Ticagrelor Amorphous Solid Dispersion tablets: formulation with Gelucire® 48/16

Elsa GATTEFOSSE[1], Diane SCHNEIDER[1], Cédric MIOLANE[1], Karan SIYODIA[2], Philippe CAISSE[1]

[1] Gattefossé SAS, 36 Chemin de Genas, 69800, Saint-Priest, France
[2] Gattefossé Corporation, 115 W Century Road, Suite 340, Paramus, NJ 07652, USA

INTRODUCTION

Amorphous solid dispersion (ASD) is one of the most promising strategies to address the bioavailability issues faced by poorly soluble Active Pharmaceutical Ingredients (API). On the other hand, surfactants can also improve API solubility but remain challenging to incorporate in tablets. Incorporation of a surfactant into a binary ASD (API and polymer) to develop a ternary ASD is an emerging trend[1] to further increase the solubility, the bioavailability and the stability of ASD while maintaining the possibility to manufacture a tablet dosage form.

In our previous work[2], we prepared ticagrelor ternary ASD by Hot Melt Extrusion (HME) and tested the obtained extrudates, showing the amorphization of the active in the binary and ternary ASDs. We also showed a strong decrease in the extrusion temperature, and a higher API dissolution compared to binary extrudates and neat API.
In this study, we formulated and tested tablets prepared either from those ternary extrudates, or from binary extrudates, or from binary physical mixture (polymer and API).

MATERIALS AND METHODS

Ticagrelor, used as a model API (BCS class IV with 60 or 90 mg of therapeutic dose), was purchased from Nantong Chanyoo Pharmatech. Polyvinylpyrrolidone vinyl acetate (copovidone / PVP-VA), used as a polymer, was provided by Ashland, while Gelucire® 48/16, utilized as a surfactant, was provided by Gattefossé.

Ternary extrudate contained 14.3% ticagrelor, 21.4% Gelucire® 48/16 and 64.3% copovidone, while binary extrudate contained 25% ticagrelor and 75% copovidone. The batches were extruded with standard twin-screw configuration (Pharma 11 from Thermo Scientific™), a 2-mm die, a screw speed of 50 rpm and a feed rate of 150 g/h. The extrudates were grinded to obtain a powder (around 500 µm particle size average).

The other tableting excipients, mannitol, silicified microcrystalline cellulose, crospovidone and magnesium stearate were provided by Roquette, JRS Pharma, BASF, and Sigma Aldrich, respectively. The internal phase was first mixed, followed by the external phase, using a Turbula blender. Tablets were manufactured using a NanoStyl'One (Medelpharm) simulator press. The different formulations are gathered in Table 1.

The API release was determined by *in vitro* dissolution testing (USP II, phosphate buffer pH 6.8, 900 mL) followed by high performance liquid chromatography (HPLC) analysis. The tablets were stored at 25°C/60% relative humidity (RH) for 3 months and release profile stability was assessed.

Table 1. Composition of tablets.

	Component	Ternary ASD tablet	Binary ASD tablet	Physical mix tablet
Internal phase	Extrudate	70%	40%	/
	Silicified microcrystalline cellulose	14%	44%	44%
	Mannitol	10%	10%	10%
	Crospovidone	5%	5%	5%
	PVP-VA	/	/	30%
	Ticagrelor	/	/	10%
External phase	Magnesium stearate	1%	1%	1%

RESULTS

The addition of Gelucire® 48/16 significantly reduces the extrusion temperature, as shown in Table 2.

Table 2. Composition of the extrudates and extrusion temperature profile.

	Composition	Extrusion temperature profile (°C)	Melt (°C)	Pressure (bar)	Torque (Nm)	Aspect / comment
Ternary extrudate	14,3% ticagrelor + 21,4% Gelucire® 48/16 + 64,3% PVP-VA	80-110-120-140-140-130-119-119	115	4- 6	2	Yellow transparent filament
Binary extrudate	25% ticagrelor + 75% PVP-VA	125-160-175-178-185-178-163-157	153	5 -> 12	2	Beige agglomerates

The tablets obtained weighed 600 mg and presented different aspects (Figure 1): tablets with binary extrudate looked matte with grey spots, tablets with ternary extrudate looked shiny with grey spots and tablets with binary physical mixture had heterogenous matte surface.

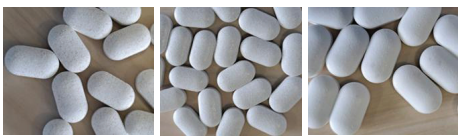

Figure 1. Photographs of obtained tablets (left: tablets with binary extrudate / middle: tablets with ternary extrudate / right: tablets with physical mixture).

During *in vitro* dissolution testing, an increase in the dissolved API quantity was measured for tablets manufactured with binary ASD (18%) compared to neat API (8%) and physical mixture tablets (10%). When Gelucire® 48/16 was added, in the ternary ASD tablet, the API release reached 92%: it represents a 5-fold and 9-fold increase compared to binary ASD tablets and physical mixture tablets respectively (Figure 2).

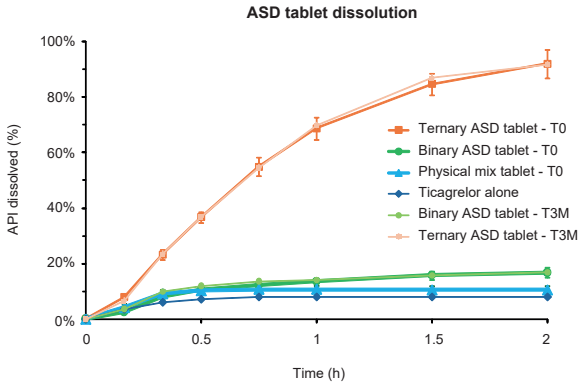

Figure 2. Ticagrelor *in vitro* dissolution profile from different tablets at T0 and T3 months.

The decrease of the API crystallinity in binary ASD tablets led to a slight increase of the percentage dissolved, but still limited, whereas the combination of amorphization and solubilization in the ternary ASD tablets achieved a full dissolution of the active.
The dissolution profile of the tablets remained unchanged after storage at 25°C/60% RH for 3 months.

CONCLUSION

Ternary ASD extrusion is a convenient way to incorporate lipid-based surfactants in tablets. The proposed ternary ASD tablet formulation, prepared from extrudates containing Gelucire® 48/16 and PVP-VA increases dramatically the release of a BCS class IV API.

REFERENCES

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