Isomalt as PVP-Binder Replacement in High-Shear Wet Granulation for Tablet Preparation

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Introduction

- Tablets are one of the most widely used oral dosage forms for oral delivery in the pharmaceutical and nutraceutical industries.
- If the drug dose per tablet is high and the formulation cannot ensure direct compression requirements, then the granulation process is required to improve the flowability, avoid powder segregation, and improve tabletability.
- High-shear wet granulation (**WG**) is one of the most popular and widely used methods, while polyvinylpyrrolidone (**PVP**) is one of the most widely used binders in wet granulation.
- **This study aimed to** investigate isomalt as a natural based alternative to PVP-binder in the high-shear WG process.

Materials

- Isomalt (**galenIQ™801**; BENEO-Palatinit GmbH, Neuoffstein, Germany),
- PVP (**Kollidon® 25**; BASF SE, Ludwigshafen, Germany),
- Microcrystalline cellulose (**MCC, Vivapur® 101**; JRS Pharma GmbH & Co. KG, Rosenberg, Germany),
- Lactose (**GranuLac® 200**; Meggle, Wasserburg, Germany), and
- Magnesium stearate (**MgSt**, Magnesia 4264; Magnesia GmbH, Lüneburg, Germany).

Fig. 1

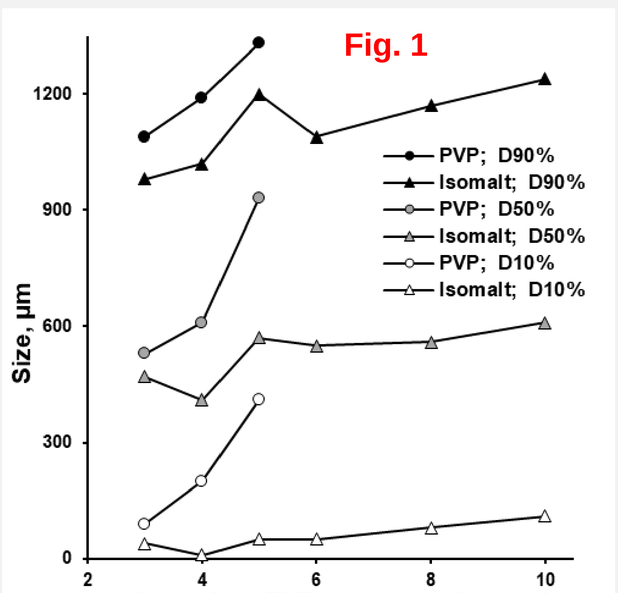


Fig. 2

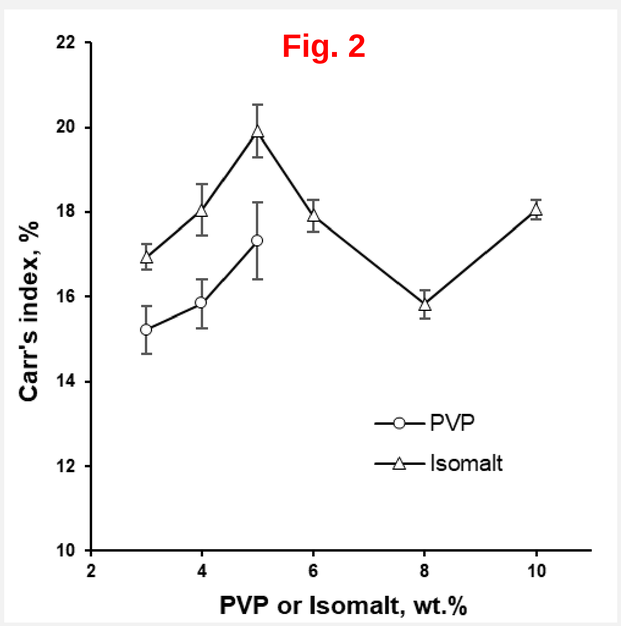


Fig. 3

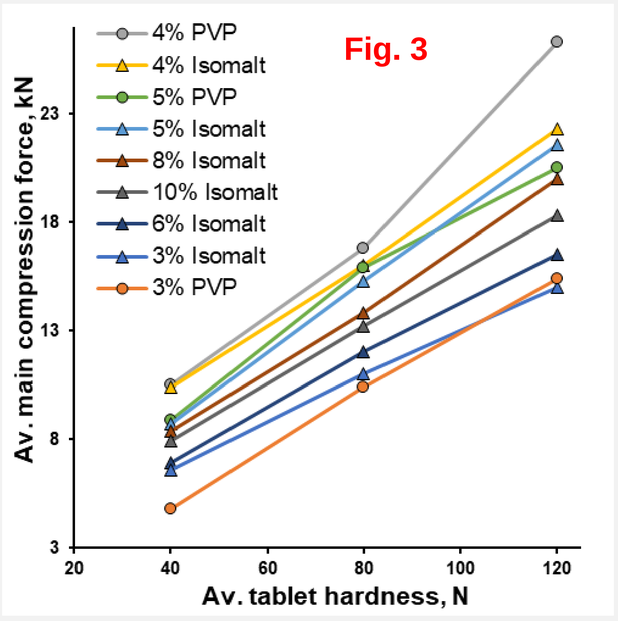
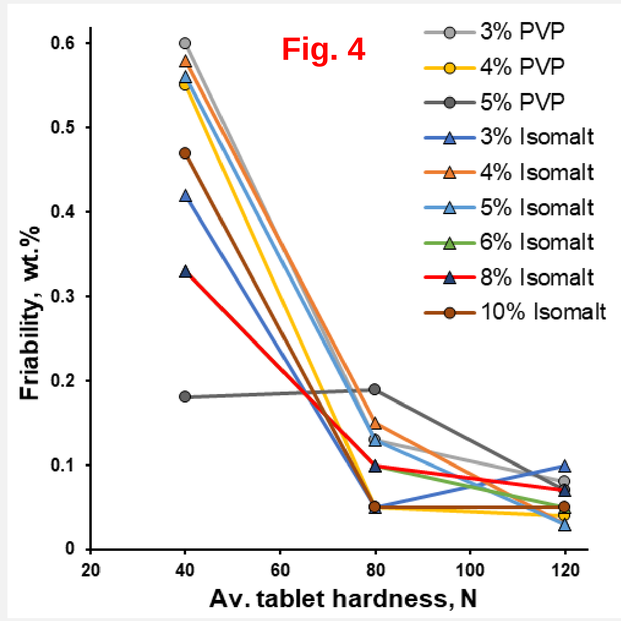


Fig. 4



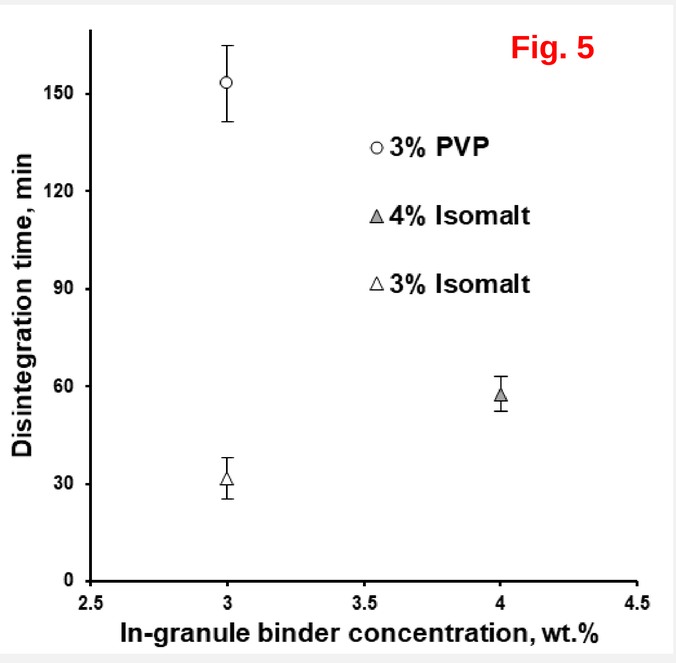
Results

- The increase in binder concentration increased the D10%, D50%, and D90% of granules for isomalt and PVP (Fig. 1). The increase in granule binder concentration from 2 to 4 wt.% resulted in an increase in D50% size from 530 to 930 µm for PVP and from 470 to 570 µm for isomalt. The additional increase in isomalt concentration up to 10 wt.% only slightly increased the D50% size to 610 µm (**Fig. 1**).
- The Compressibility index of all granules was found in the range of 15.2 and 19.9 (**Fig. 2**) and can be classified as acceptable for tableting purpose.
- To achieve the goal hardness of tablets at 40, 80 and 120 N, average main compression force increased proportionally, following the same trend (**Fig. 3**).
- Tablet friability decreased with higher tablet hardness (**Fig. 4**). Both binders and every concentration showed the same trend – friability decreased sharply from 40 N tablet hardness, however 5% PVP was an outlier with slight friability increase (0,18% to 0,19% from 40N to 80N). Overall, all tablets showed friability lower than 1%.
- The disintegration time of 80 N target hardness tablets increased with higher binder concentration (**Fig. 5**). At 3% Isomalt as binder concentration it took 22 minutes for first tablet to fully disintegrate, however with 3% PVP fastest disintegration was seen at 2 hours 14 minutes.
- Every other concentration showed no disintegration during the first hour, after which the test was abandoned.

Methods

- **High-shear WG**. Isomalt or PVP as a binder was pre-dissolved in 240 g of purified water in a specific concentration (wt.%). 1 part of MCC and 4 parts of lactose with a total mass of **800 g** were preliminary mixed in a granulator (P1-6; DIOSNA Dierks & Söhne GmbH, Osnabrück, Germany) for 3 min at impeller speed of 200 rpm. A liquid binder was added to the granulator for approx. 80 s at a rate of 3 mL/s via a pressurized 0.8 mm nozzle at 450 rpm impeller and 1500 rpm chopper speed. Then, the material was additionally processed for 4 min at the same impeller and chopper speed. After discharging, wet granules were calibrated via a sieve with a 2 mm mesh size and dried in the vacuum oven for 20 h at 60℃. Then, dry granules were calibrated via the same 2 mm mesh sieve. The granules obtained were tested in terms of moisture content (Karl Fischer), particle size distribution (by sieving) (AS 200; Retsch, Haan, Germany), and bulk/tapped (1250 taps) density (STAV 2003; JEL, Ludwigshafen, Germany) represented as the Carr's index.
- **Tableting**. Magnesium stearate was added to granules to achieve 1.0 wt.%, and powder was mixed manually in the polyethylene bag for 3 min. To obtain 600 mg weight biconvex tablets (diameter of 12 mm), the instrumented rotary tablet press was utilized (**FP1200i;** Fette Compacting GmbH, Schwarzenbek, Germany) at a constant: turret speed of 21 rpm); feed frame forced die filling speed (with the rectangular straight paddle geometry) of 12 rpm; lower punch position during the filling process of 7.5-8.9 mm. The main compression force was adjusted to achieve tablets with target hardness of 40, 80, and 120 N. The main compression force and ejection force were registered by inbuild detectors. The tablets obtained were tested in terms of weight, thickness, diameter, hardness (Checkmaster 4; Fette Compacting GmbH, Schwarzenbek, Germany), friability (TA10; ERWEKA, Langen, Germany), and disintegration time (ZT302; ERWEKA, Langen, Germany).

Fig. 5



Conclusion

- Granules with isomalt showed a lower D50% sensitivity to the granule binder concentration compared to PVP.
- The tablet hardness and friability as well as Carr's index were comparable for PVP and isomalt. Isomalt-tablets had a faster disintegration time even at higher concentrations.
- At 3% in granule binder concentration the highest similarity to PVP was obtained.
- Overall Isomalt demonstrated promising results to be regarded as an alternative to PVP.

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