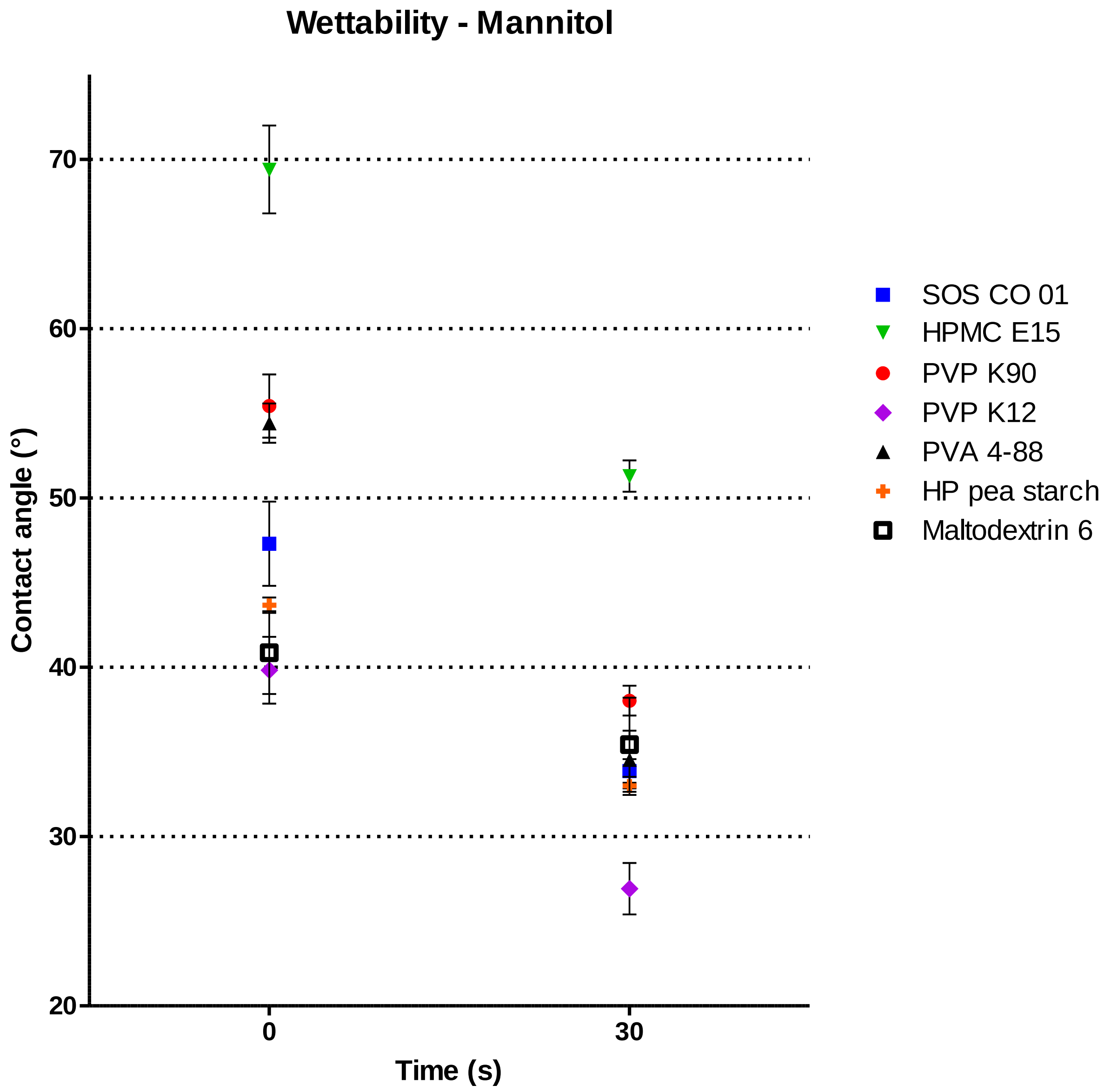
1. Extensive raw binder characterization
2. Granulation experiments with poorly/highly soluble formulation + binders (5%)
3. Link granule quality to binder attributes
4. Identify which attributes are critical in a continuous wet granulation process

   → Facilitate binder selection!

RAW BINDER CHARACTERIZATION

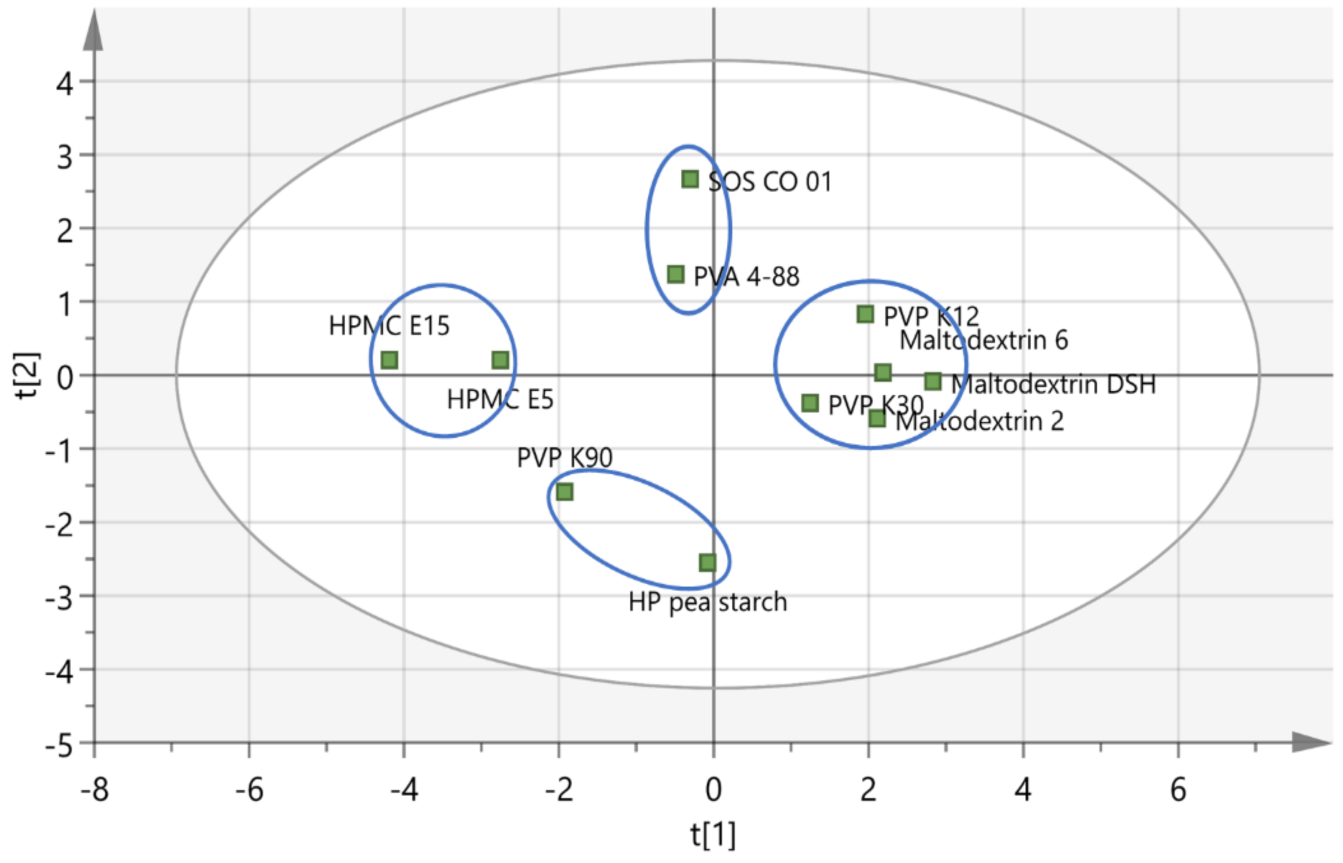
- Selection of binders covering the different chemical natures of most commonly used binders for TSG:
  - HPMC, PVP, PVA, Starch-based binders

- Binder characterization:
  - Wettability
    - E.g. binder wetting, binder on different surfaces
  - Viscosity properties
  - Dissolution kinetics
  - Surface tension
  - Particle size distribution



RAW BINDER CHARACTERIZATION

- Principle Component Analysis



Focusing on:

- Wettability
- Viscosity
- Dissolution kinetics
- Surface tension
- Particle size distribution

4 main clusters were identified

Binder selection based on binder attributes to maximize variability to perform granulation experiments

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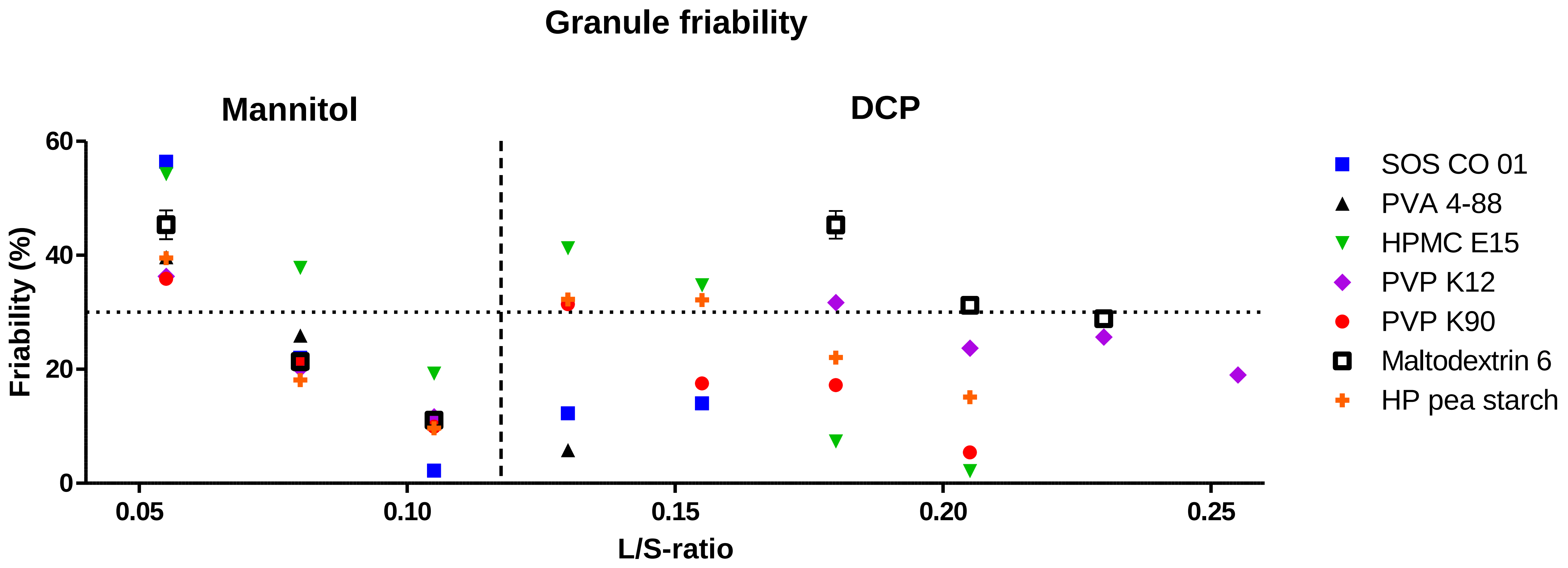
GRANULATION EXPERIMENTS

- Granulator (ConsiGma-25 line) – tray drying
    - DCP vs Mannitol
    - Granule characterization (granule friability)



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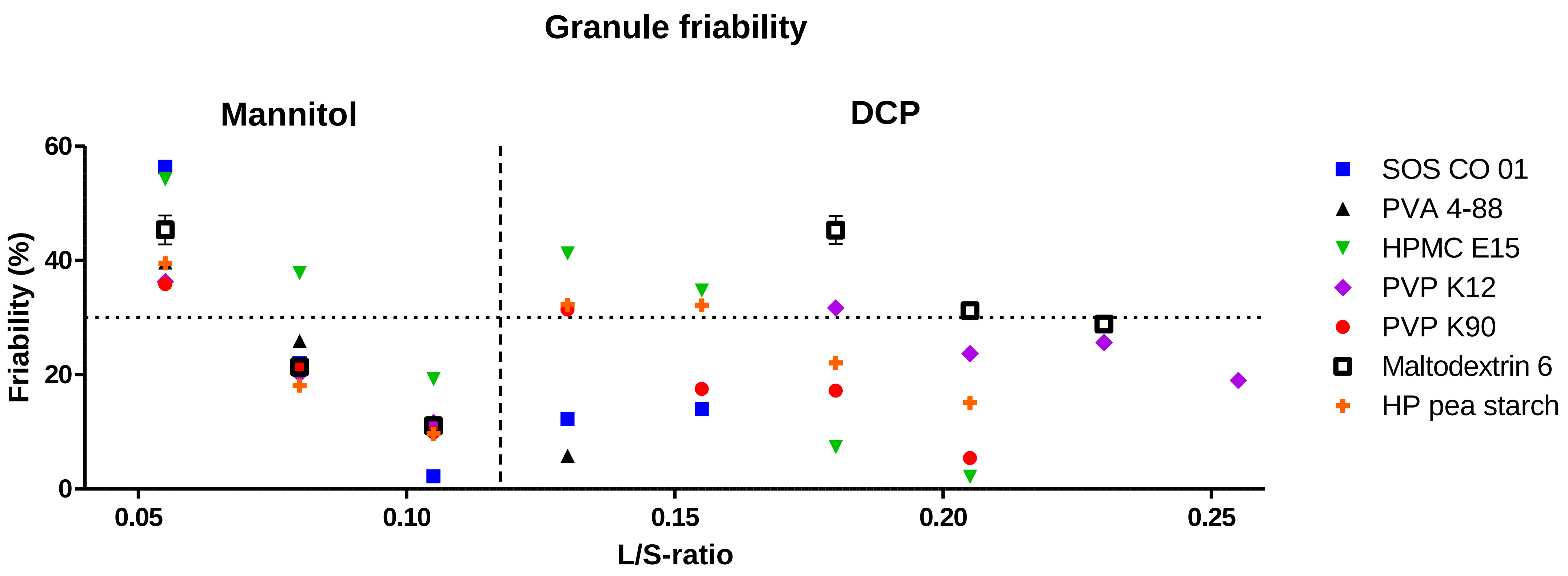


Efficient granulation with both formulations required different processing settings:

→ Lower liquid content for mannitol – importance of the included filler

→ Broader range for L/S-ratio where binders are active for DCP

→ Binder addition is especially valuable for a poorly soluble formulation

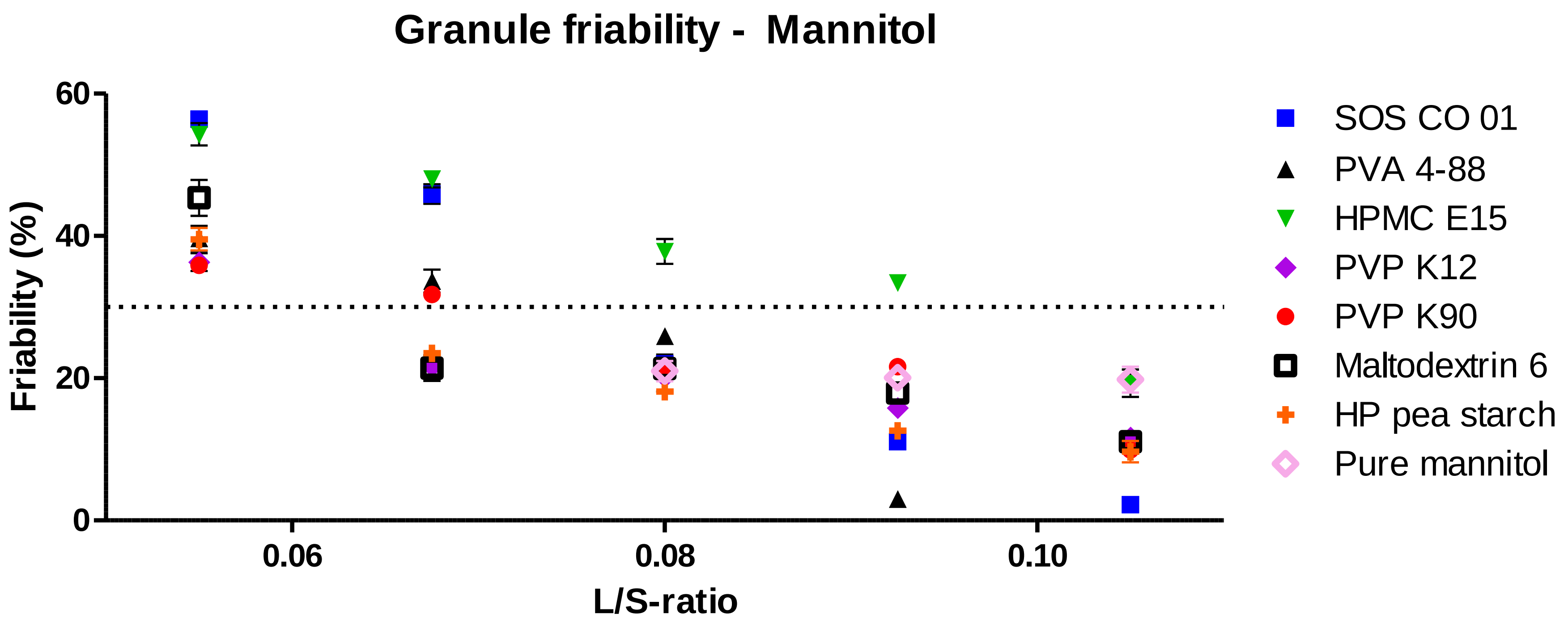
Binders showing different effectiveness in combination with mannitol or DCP

→ Binder attributes guiding binder selection differ in function of the solubility of the formulation

GRANULATION EXPERIMENTS

Binder attributes guiding binder selection differ in function of the solubility of the formulation

<u>Mannitol – highly soluble</u>



- Binder effectiveness:
  - L/S-ratio to reach 30% granule friability threshold

High: 0.0675	**Average: 0.0800**	**Low: 0.1050**
PVP K12	SOS CO 01	HPMC E15
HP pea starch	PVA 4-88	
Maltodextrin 6	PVP K90	

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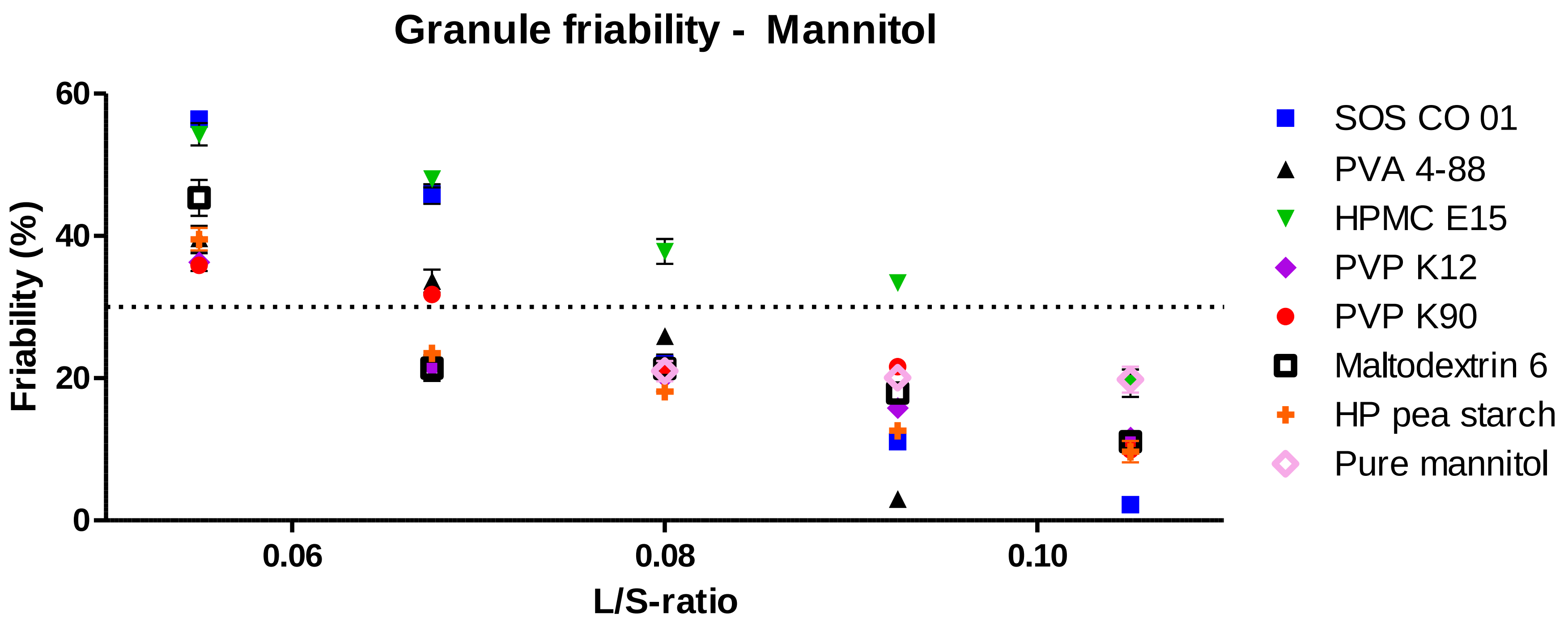

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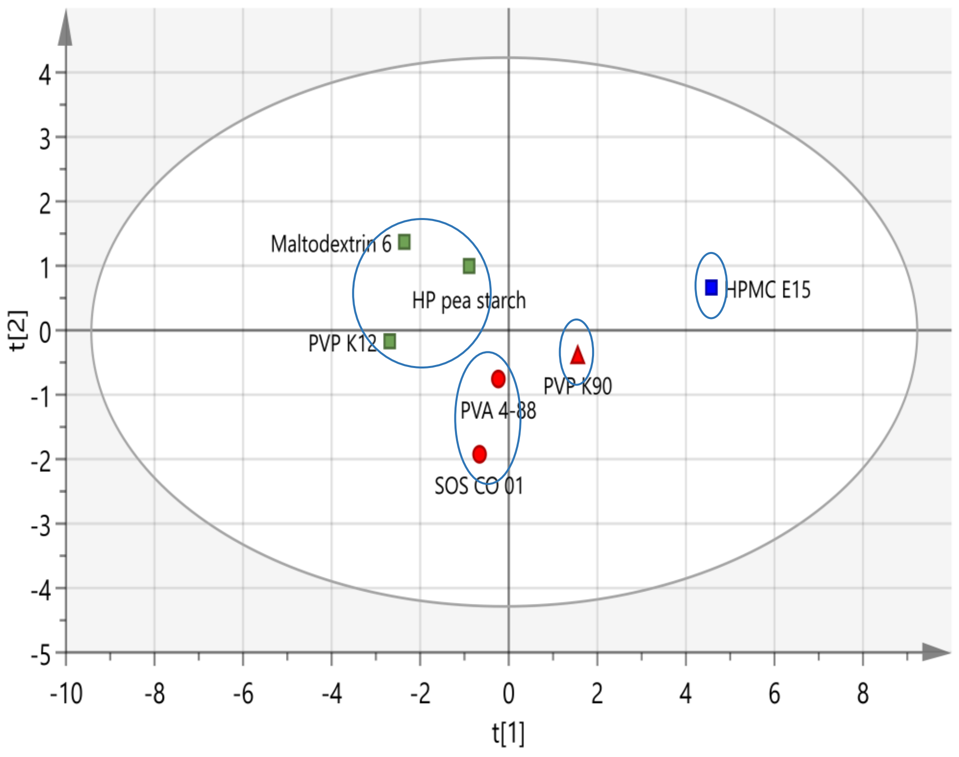

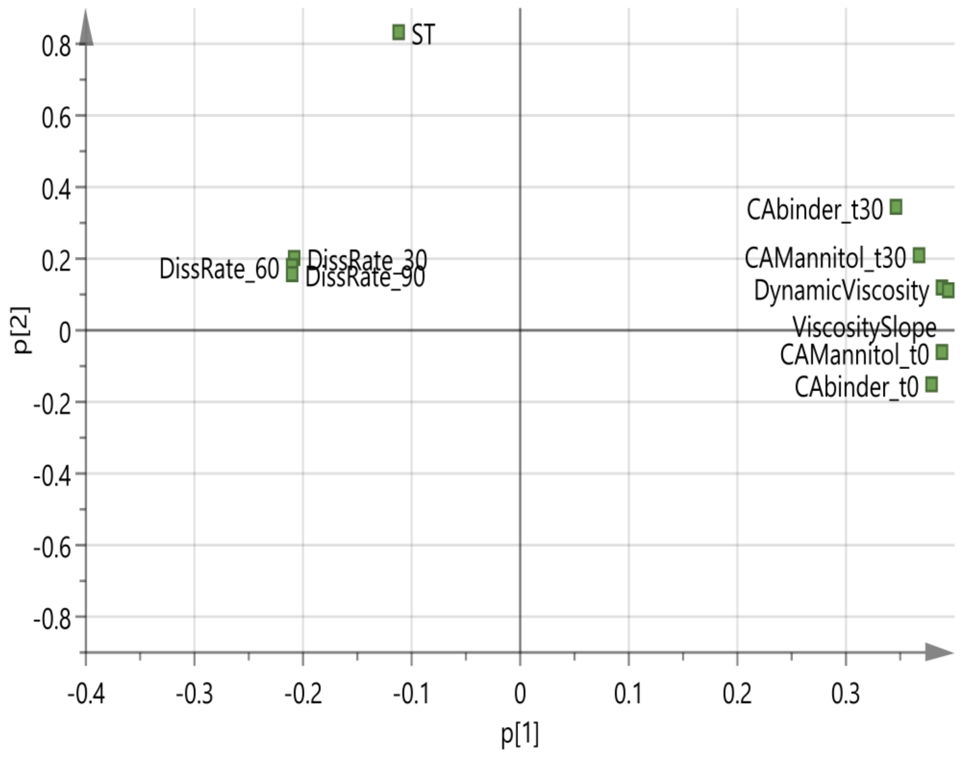

Binders clustered on score scatter plot:

→Binder effectiveness related to binder properties

→High effectiveness was linked to:

→Fast dissolution

→Good wetting of mannitol particles

GRANULATION EXPERIMENTS

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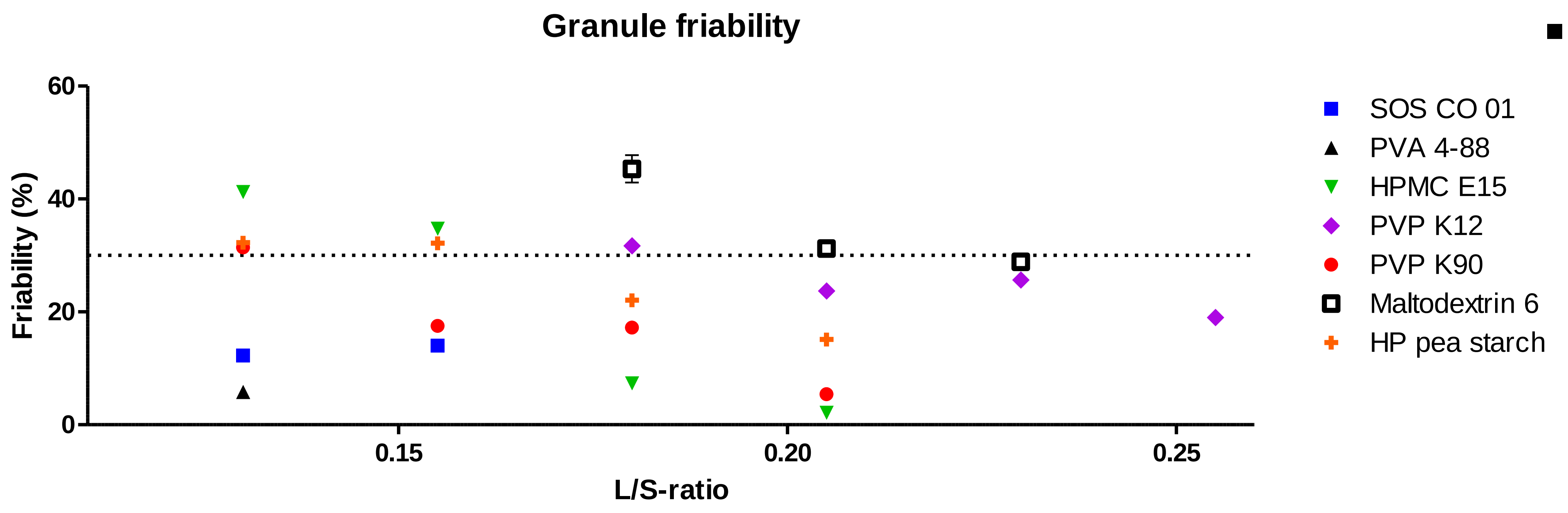

- Binder effectiveness:
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High: 0.130	Average: 0.155 - 0.180	Low: > 0.205
SOS CO 01	HPMC E15	PVP K12
PVA 4-88	HP pea starch	Maltodextrin 6
	PVP K90	

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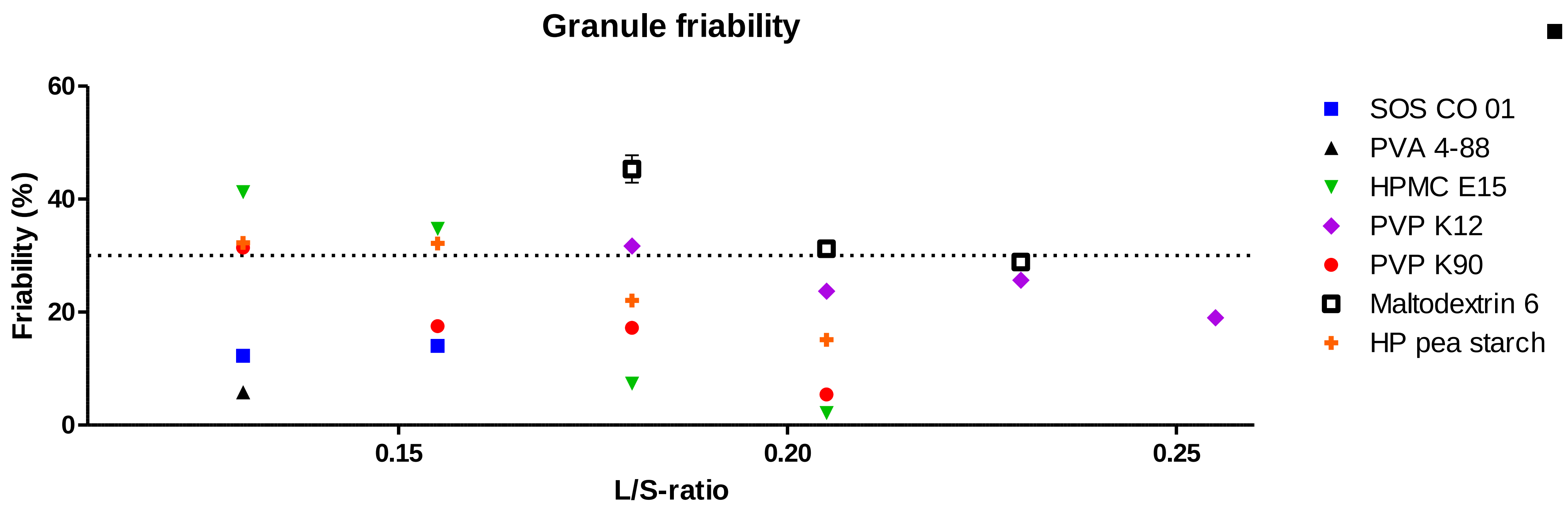

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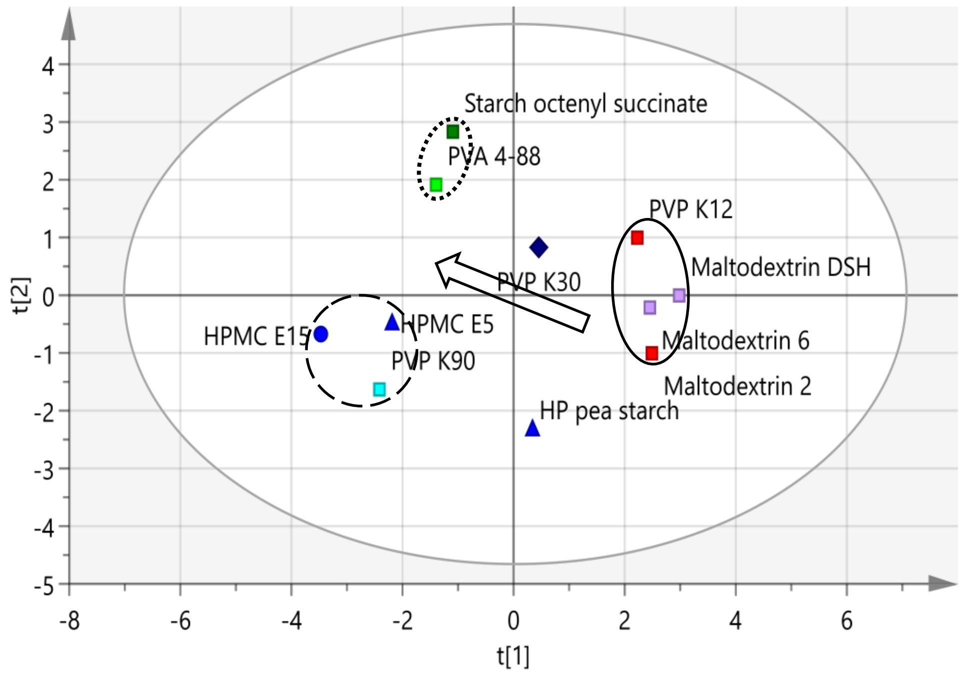

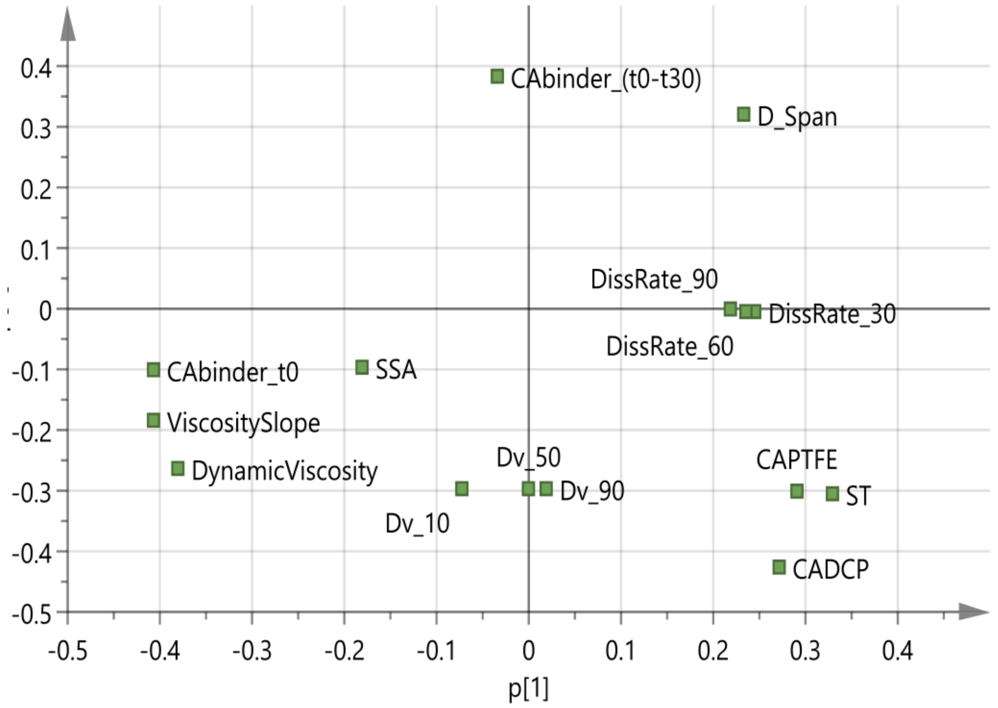

Binders clustered on score scatter plot:

→ Binder effectiveness related to binder properties

→ High effectiveness was linked to:

→ Fast wetting

→ Good wetting of DCP particles

→ Additive: high viscosity properties

GRANULATION EXPERIMENTS

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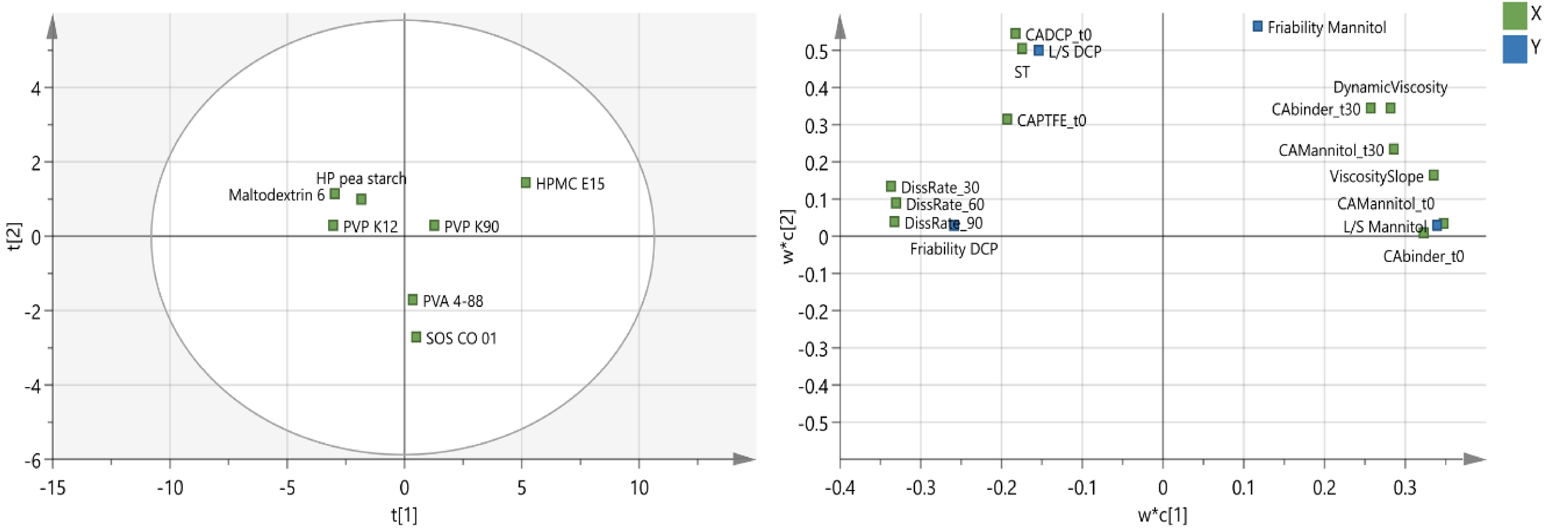

- Vandevivere, L.; Denduyver, P.; Portier, C.; Häusler, O.; De Beer, T.; Vervaet, C.; Vanhoorne, V. Influence of binder attributes on binder effectiveness in a continuous twin screw wet granulation process via wet and dry binder addition. *Int. J. Pharm.* **2020**, *585*, 119466, doi:10.1016/j.ijpharm.2020.119466.

- Vandevivere, L.; Vangampelaere, M.; Portier, C.; de Backere, C.; Häusler, O.; De Beer, T.; Vervaet, C.; Vanhoorne, V. Identifying Critical Binder Attributes to Facilitate Binder Selection for Efficient Formulation Development in a Continuous Twin Screw Wet Granulation Process. *Pharmaceutics* **2021**, *13*, 210. https://doi.org/10.3390/pharmaceutics13020210

GRANULATION EXPERIMENTS

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Concise overview of critical binder attributes

Continuous TSG

Binder selection

Highly soluble formulation	Poorly soluble formulation
Fast binder dissolution kinetics	Slow binder dissolution kinetics
Low viscosity attributes	High viscosity attributes
Good binder wetting	Good binder wetting
When activated: good wetting properties by the binder of the highly soluble formulation	When activated: good wetting properties by the binder of dispersive surfaces
Low surface tension was important to achieve the lowest granule friability	Low surface tension was important to result in higher binder effectiveness

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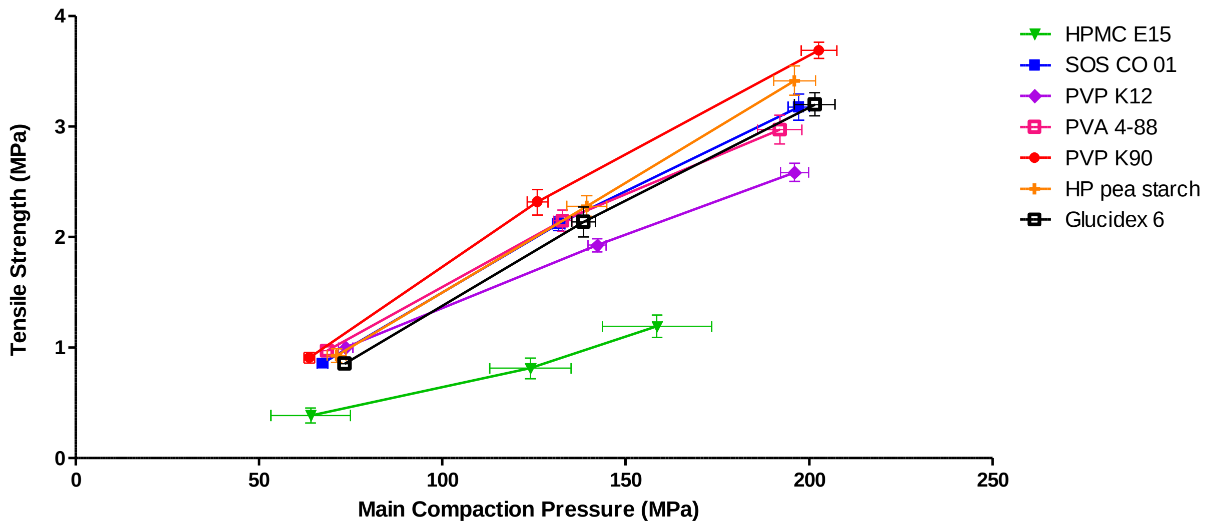
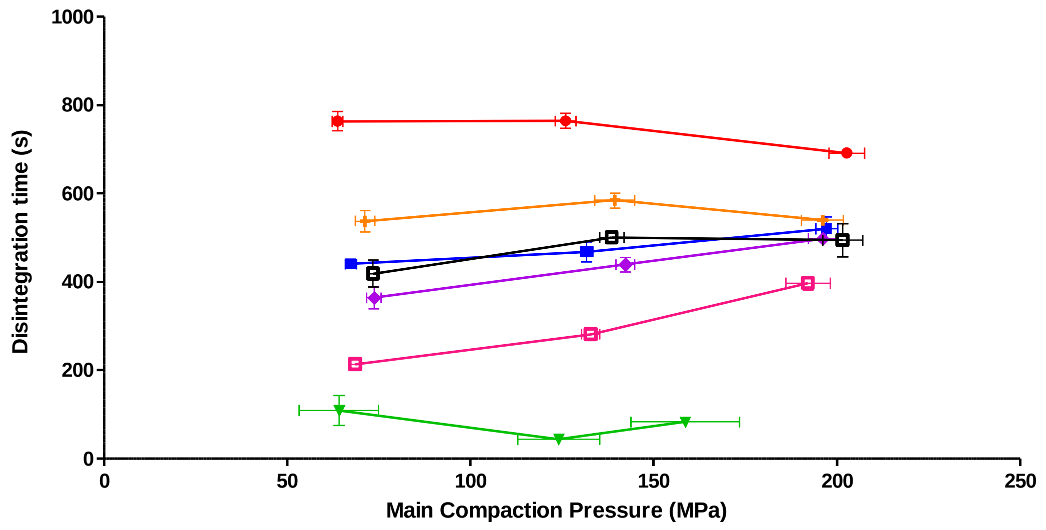
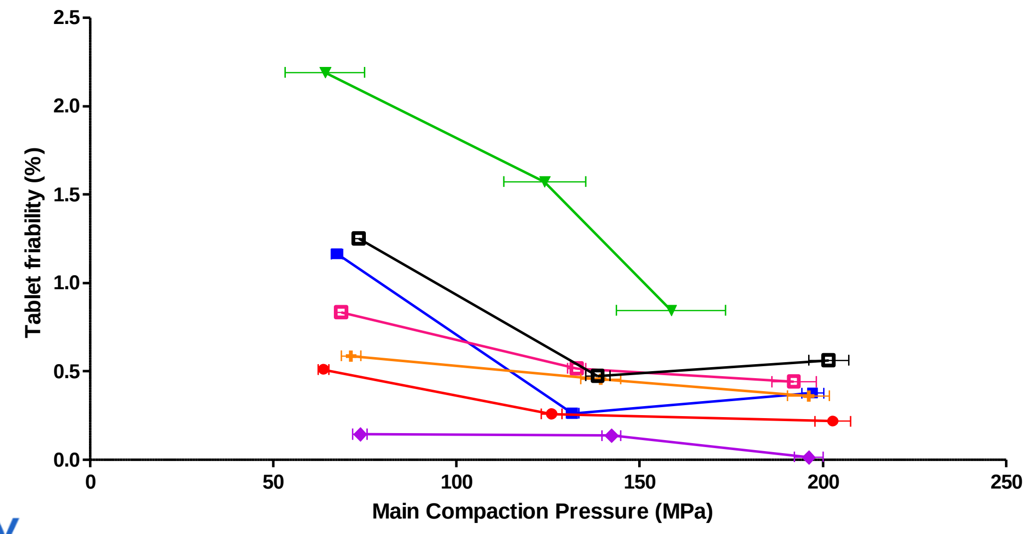
TABLET EXPERIMENTS – MANNITOL FORMULATION







At similar compaction pressures:

- Tablets containing HPMC E15 resulted in low tensile strength (<1 MPa), all other binders yielded tablets with tensile strengths higher than 2 MPa.
  - Lower plasticity factor

Binder	Plasticity Factor (%)
PVP K12	94.72 (±0.26)
PVP K90	94.75 (±0.09)
HPMC E15	88.01 (±0.08)
PVA 4-88	94.68 (±0.04)
Maltodextrin 6	95.69 (±0.01)
SOS CO 01	96.15 (±0.04)
HP pea starch	96.38 (±0.05)

  - Tablet friability at highest main compaction pressure compliant to EP (< 1.0%)
    - PVA, HP pea starch, PVP K90 / K12 already met this limit at low compaction pressures.

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CONCLUSION

- Binder effectiveness in a continuous twin screw wet granulation process depended on the solubility of the formulation
- Critical binder attributes influencing binder effectiveness were identified for a poorly and highly soluble formulation
- Binder addition especially valuable for poorly soluble formulation
- Future perspective: downstream processing

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Questions?

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Lise Vandevivere

PhD researcher

LABORATORY OF PHARMACEUTICAL TECHNOLOGY

E Lise.Vandevivere@ugent.be

Ghent University

@ugent

Ghent University

www.ugent.be

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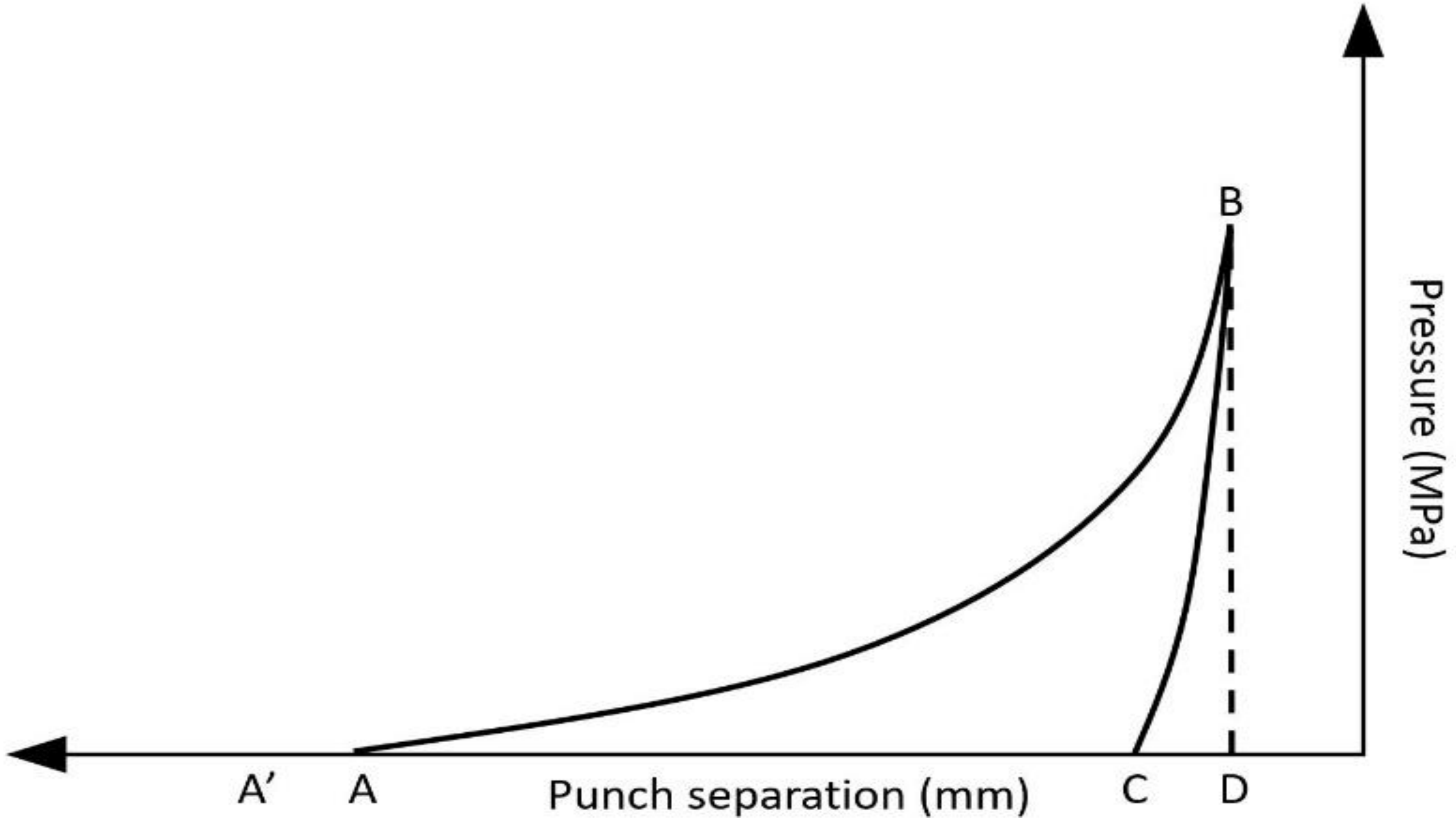
ENERGY PLOT



- Force-displacement curves plotting compaction pressure against punch separation:
  - A – A': powder particle rearrangement and packing
  - A – B: Increase of compaction pressure until a maximum pressure (B) with a corresponding minimal punch separation (D)
  - B – C: decompression or unloading: applied pressure is released

→ ABD: work of compression
→ BCD: work of elastic recovery
→ ABD – BCD = work of compaction

The plasticity factor (PF) of a binder (%)

$$PF\ (\%) = \frac{Work\ of\ compaction}{Work\ of\ compression} * 100$$