Effect of PVP and isomalt as moisture-activated granulation binders on the acetaminophen release from tablets under simulated fasted-state conditions

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Introduction

- Immediate-release (**IR**) solid dosage forms dominate the market due to their manufacturing cost-efficiency, easiness of administration, good adherence and fast therapeutic effect. [1,2]
- Excipients used as diluents and granulation binders affect disintegration and dissolution in fasted and fed conditions. [3]
- Acetaminophen (**AMP**), a widely used and well-known analgesic and antipyretic, proves a great model drug, as it belongs to BCS Class III (**Fig. 1**) at most clinically relevant doses and is not ionised in gastric pH (**Fig. 2**). [4]
- **This study aimed** to **investigate the effect of 2 granulation binder types** (PVP vs. isomalt) on the disintegration and *in vitro* release of AMP from IR tablets.

Materials & Methods

- AMP (Caesar&Loretz GmbH), microcrystalline cellulose (MCC; Ceolus™ PH-101), and isomalt (galenIQ™ 801) or Polyvinylpyrrolidone (PVP; Kollidon® 25; BASF) were mixed and granulated with water in a high-shear mixer (TMG; Glatt GmbH, Binzen, Germany). Granules were dried at room conditions, calibrated (2 mm), mixed with lactose (Tablettose® 80) and lubricated with MgSt (Magnesia 4264). Then 2 formulations were obtained (**Table 1**), using STYL'One Nano compaction simulator (Medelpharm, France).
- Particle size distribution (PSD) was determined by a laser diffraction particle size analyser using an 'Aero S' module for dry dispersions (Mastersizer 3000, Malvern Instruments, UK).
- The mean yield pressure (Py) under slow (1 mm/s) and fast (90 mm/s) compression was determined using in-die Heckel plot analysis (Alix software ver. 20220711; Medelpharm). [5, 6]
- Dissolution (USP II, 75 rpm) and disintegration test were performed in fasted state medium (pH 1.2; according with EP).

Table 1.

		Formulations, wt.%	
	Ingredients	**A2**	**B2**
intra-gr.	Acetaminophen	66	66
	MCC	11	11
	Isomalt (galenIQ™ 801)	**4**	
	PVP (Kollidon® 25)		**4**
extra-gr.	Lactose	**15**	**15**
	Na Croscarmellose	3	3
	MgSt	1	1
	∑, wt.%	100	100
	Tablet weight, mg	*493*	*493*

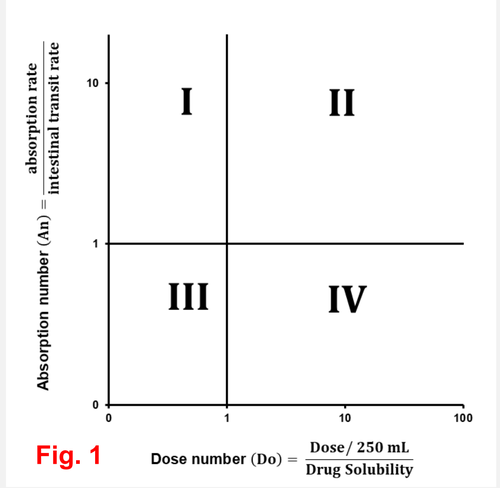

Fig. 1

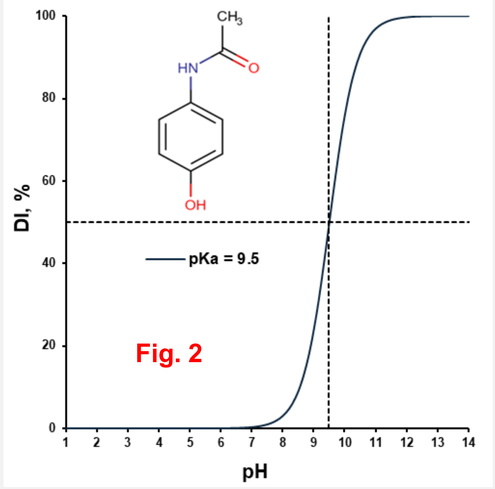

Fig. 2

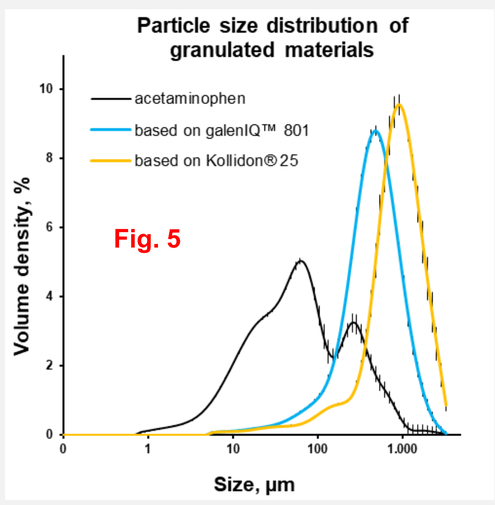

Fig. 5

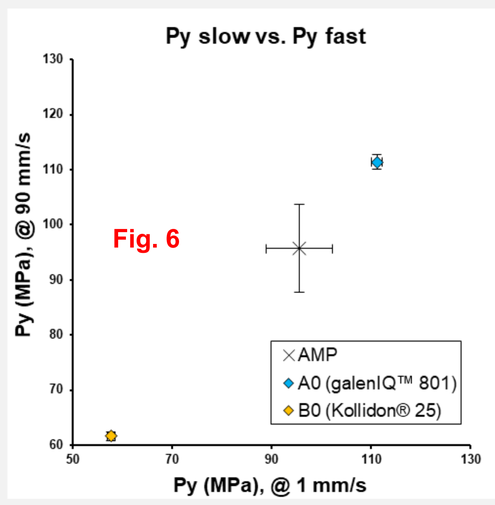

Fig. 6

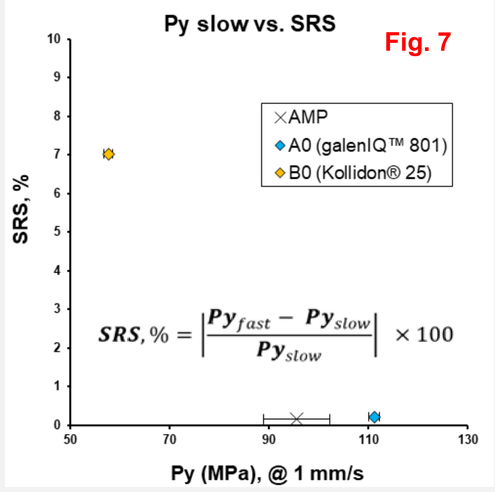

Fig. 7

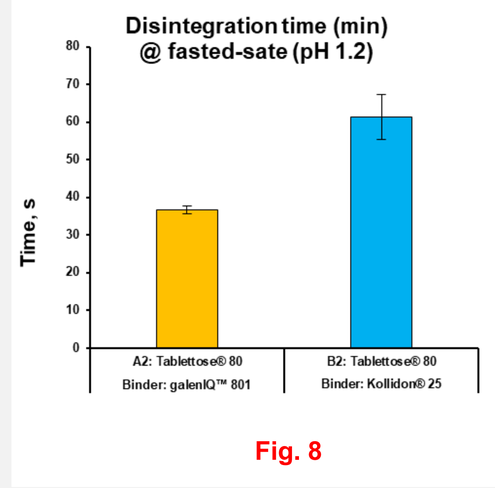

Fig. 8

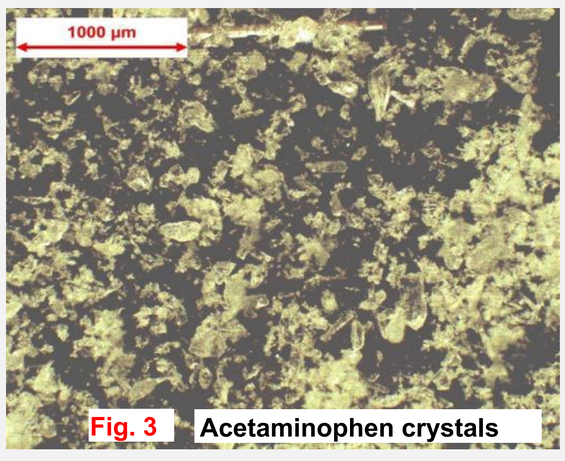

Fig. 3 Acetaminophen crystals

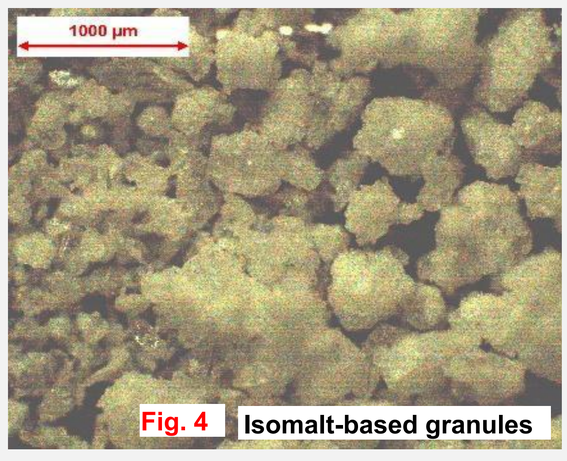

Fig. 4 Isomalt-based granules

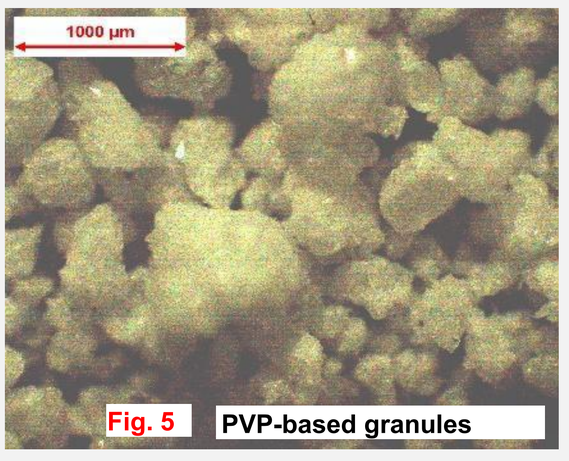

Fig. 5 PVP-based granules

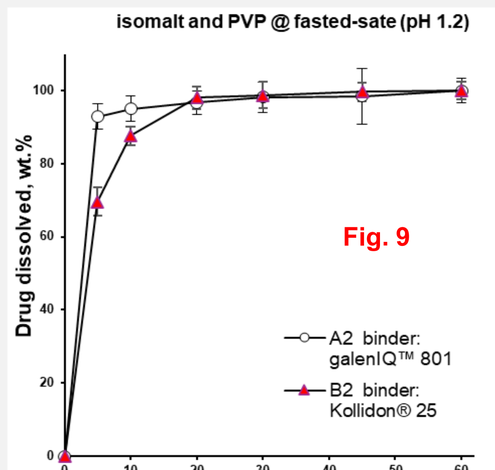

Fig. 9

Results

- AMP is white crystals with irregular shape and rough surface ($D_{50\%}$ 59.1 µm; span – 6.1; **Fig. 3** & **5**).
- Granules with isomalt (**Fig. 4 A**) and PVP (**Fig. 4 B**) as granulation binder are close to spherical shape and visually similar in structure.
- Resulted PVP granules are bigger than isomalt granules (mode 916 vs. 484 µm; **Fig. 5**).
- For AMP, Py comprised 95.6 MPa, while for isomalt and PVP granules, 111.3 and 59.7 MPa (**Fig. 6**).
- Strain rate sensitivity (**SRS**) for isomalt granules was low, while PVP granules were more sensitive to tableting speed, indicating higher elasticity of granules (**Fig. 7**).
- Tablets were prepared with a comparable porosity of 11.98 ± 0.65%.
- Disintegration time was faster for isomalt-binder formulations compared to PVP (**Fig. 8**).
- Under fasted-state conditions, the isomalt-based formulation exhibited a consistently faster drug release (**Fig. 9**).

Conclusion

- When used as a dry added granulation binder, isomalt promoted faster tablet disintegration compared with polyvinylpyrrolidone (PVP).
- Isomalt-based granules exhibited reduced strain-rate sensitivity (tableting speed) and enhanced in-vitro drug release relative to PVP-based granules.

Ref. 1: Oh, D.M., Curl, R.L. and Amidon, G.L., 1993. *Estimating the fraction dose absorbed from suspensions of poorly soluble compounds in humans: a mathematical model.* Pharm. research, 10(2), pp.264-270.
Ref. 2: Amidon, G.L., et al., *A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability*. Pharm Res, 1995. 12(3): p. 413-20.
Ref. 3: Pekša MM, Luhn O, Mohylyuk V. Isomalt as PVP-Binder Replacement in High-Shear Wet Granulation for Tablet Preparation. 5th European Conference on Pharmaceutics; Porto, Portugal, 2025.03.24-25.
Ref. 4: Kalantzi L, Reppas C, Dressman JB, Amidon GL, Junginger HE, Midha KK, et al. *Biowaiver monographs for immediate release solid oral dosage forms: acetaminophen (paracetamol)*. J Pharm Sci. 2006;95(1):4-14, 10.1002/jps.20477.
Ref. 5: Armstrong, N.A., *Tablet Manufacture*, in Encyclopedia of Pharmaceutical Technology, J. Swabrick, Editor. 2007, Informa Healthcare USA, Inc. : USA. p. 3653-3672 DOI: 10.1081/E-EPT-100001726.
Ref. 6 Heckel, R.W., *Density-pressure relationships in powder compaction*. Trans Metall Soc AIME, 1961. 221(4): p. 671-675.