PVA as binder in continuous twin-screw granulation

G. Birk[1], A. von der Brelie[1], A.-N. Knüttel[1], P. Denduyver[2], V. Vanhoorne[2]

Introduction

Granulation of powder blends is a **commonly applied technique** for pharmaceutical formulations which have **no suitable flowability or compactability or** are **inhomogeneous** with regards to the API content. Mainly wet granulation is applied[3] and here, especially **continuous twin-screw granulation (TSG)** is a technique that offers **several benefits**. TSG is **more efficient, requires less water** compared to batchwise techniques such as high shear granulation[4,5] and **granules have more favorable properties** (more porous, less spherical).

Objectives

Generally, a binder is added to the powder blend to improve the characteristics of the granules. Most preferably, the binder – often HPMC, HPC or PVP based – is included in the dry blend and granules are formed by the addition of pure water. Low viscous grades of PVA (polyvinyl alcohol) are already used, however, not systematically evaluated.

Therefore, this **work assesses** the **applicability** and **suitability** of **different grades of PVA as binder in twin-screw granulation**. **Different** formulation **compositions** are tested **representing hydrophilic and hydrophobic** nature.

Methods

Dicalcium phosphate (DCP, Calipharm A, Innophos, USA) was used as **hydrophobic excipient**, **Mannitol** (Pearlitol 50C, Roquette, Lestrem) as **hydrophilic filler**. **Different grades of PVA** (4-88, 18-88, 40-88, MilliporeSigma, Germany) were used as binder, **5% w/w** was **added to the filler**. Additionally, formulations with 50% w/w paracetamol semi-fine (Mallinckrodt, USA) as **model compound** were assessed.

Twin screw granulator of ConsiGma™-25 system (GEA, Belgium) was used at powder throughput of 20 kg/h and barrel temperature of 30°. Screw speed was set at 300, 500 and 700 rpm for hydrophobic, hydrophilic, and model compound formulation, respectively.

Granules were **characterized** with respect to **size** (QicPic, Sympatec, Germany), friability (PTF 300, Pharma Test, Germany) and **compactability** (STYL'One, Kilian, France). Before compaction, granules were milled (ConsiGma™-25 system, GEA, Belgium) with grater screen of 1,500 µm on 900 rpm, 2% Magnesium stearate is added, and 400 mg tablets are produced (different forces).

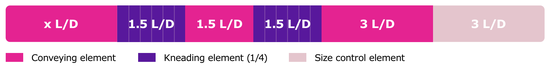

Figure 1.
Screw configuration, kneading elements at stagger angle of 60°.

Results

Influence of PVA grades on granule quality of hydrophilic and hydrophobic formulations

- **Mannitol formulation: All** tested **PVA grades are effective binders demonstrated by low friability values at low liquid-to-solid (L/S) ratios** (Fig. 2). PVA 40-88 is the most effective binder (granules with friabilities below 30%, i.e. considered as good friability values) at the lowest L/S-ratio. PVA 18-88 produces granules with the lowest absolute friability. But both grades resulted in high torque values limiting the advantage of those. **PVA 4-88** is considered the **best PVA grade for granulation** as it yields **granules with good friability** (i.e. below 30%) **with** relatively **low torque values**.
- **PVA 4-88** is the **most effective binder at lowest L/S-ratios for the DCP formulation**. No significant differences are seen for the lowest absolute friability between the PVA binders.
- **Low amounts of fines** are seen for all formulations on the highest L/S-ratios.

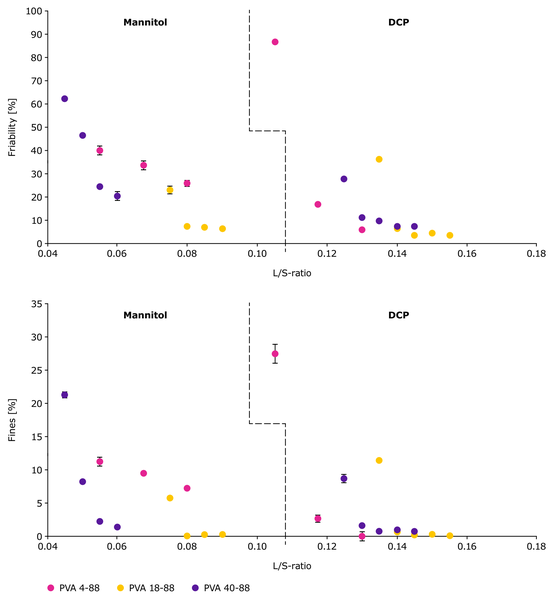

Figure 2.
Friability (top) and fines (bottom) in function of L/S-ratio for formulations containing 95% of mannitol or DCP are included and 5% PVA (w/w).

Influence of PVA grades on granule and tablet quality of model compound formulation

- **PVA 4-88** is the **most effective filler in this formulation** as it produces the strongest granules at the lowest L/S-ratios. However, **with all PVA grades very low granule friability can be achieved** (<5%), consequently **all PVA grades are suitable binders** in this formulation (Fig. 3, top).
- **Low amounts of fines** (Fig. 3, middle) are seen for all formulations on the highest L/S-ratios.
- Overall, the **hardness** is **very similar for all granules** which finally leads to comparable tablet hardnesses (Fig. 3, bottom). Good tablets are produced at a compaction pressure of 127 MPa since the tensile strength is higher than 1.7 MPa (dotted horizontal line).

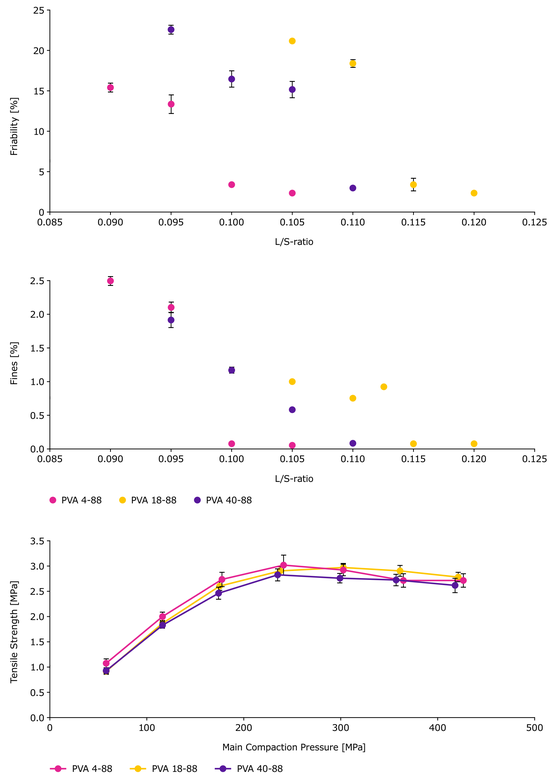

Figure 3.
Friability of granules (top) as a function of L/S-ratio, particle size distribution at lowest and highest L/S-ratio for each PVA grade (middle). Granules contain 50% Paracetamol, 45% Mannitol, 5% PVA (all w/w). Tableting performance of granules (bottom) as a function of compression pressure.

Conclusions

The use of PVA as binder in TSG is comprehensively evaluated by using different grades and excipients differing in hydrophilicity and hydrophobicity.

- **PVA is an efficient binder** for various pharmaceutical formulations as.
- **PVA produces strong granules on low L/S-ratios** which are favorable since these enable **short drying times** during downstream processing.
- **Low amounts of fines** are obtained.
- The granules show **superior tableting performance**.
- **PVA 4-88 is preferred** as granules with good friability are yielded with low torque values.

References

1. MilliporeSigma, MilliporeSigma is the U.S. and Canada Life Science business of Merck KGaA, Darmstadt, Germany.
2. Laboratory of Pharmaceutical Technology, Ghent University, Ottergemsesteenweg 460, 9000 Ghent, Belgium.
3. Pharmaceutics. 2021 May; 13(5): 668, Continuous Twin Screw Granulation: A Review of Recent Progress and Opportunities in Formulation and Equipment Design, Christoph Portier, Chris Vervaet, and Valérie Vanhoorne.
4. Beer, P., Wilson, D., Huang, Z., De Matas, M. Transfer from high-shear batch to continuous twin screw wet granulation: A case study in understanding the relationship between process parameters and product quality attributes. J. Pharm. Sci. 2014, 103, 3075–3082.
5. Megarry, A., Taylor, A., Gholami, A., Wikström, H. Tajarobi, P. Twin-screw granulation and high-shear granulation: The influence of mannitol grade on granule and tablet properties. Int. J. Pharm. 2020, 590, 119890.

Contact details: Gudrun.Birk@emdgroup.com

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Lit. No. MK_PS12786EN 09/2023