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Use of Amino Sugar as Novel Plasticizer for Hot Melt Extrusion

M. Zheng*, N. Di Gallo, A. G. Elia, A. N. Knuettel, E. Weiskircher-Hildebrandt, F. Bauer, D. Lubda[1]

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Purpose

Hot melt extrusion (HME) has been introduced to the pharmaceutical industry as an effective solid dispersion formulation technology to improve the solubility and bioavailability of active pharmaceutical ingredients (APIs). When necessary, plasticizers with relatively low molecular weight, for example sorbitol, can be used to reduce the glass transition temperature (Tg) and melting point (Tm) of a polymer for HME through the reduction of interactions of polymer-chain secondary bonding, resulting in higher mobility [1]. In this study, we evaluated meglumine (or (D-(-)-N-methylglucamine), an amino sugar derived from sorbitol (Figure 1), as a novel plasticizer used to optimize a Polyvinyl alcohol-based composition for HME.

Methods

In this study itraconazole (non-acidic), ibuprofen (acidic) and telmisartan (acidic) were selected as model APIs. PVA (Polyvinyl alcohol with an 87 to 89 % hydrolysis grade, MW approx. 32,000, Emprove® exp., Merck KGaA, Darmstadt, Germany) was used as a thermoplastic polymer for HME. Meglumine and sorbitol are commercially available from Merck KGaA, Darmstadt, Germany. The mixture of plasticizer/polymer/API was homogeneously blended using a TURBULA® Shaker-Mixer and then loaded into the twin screw extruder (Brabender® Mini-Compounder KETSE 12/36D) and processed at different extrusion parameters. The obtained extrudate was micronized into fine particles (<1000µm) using a lab miller and analyzed using DSC (differential scanning calorimetry) and NMR spectroscopy; and real-time dissolution was analyzed with an Sotax AT7 on/offline system. For the long-term stability study, the milled extrudate was selected and stored under different conditions (25 °C/60 %; 40 °C/75 %; 2–4 °C) for at least 3 months.

Results

We investigated meglumine in this study as a novel plasticizer for HME with advantages over its derivate, sorbitol. Our resulting data demonstrated that compositions comprised of PVA as a carrier matrix in combination with meglumine can be processed by HME at a much lower temperature than PVA alone (Table 1). The Tm of the polymer could be reduced from 190-200 °C to 140 °C with the addition of 25 % meglumine as a plasticizer. Additionally, no degradation of meglumine after HME was observed. In the case of itraconezole, an extrusion temperature of 210 °C was necessary for the extrusion of PVA/itraconazole (70:30). However, with the addition of 17.5 % meglumine as a plasticizer, the extrusion temperature could be reduced to 180 °C. The dissolution of itraconazole with meglumine as well as without meglumine was unchanged. These observations indicate that, for the extrusion of a non-acidic API, meglumine works effectively as a plasticizer but shows no additional advantage over sorbitol (Figure 2).

As an FDA approved functional excipient, meglumine is well-known as a stabilizer for APIs. To evaluate the performance of meglumine as a stabilizing agent and solubility enhancer for acidic active ingredients, we chose ibuprofen and telmisartan as model APIs (Table 2). In the case of ibuprofen, the extrusion of ibuprofen (30%) and PVA (70 %) was not feasible because the Tm of ibuprofen (Tm = 78 °C; boiling point = 157 °C) was too low for HME application using PVA alone (Tm = 190 °C). However, the extrusion of ibuprofen (30 %) and PVA (52.5 %) with the addition of meglumine (17.5%) could be performed at 150 °C without the degradation of ibuprofen; and the extrudate also showed an enhanced solubility with the ibuprofen (Figure 3). Moreover, because of the stabilizing effect of meglumine, no degradation of ibuprofen was observed after HME. Compared with meglumine, sorbitol could also be used as a plasticizer for ibuprofen, but re-crystallization of sorbitol was observed after one week. Regarding telmisartan, extrusion without meglumine as a plasticizer was feasible but the solubility enhancement was limited. The solubility of telmisartan could be improved effectively with the addition of 21.25 % meglumine, resulting in a solubility 5.8-fold higher than the extrusion without any plasticizer and a solubility 3.5-fold higher than the extrusion with sorbitol as a plasticizer (Figure 4); this could be because with the addition of meglumine, 100 % amorphous solid dispersion of telmisartan during its formulation is possible (Figure 5 and 6). For the long-term stability studies, milled extrudates of ibuprofen/PVA/meglumine and itraconazole/PVA/meglumine were stored under 25 °C/60 %, 40 °C/75 % and 2-4 °C for at least 3 months (ibuprofen) and 6 months (itraconazole), respectively. No re-crystallization of APIs or meglumine were observed and the dissolution performance of API was not changed over time under all conditions.

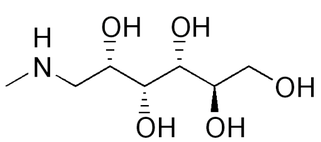

Figure 1: Structure of D-(-)-N-methylglucamine.

Composition	HME Temperature	Extrudate	Stability
PVA4-88	190 °C	Transparency	-
PVA4-88 /meglumine=5/1	165 °C	Transparency	no recrystallization of meglumine
PVA4-88 /meglumine=4/1	160 °C	Transparency	no recrystallization of meglumine
PVA4-88 /meglumine=3/1	140-150 °C	Transparency	no recrystallization of meglumine
PVA4-88 /meglumine=2/1	140 °C	Transparency	no recrystallization of meglumine
PVA4-88 /meglumine=1/1	140 °C	Transparency	no recrystallization of meglumine
PVA4-88 /meglumine=1/2	Not extrudable, too liquid	-	-

Table 1: HME processing temperatures of PVA/meglumine mixture at different concentrations.

API	Plasticizer	Extrudability	Solubility Enhancement
Ibuprofen (30% loading T_m = 78 °C)	none	Not feasible	No data
	sorbitol	Feasible at 150 °C	No data/ extrudate not stable
	meglumine	Feasible at 150 °C	2-fold
Telmisartan (15% loading T_m = 260 °C)	none	Feasible at 245 °C	6-fold
	sorbitol	Feasible at 240 °C	12-fold
	meglumine	Feasible at 200 °C	35-fold
Itraconazole (30% loading T_m = 166 °C)	none	Feasible at 210 °C	80-fold
	meglumine	Feasible at 180 °C	80-fold

Table 2: List of APIs with HME-matrix containing 75 % PVA and 25 % plasticizers.

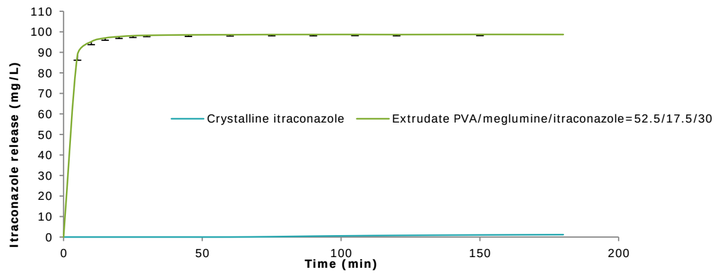

Figure 2: Dissolution of itraconazole (900 mL SGF, 37 °C, 100 rpm, 100 mg itraconazole, 30 % drug load; N=3).

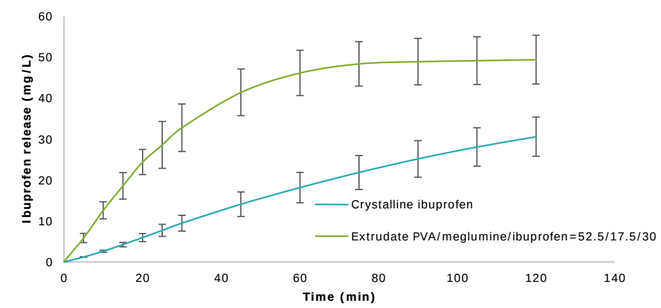

Figure 3: Dissolution of ibuprofen (1000 mL SGF_sp, 37 °C, 75rpm, 50mg ibuprofen, 30 % drug load; N=3).

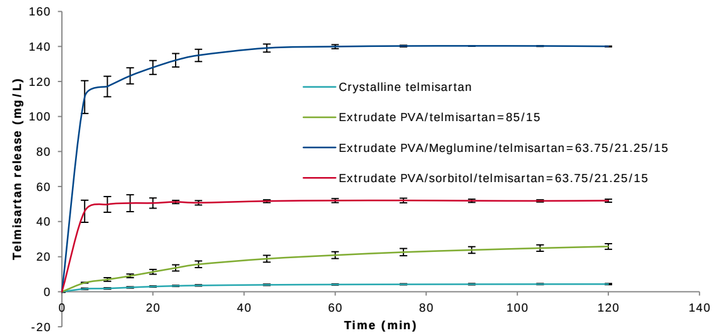

Figure 4: Dissolution of telmisartan (500 mL phosphate buffer pH 7.5, 37 °C, 75 rpm, 75 mg telmisartan, 15 % drug load; N=3).

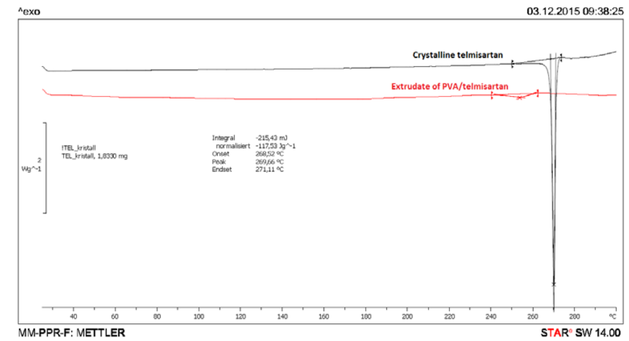

Figure 5: DSC of extrudate PVA/telmisartan (85/15).

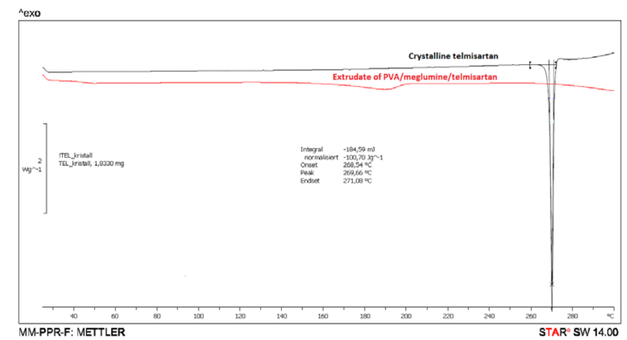

Figure 6: DSC of extrudate PVA/meglumine/telmisartan (63.75/21.25/15).

Conclusion

We evaluated that meglumine was able to reduce the Tg/Tm of extrusion mixtures effectively. At the same time, dissolution properties for neutral and/or weak basic APIs remained unchained. For acidic APIs, however, additional benefits could be observed; for these APIs, the stabilization to withstand higher extrusion temperatures and solubility enhancement were both demonstrated.

REFERENCES
1. Repka, M. A.; Shah, S.; Lu, J.; Maddineni, S.; Morott, J.; Patwardhan, K.; Mohammed; N. N., Melt extrusion: process to product. Expert Opin. Drug Deliv. (2012) 9(1):105-125

[1] Merck KGaA, Frankfurter Str. 250, 64293 Darmstadt, Germany
*Corresponding author: mengyao.zheng@merckgroup.com