Advantages of combining polymers and lipids in extrusion processes

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INTRODUCTION

Hot melt extrusion (HME) has become increasingly popular in pharmaceutical manufacturing over the last decade[1]. This innovative method is a solvent-free, dust-free and continuous process offering a reduced number of processing steps and ensuring reproducibility with minimal batch-to-batch variation.

Today, polymers are largely dominating the market of excipients for HME, however, plasticizers are often required to soften the material and facilitate the extrusion process. Surprisingly lipids are not widely used, despite their outstanding process advantages. Lipid excipients can be used at low dose as plasticizers in combination with polymers or alone at higher dose: they lower the extrusion temperature, enabling the processing of heat-sensitive active pharmaceutical ingredients (APIs) like macromolecules. Low energy input allows significant cost reductions and contribute to process sustainability.

The aim of the study is to demonstrate the ability of lipid excipients to lower the glass transition temperature of polymers, enabling processing at lower engine torque for better processability. Different polymers and lipid combinations have been tested to explore their potential in extrusion processes.

MATERIALS AND METHODS

Materials
Different lipid excipients from Gattefossé (St Priest, France) have been tested: Compritol® 888 ATO [glyceryl dibehenate] (Compritol), Gelucire® 48/16 [polyoxyl-32 stearate] (G48/16), Gelucire® 50/13 [stearoyl polyoxyl-32 glycerides] (G50/13), Labrasol® ALF [caprylocaproyl polyoxyl-8 glycerides] (Labrasol) and Maisine® CC [glyceryl monolinoleate] (Maisine).

The following polymers have been tested:
Kollidon® 30 [povidone or poly(1-vinyl-2-pyrrolidone)], and Soluplus® [polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft co-polymer], from BASF (Ludwigshafen, Germany) and Aqoat® AS-MMP [hypromellose acetate succinate] (HPMC AS) from Shin-Etsu (Tokyo, Japan).

The tested combinations (lipid excipients/polymers) are gathered in Table 1.

Methods
Soluplus® and Aquoat® AS-MMP are suitable for extrusion; however, Kollidon® 30 being a pure polymer, it is only processable with melt granulation[1], meaning no die was used at the extruder exit, to test this polymer in combination with two lipid excipients.
Lipid excipients are used at 0, 5, 10 and 20% (w/w) in the polymer. The 250 or 500 g mixtures are mixed in a Turbula® blender for 5 min. The batches are extruded with the standard twin-screw configuration (Thermo Scientific™ Pharma 11 TSE, Thermo Fisher Scientific, Karlsruhe, Germany), a 2 mm die (or open discharge for melt granulation), a screw speed of 50 rpm (or 250 rpm for melt granulation) and a feed rate of 150 g/h for melt granulation, and of 142, 135 and 120 g/h & 8, 15 and 30 g/h for powder and liquid mixtures depending on the liquid concentration.
During extrusion, the temperature (mixing zone and die), the pressure and the torque are registered.
Extrudates are sampled and tested by Differential Scanning Calorimetry (DSC8000, PerkinElmer Scientific, USA) to determine the glass transition temperature (sample size: approximately 8 mg, temperature range: 30-200°C, ramp rate: 20°C/min).

Table 1: Combination lipid excipients/polymers tested.

Lipid excipient	Polymer	Process
Compritol® 888 ATO	Aqoat® AS-MMP	Extrusion
	Kollidon® 30	Melt Granulation
	Soluplus®	Extrusion
Gelucire® 48/16	Aqoat® AS-MMP	Extrusion
	Kollidon® 30	Melt Granulation
Gelucire® 50/13	Soluplus®	Extrusion
Labrasol® ALF	Aqoat® AS-MMP	Extrusion
	Soluplus®	Extrusion
Maisine® CC	Aqoat® AS-MMP	Extrusion
	Soluplus®	Extrusion

RESULTS AND DISCUSSION

In this study, the focus was on the influence of lipid concentration on torque and glass transition temperature. Therefore, the impact of the lipid concentration on the engine torque is represented in Figure 1. For the same combination of polymer/lipid, the extrusions or the melt granulations are performed at the same temperature whatever the lipid concentration (5, 10 or 20%).

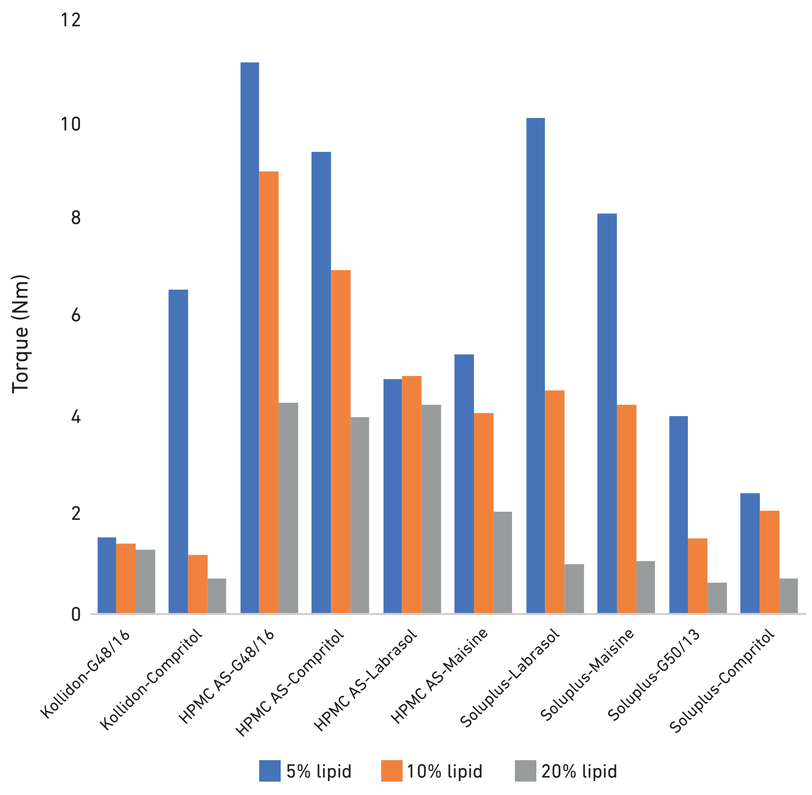

Figure 1. Engine torque according to lipid concentration.

A significant reduction of the torque in all combinations, whatever the polymer or lipid, is observed and the torque reduction is more important for higher lipid concentration. For instance, with Kollidon® 30, the torque is reduced by 9-fold between 5 and 20% of Compritol® 888 ATO, and with Soluplus®, the torque decreases by 10-fold when adding 20% Labrasol® ALF versus 5%.
The results for 0% lipid are not included as the process temperature used differs, preventing an accurate comparison.
The temperature of extrusion/melt granulation of the polymer alone (T° pol) and the one for the combination polymer/lipids (T° comb) are shown in Table 2 below.

The temperature is dramatically reduced when lipids are added: e.g. around 100°C for Kollidon® 30 with Compritol® 888 ATO and around 80°C for Aqoat® AS-MMP with Gelucire® 48/16.

Figure 2 shows the impact of the lipid concentration on the glass transition temperature. The glass transition temperature of combinations of Soluplus® or Aqoat® AS-MMP with 20% Labrasol® ALF could not be defined due to a thermal event masking the reading of this temperature. In view of the other results, it is possible to deduce these values by linear extrapolation.
Lipid excipients reduce the glass transition temperature, whatever the combination of polymer and lipid. This property is correlated to the concentration of the lipid excipient in the extrudate or granule.

Table 2: Extrusion/granulation temperatures for polymer alone and combination polymer/lipids.

Polymer	T° pol (°C)	Lipid	T° comb (°C)
Aqoat® AS-MMP	215°C	Compritol® 888 ATO	146°C
		Gelucire® 48/16	135°C
		Labrasol® ALF	160°C
		Maisine® CC	160°C
Kollidon® 30	250-220°C	Compritol® 888 ATO	160°C
		Gelucire® 48/16	160°C
Soluplus®	170-150°C	Compritol® 888 ATO	130°C
		Gelucire® 50/13	130°C
		Labrasol® ALF	100°C
		Maisine® CC	100°C

For example, the glass transition temperature of Aqoat® AS-MMP with 20% Gelucire® 48/16 decreases from 124°C to 66°C, and for Soluplus® with 20% Maisine® CC, it decreases from 75°C to 42°C.
An explication could be that lipid excipients locate at the interspace of the entangled polymer chains and increase their mobility, facilitating polymer extrusion at a concentration as low as 5 -20%.

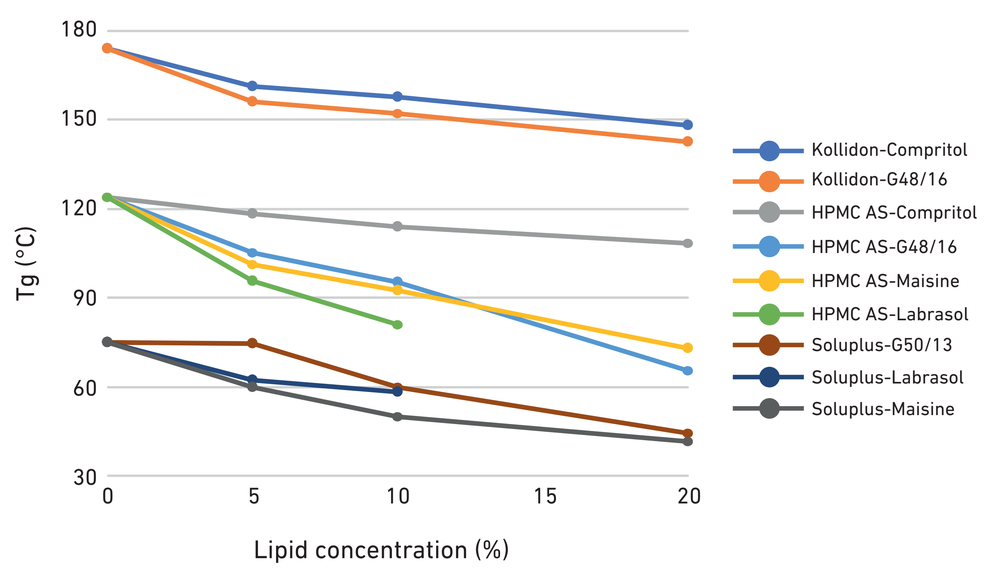

Figure 2. Glass transition temperature according to the lipid excipient concentration in the extrudate/granule.

CONCLUSION

When mixed with polymers, lipid excipients act as plasticizers and drastically reduce the torque value and the glass transition temperature of the polymer, and consequently the extrusion temperature. Their role in this case is to facilitate extrusion, lower energy consumption and limit API degradation.

REFERENCES

[1] Karl M. *et al* – Suitability of pure and plasticized polymers for Hot Melt Extrusion – BASF poster – CRS 2010