HOT MELT EXTRUDED AMORPHOUS SOLID DISPERSIONS CONTAINING LUMEFANTRINE AND SOLUPLUS.

T1330-07-39

M.Gallas[1,2], S.Li[3],P.Boulet[2], V. De Margerie[1] and G.P.Andrews[3]

1: Rondol Industrie, Site Artem, 2 allée André Guinier , 54000 Nancy , France

2: Institut Jean Lamour, CNRS-Université de Lorraine, Site Artem, 2 allée André Guinier , 54000 Nancy, France

3: School of Pharmacy, Queen's University Belfast, 97 Lisburn Rd, Belfast BT9 7BL, United Kingdom

CONTACT INFORMATION: mael@rondol.com

RATIONAL

OBJECTIVES

Fixed dose combination (FDC) of Artemether and Lumefantrine (AT-LM) are the first line antimalarial of choice endorsed by WHO[1]. Despite the extensive prescription of the AT-LM commercial product (Riamet®), incorporated drugs are known to suffer from poor solubility & bioavailability (mainly LM)[2]. The aim of the collaborative project of BASF-RONDOL-QUB was to develop and manufacture a robust, child-friendly fixed dose combination for the antimalarial agents using hot-melt extrusion (HME) technology as a continuous manufacturing platform. The objective of this first study is to address the poor solubility of lumefantrine (LUM) in gastrointestinal fluids while using hot melt extrusion (HME) to create amorphous solid dispersions (ASDs) of LUM within Soluplus® based matrices as a first step to develop more efficient and lower cost treatment of child malaria.

METHODS

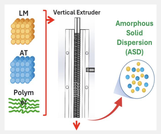
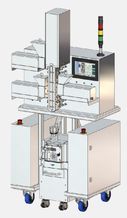


Table 1 : The temperature profiles (TP) used in this study

TP Nomenclature	Extruder L/D	Z1 °C	Z2 °C	Z3 °C	Z4 °C	Z5 °C	Z6 °C	Z7 °C	Z8 °C	Die °C
HTP1	Horizontal 20/1	100	120	130	120	/	/	/	/	100
HTP2		100	120	130	120	/	/	/	/	120
HTP3		105	140	170	170	/	/	/	/	150
VTP1	Vertical 40/1	40	100	120	120	130	130	120	120	120
VTP2		40	100	140	170	170	170	150	150	150

Table 2 : Nomeclature of the formulations extruded in this study.

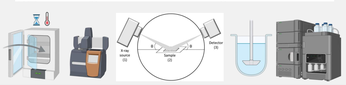
Extrudates	LUM	SOL	Extruder	TP
F1_HTP1	3	7	Horizontal 20/1	HTP1
F1_HTP2	3	7		HTP2
F1_HTP3	3	7		HTP3
F1_VTP1	3	7	Vertical 40/1	VTP1
F1_VTP2	3	7		VTP2
F2_HTP1	5	5	Horizontal 20/1	HTP1
F2_HTP2	5	5		HTP2
F2_HTP3	5	5		HTP3
F2_VTP1	5	5	Vertical 40/1	VTP1
F2_VTP2	5	5		VTP2



Vertical All in One twin screw extruder 10.5 mm 40:1 L:D and Microlab Horizontal twin screw extruder 10.5 mm 20:1 L:D

Table 3 : Screw configurations used for the horizontal and vertical extruder.

Type of Element	Number of elements on each shaft Horizontal extruder	Number of elements on each shaft Vertical extruder
Forward convey	5	10
60° Kneading	1	2
90° Kneading	1	2
60° Kneading	1	2
Forward convey	3	6
60° Kneading	1	2
90° Kneading	1	2
60° Kneading	1	2
Forward convey	6	12
Total	20	40



Amorphous solid dispersions of lumefantrine with Soluplus® were prepared using hot melt extrusion. Various processing parameters, including temperature profiles and production scales, were evaluated to optimize the drug loading and physical stability. Techniques like DSC, PXRD, and in-vitro dissolution testing were employed to characterize the formulations and assess their performance. The stability studies were carried out over 6 months using the ICH accelerated stability testing condition involving a stability chamber set to a controlled temperature of 40±0.5 °C and a relative humidity of 75±0.5%. The extrudates were analysed using PXRD and DSC analyses, to determine any alteration in the physical state of LUM within the extruded matrices.

RESULTS

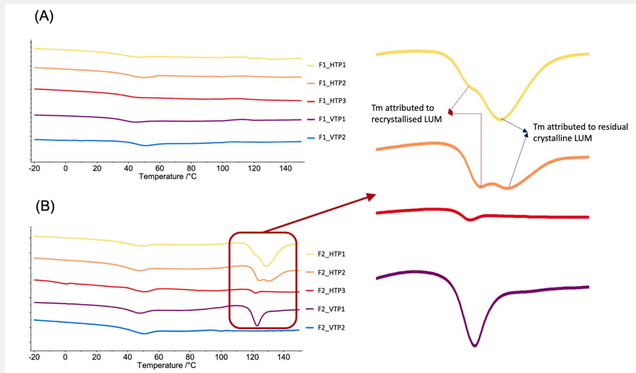


Fig1. Representative DSC thermograms of extruded formulations. (A) F1 extrudates and (B) F2 extrudates, processed using, from top to bottom, horizontal extruder with HTP1 (yellow), HTP2 (orange) and HTP3 (red), and vertical extruder with VTP1 (purple) and VTP2 (blue), respectively. The zoomed region illustrates the occurrence of overlapped multiple melting events in the F2_HTP1 and F2_HTP2 extrudates.

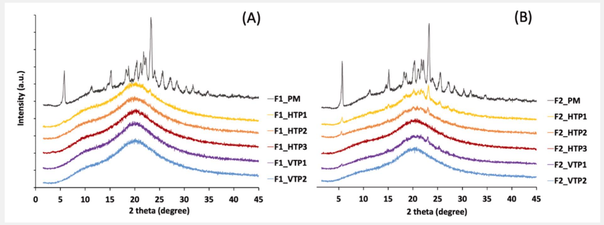


Fig 2. Representative PXRD patterns of formulations immediately following extrusion. Note that the PXRD pattern of the physical mixture of each formulation is presented at the top of each diffractogram for comparison.

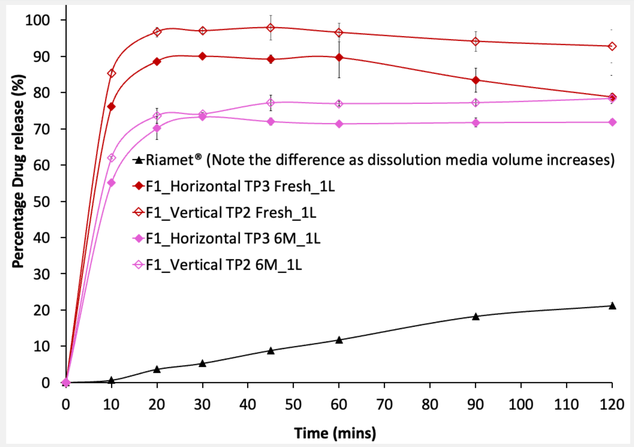


Fig 3. In-vitro drug dissolution profiles of the two most promising F1 formulations, F1_HTP3 and F1_VTP2, respectively, following storage under accelerated conditions for 6 months. Note that these dissolution tests were performed by putting formulations containing equivalent to 120 mg of LUM into 1 L of 0.1 N HCl solution containing 1 % (w/v) SLS. The dissolution profile of the commercial product (Riamet@), obtained using the same dissolution method.

ASDs were successfully produced with different drug loadings (30% and 50% w/w LUM) and extrusion conditions. Higher processing temperatures and vertical scaled-up production improved amorphization and dissolution rates. F1 formulations with 30% w/w LUM showed superior dissolution compared to F2 with 50% w/w. Stability studies indicated some recrystallization over six months, but formulations still exhibited much better performance than commercial Riamet® tablets.

CONCLUSION

In this work, hot-melt extrusion was used to probe the drug loading capacity of Soluplus® to accommodate lumefantrine in a binary amorphous solid dispersion. This was used as an example of challenging drug compounds that possess extremely low aqueous solubility and strong tendency for self-aggregation. It was found that via adjustment of extrusion conditions, dissolution performance of F1 solutions (30% drug loading), even after 6 months aging, outperformed the Riamet tablets by approximately 3.5-fold. The high supersaturation concentration of LUM in these ASDs, however, renders the extrudates susceptible to recrystallisation when exposed to high temperature and or humidity.

The results presented in this work provide evidence for the need to balance high drug loading in an amorphous solid dispersion with physical stability and drug release enhancement. It is possible to achieve high amorphous drug loadings using techniques such as HME are utilised, however formulation success is highly dependent formulation factors, i.e. presence of drug polymer interactions, sufficient physical hindrance to prevent rapid recrystallisation. This is an important note when generating an ideal design space for ASD formulations and should be used to balance processing and formulation design spaces to success. For more precise information, the complete study have been very recently published in the following reference 3.

REFERENCES

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3.Li, S., Zhang, Z., Gu, W., Gallas, M., Jones, D., Boulet, P., Johnson, L.M., de Margerie, V., & Andrews, G.P. *Hot melt extruded high-dose amorphous solid dispersions containing lumefantrine and Soluplus* IJP, Volume 665, 124676, (2024).