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IS COMPRITOL® 888 ATO CHEMICALLY STABLE IN HOT MELT EXTRUSION PROCESSED AT HIGH TEMPERATURE?

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GATTEFOSSÉ

INTRODUCTION

In pharmaceutical hot melt extrusion amorphous polymers are widely used. Their long, entangled chains however lead to low material flexibility. Therefore, polymers must be heated to their glass transition temperature (Tg) to become extrudable. These high extrusion temperatures can be lowered by the addition of chemical plasticizers. An interesting alternative to these chemical plasticizers is Compritol® 888 ATO; a GRAS status, lipid excipient of plant origin that lubricates the polymer and facilitates extrusion[1]. Compritol® 888 has a melting point (MP) of 70°C, however, extrusion temperatures for polymer: lipid blends can be above 100°C. This study therefore demonstrates the chemical stability of Compritol® 888 when exposed to such high temperatures.

EXPERIMENTAL METHODS

Hot melt extrusion

Compritol® 888 (glyceryl behenate NF) was extruded with a twin-screw hot melt extruder (Pharma 11 HME, Figure 1) using two temperature profiles: one around the lipid melting point at 60-63-68-67-65-67-67-68°C and one above the melting point at 65-68-30-30-180-180-180-30°C towards a 1mm die. Low feed rate and screw speed (80 g/h and 50 rpm respectively) were used to lengthen the residence time of Compritol® 888 within the extruder (worst case scenario). In a second part of the study 75% niacin (a strong acidic drug with a pKa of 2.79) was blended to Compritol® 888 and extruded at 60-63-68-73-68-73-73-74°C and 60-63-68-45-180-180-180-(20)°C (80 g/h, 50 rpm).

Analysis of chemical degradation

The extruded masses (with and without niacin) were analyzed for their mono-, di- and triglycerides content. The results were compared with the glyceride content of non-processed Compritol® 888 powder (or Compritol® 888: niacin) in order to detect chemical degradation.

RESULTS AND DISCUSSION

Compritol® 888 is a defined mixture of mono-, di- and triglycerides of behenic acid. However esters can undergo chemical degradation induced by high temperatures or acid catalyzed hydrolysis. Therefore the content of mono-, di- and triglycerides of Compritol® 888 was measured before and after extrusion at high temperatures. An increase of the monoglyceride content and a decrease of triglycerides would indicate ester degradation which may propergate changes in the performance of Compritol® 888 in the final drug product or undesirable color changes.

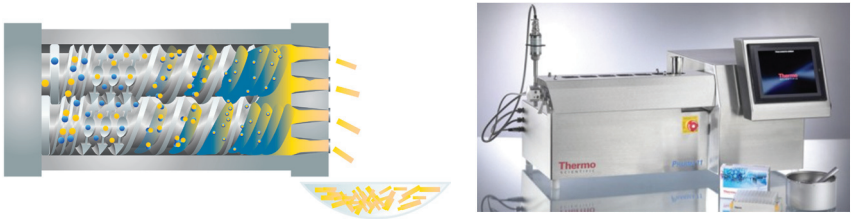

Figure 1: Schematic presentation of the extrusion process and the Pharma 11 HME (ThermoFisher).

Figure 2a shows that the composition of Compritol® 888 does not change after extrusion even upon exposure to 180°C (> MP). The residence time of the material at 180°C was about 3 min (8 min in total barrel). This indicates that Compritol® 888 withstands extrusion at elevated temperatures in combination with pharmaceutical polymers.

In the second part of the study the acidic drug niacin was blended to Compritol® 888 (ratio 3:1) and the mixture processed under similar temperature conditions (74°C and 180°C). Figure 2b represents the glyceride content monitored for Compritol® 888: niacin extrudates.

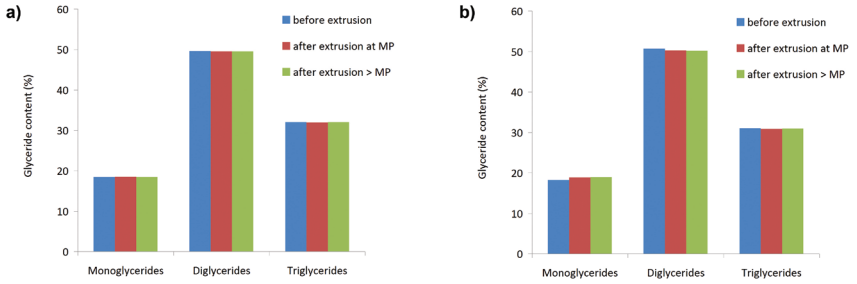

Figure 2: Effect of: a) extrusion temperature and b) extrusion temperature + niacin on Compritol® 888 composition.

The results show that the presence of an acidic drug does not affect the chemical composition of Compritol® 888 even at elevated extrusion temperatures. The glyceride content remains unaltered. Therefore, drug release is similar from extrudates obtained at temperatures around and above the MP of Compritol® 888 (Figure 3). In addition, the higher extrusion temperature (180°C) does not lead to any color change of Compritol® 888: niacin extrudates, they remain white (Figure 4).

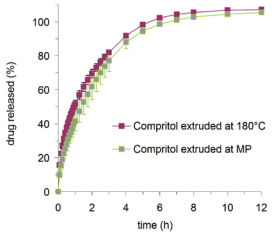

Figure 3 : Drug release from Compritol® 888: niacin extrudates ratio 3:1 after extrusion around the lipid MP (74°C) and above the MP (180°C).

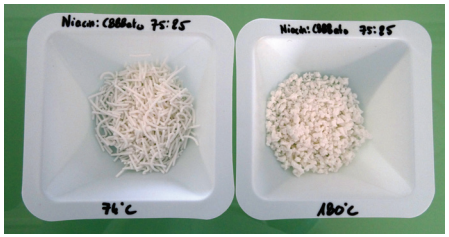

Figure 4: Aspect of Compritol® 888: niacin extrudates ratio 1: 3 after extrusion around the lipid MP (74°C) and above the MP (180°C).

CONCLUSION

Compritol® 888 is a plant-derived GRAS status excipient that can be used as processing aid as an alternative to chemical plasticizers in hot melt extrusion with polymers. The lipid excipient does not undergo chemical degradation (e.g. acid hydrolysis) when exposed to high temperature or when associated with acid drugs.

REFERENCES

[1] Keen, J. et al. Preparation of Hot Melt Extruded Supersaturating Solid Dispersions Containing Glyceryl Behenate: Effects on Processability, Supersaturation and Rate of Release. AAPS Washington 2011, Poster W4327.