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INTRODUCTION

An increasing number of active pharmaceutical ingredients (API) are currently encountering challenges with their bioavailability. This is due, among other causes, to a lack of solubility in aqueous media. To overcome this issue, the dispersion of the API in a polymer keeps it in an amorphous form and therefore

increases its solubility¹. When this amorphous solid dispersion (ASD) is produced by hot melt extrusion (HME), the use of a neat polymer requires high process temperatures, and the drug release is not always complete^{2,3}. Adding Gelucire® in the formula is a promising strategy to address these issues.

MATERIALS AND METHODS

Materials

Ticagrelor, purchased from Chanyoo, was used as a model API. Poly(1-vinyl-2-pyrrolidone-co-vinyl acetate) (PVPVA) was used as a polymer matrix and provided by Ashland. The two surfactants, polyoxyl-32 stearate (Gelucire® 48/16, G48/16) and stearyl polyoxyl-32 glycerides (Gelucire® 50/13, G50/13) were provided by Gattefossé.

Methods

Formulation

ASD were produced in 200 g batches. API, PVPVA and/or Gelucire® were mixed in a Turbula blender for 15 min. The different formulations are gathered in Table 1. To obtain a dispersion, the API concentration was determined so that it is above its saturation solubility in Gelucire®. The starting ratio polymer:surfactant was chosen after the work of Maniruzzaman et al.³. The batches were extruded with standard twin-screw configuration (Pharma 11 Thermo Fisher Scientific), a 2 mm die, a screw speed

of 50 rpm and a feed rate of 150 g/h. During the extrusion, the temperature was set so that the torque did not exceed 0.9 N and the extrudates were solid on exit.

Characterization

Extrudates were sampled and tested by Differential Scanning Calorimetry (DSC8000, PerkinElmer, USA) to determine the ASD's crystalline state (sample weight: approximately 7 mg, temperature range: 30-200°C, ramp rate: 20°C/min).

The API release was determined by *in vitro* dissolution (USP II, phosphate buffer pH 6.8, 900 mL) followed by high performance liquid chromatography (HPLC) analysis.

Stability

Formulations A, D and E were placed in an oven at 25°C and 75% relative humidity (RH) for 6 months and the crystallinity state of the drug was evaluated by X-Ray diffraction. The analysis was performed by a powder diffractometer (D8-Advance, Bruker AXS) from 5° to 70°, in steps of 0.02° at 2 thetas.

RESULTS AND DISCUSSION

Table 1: Description of formulations.

Formula designation	API solubility saturation in surfactant	Surfactant	Ratio polymer:surfactant	API: PVPVA : Gelucire (wt%)	Temperature in the mixing area (°C)
A	/	/	/	25:75:0	195
B	200%	G48/16	1:1	25:37.5:37.5	125
C	200%	G50/13	1:1	25:37.5:37.5	125
D	200%	G48/16	3:1	14.3:64.3:21.4	140
E	200%	G50/13	3:1	14.3:64.3:21.4	140

With the polymer alone (Formulation A), the extrusion temperature reaches nearly 200°C, which can be deleterious to heat sensitive APIs. Addition of a surfactant enables to decrease the extrusion temperature down to 125 or 140°C depending on the ratio polymer:surfactant. The two Gelucire® grades have similar melting points, and decrease the extrusion temperature to the same extent, i.e. around 70°C.

The thermograms (Figure 1) of the formulations with polymer and surfactants do not show the characteristic peak of the crystalline API at 140°C, therefore suggesting that the formulations are amorphous.

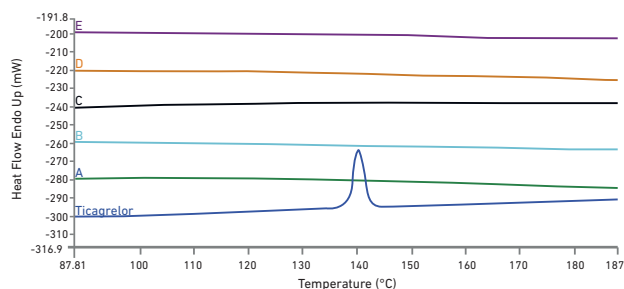


Figure 1. DSC thermal transitions of bulk Ticagrelor and all formulations.

Ticagrelor is poorly soluble in water (BCS class IV): without any excipient it was impossible to dissolve more than 10% of the drug in the media (Figure 2). The dispersion of this API in PVPVA allowed a 55% release of ticagrelor (A). The addition of G50/13 (C) led to almost the same final release however at a lower speed. This can be due to the presence of glycerides, that are not soluble in water. The G48/16 (B), which is glyceride-free and completely water-soluble, seemed to be more efficient as the API release reached 70%. The concentration of Gelucire® was decreased to study its effect. By decreasing by almost two the amount of Gelucire®, it was possible to improve the release. The G48/16 showed once again better results (D): it was possible, with this lipid excipient, to release 90% of the API.

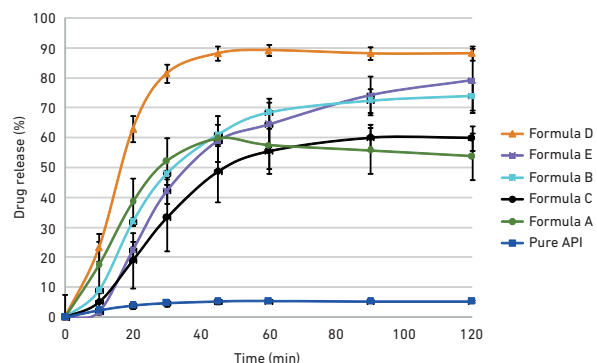


Figure 2. *In vitro* release profile of all formulations.

Stability

The crystallinity of the formulations was analysed after 6 months. The diffractogram (Figure 3) of the formulation A without Gelucire® does not show any peak, suggesting that the product is completely amorphous. The formulations D and E, which contained Gelucire®, have diffractograms that evoke an essentially amorphous product, the only two visible peaks are characteristic of the polyethylene glycol contained in Gelucire®. Therefore, the formulations are physically stable for 6 months at 25°C and 75% RH.

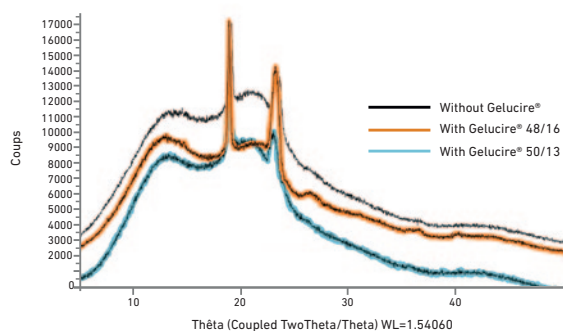


Figure 3. Diffractogram after 6 months of formulations A, D and E.

CONCLUSION

The addition of Gelucire® in an ASD presents multiple advantages. It results in a lower process temperature, which is convenient to process heat sensitive drugs and results in lower production cost. The choice of the surfactant and its concentration in the formulation is crucial. In this study, a 3:1 ratio of PVPVA:G48/16 provides 90% release of ticagrelor during the dissolution.

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