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White Paper

Use of Polyvinyl Alcohol as an effective Binder in Continuous Twin-Screw Granulation

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Granulation of powder blends is a commonly used technique for pharmaceutical formulations which lack suitable flowability or compactability, or lack homogeneity in terms of the active pharmaceutical ingredient (API) content. In these cases, wet granulation can be used and is performed in batch mode using high shear or a fluidized bed. Continuous twin-screw granulation (TSG) offers several advantages here[1] as it is more efficient, requiring less water compared to batchwise techniques[2,3] and producing granules have more favorable properties (more porous, less spherical). In TSG, the components are gravimetrically fed into a blender and then the blend is gravimetrically fed into the granulator in a continuous line.

To facilitate granulation, a binder is usually dissolved in solution and then added to the formulation to create a cohesive network between the formulation ingredients. The binder helps to ensure that the resulting granules and tablets meet predetermined quality targets including granule size distribution, granule friability, tablet tensile strength, and tablet content uniformity. Among the binders used in TSG are hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), and polyvinyl alcohol (PVA). Given the important role of the binder, selection of a suitable material is essential for the ideal agglomeration of the API with excipients, and to ensure good process efficiency in terms of an accurate feeding process and reduced drying times.[4]

This white paper describes an assessment of the applicability and suitability of PVA when used as a binder in TSG for formulation compositions with different hydrophilicity and hydrophobicity. PVA is widely known and commonly used in pharmaceutical products across different formulations.

PVA can be found in various formulations, e. g. ophthalmic, topical, and transdermal dosage forms, while PVA is predominantly applied in oral formulations as a tablet coating. In TSG it is most efficient adding binder as physical powder via a feeder instead of first preparing a solution. However, it is crucial to achieve sufficient hard granules by forming bridges between filler and binder with just the addition of water and within such short process times as it is the case in TSG.

Experimental Methods

In all experiments, dicalcium phosphate (DCP, Calipharm A, Innophos, USA) was used as a hydrophobic excipient and mannitol (D(-)-Mannitol Emprove® Essential, Merck KGaA, Germany) used as a hydrophilic filler. Different grades of PVA (4-88, 18-88, 40-88, Merck KGaA, Germany) were used as a binder and 5% w/w was added to the filler. Formulations with 50% w/w paracetamol semi-fine (Mallinckrodt, USA) were assessed as model compounds.

A twin-screw granulator of ConsiGma™-25 system (GEA, Belgium) was used at powder throughput of 20 kg/h and barrel temperature of 30 °C. Screw speed was set at 300, 500 and 700 rpm for hydrophobic, hydrophilic, and model compound formulations, 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) using a grater screen of 1,500 µm on 900 rpm, 2% magnesium stearate was added, and 400 mg tablets are produced using different forces. Figure 1 shows the screw configuration and kneading elements at a stagger angle of 60°.

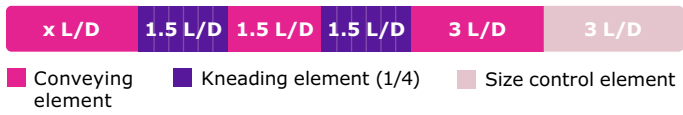

Figure 1.

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

Influence of PVA grades on Granule Quality

All tested PVA grades were shown to be effective binders as demonstrated by low friability values at low liquid-to-solid (L/S) ratios (Figure 2). In the mannitol formulation, PVA 40-88 was the most effective binder (granules with friabilities below 30% considered as good values) at the lowest liquid/solid (L/S) ratio. PVA 18-88 produced granules with the lowest absolute friability. Both grades resulted in high torque values limiting the advantage offered. PVA 4-88 was considered to be the best PVA grade for granulation as it yields granules with good friability (i. e. below 30%) with relatively low torque values.

In this study, PVA 4-88 was the most effective binder at the lowest L/S ratios for the dicalcium phosphate formulation. No significant differences were observed for the lowest absolute friability among the PVA binders. Low amounts of fines were obtained for all formulations on the highest L/S ratios.

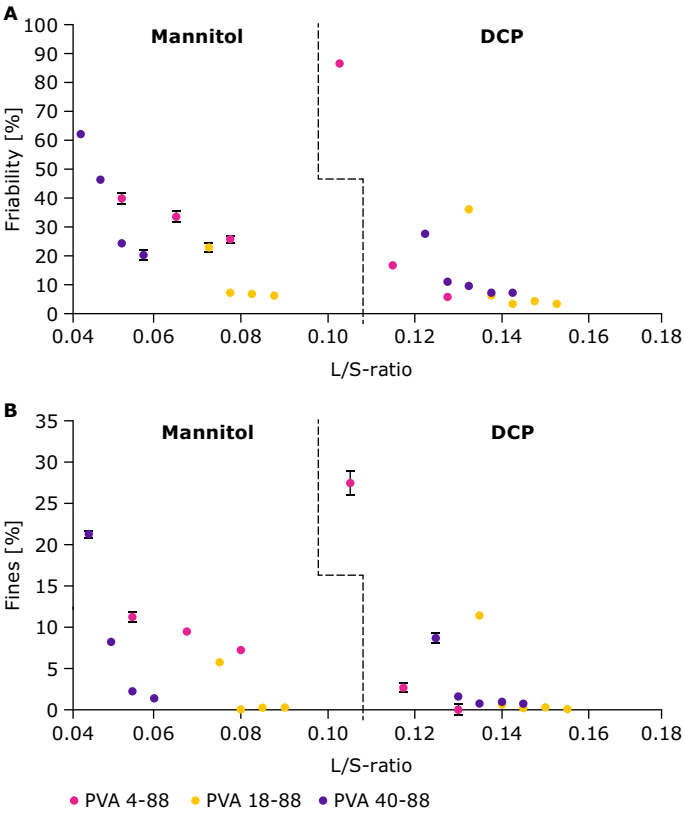

Figure 2.

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

PVA 4-88 was the most effective filler in the model compound formulation as it produced the strongest granules at the lowest L/S ratios. However, with all PVA grades, very low granule friability can be achieved (<5%), and as such, all grades were suitable binders in this formulation (Figure 3A).

Low amounts of fines were obtained for all formulations on the highest L/S ratios (Figure 3B).

Overall, tablet hardness was similar for all granules which leads to comparable tablet harnesses (Figure 3C). Good tablets were produced at a compaction pressure of 127 MPa as the tensile strength was higher than 1.7 MPa.

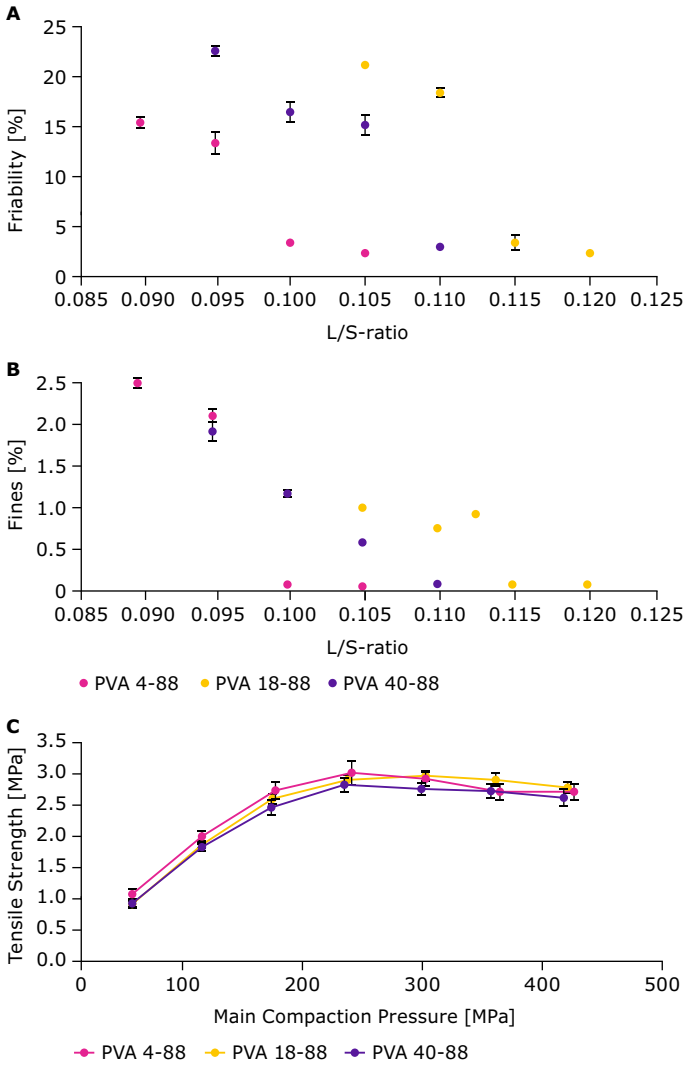

Figure 3.

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.

Conclusion

The use of PVA as binder in TSG was comprehensively evaluated with the use of different grades and excipients which varied in hydrophilicity and hydrophobicity. PVA was shown to be an efficient binder for various pharmaceutical formulations. It produces strong granules on low L/S ratios which are favorable since these enable short drying times during downstream processing. Low amounts of fines were obtained and the granules showed superior tableting performance. Overall, PVA 4-88 was preferred as the granules had good friability and yielded with low torque values.

Selecting a PVA Grade

Typically, PVAs are classified according to their viscosity and degree of hydrolysis. The typical two figure nomenclature for the different grades is thus made up of the viscosity of a 4% solution at 20 °C (first figure) and the degree of hydrolysis of the polymer (saponification level; second figure). For example, PVA 4–88 indicates a PVA grade with a viscosity of 4 mPa·s that is 88% hydrolyzed. Both parameters have a substantial effect on the polymer's performance. For example, as hydrolysis increases, so do crystallinity, melting temperature, and mechanical strength, due to the high level of hydrogen bonding between chains. A lower hydrolysis grade has higher solubility in water and may show better compatibility with other excipients.

Viscosity, determined by the polymer chain length, also has a great influence on the performance of a formulation. As the chain length rises and with it the molecular weight (MW), the viscosity in solution also increases. However, while all PVAs are water-soluble, the dissolution time and the maximum amount in solution are strongly dependent on the PVA's MW. With increasing MW, the time required for dissolution increases while the maximum soluble amount decreases.

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