British Journal of Pharmacy

https://doi.org/10.5920/bjpharm.1156

British Journal of Pharmacy

www.bjpharm.hud.ac.uk

Proceedings of the 13th APS International PharmSci 2022

Selecting the most appropriate formulation excipient for manufacture of amorphous solid dispersions: a case study of lumefantrine

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ARTICLE INFO

Received: 17/06/2022
Accepted: 07/07/2022
Published: 04/11/2022

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KEYWORDS: Amorphous solid dispersion, Polymer, Pre-formulation study, Drug enabling

SUMMARY

This work demonstrates the importance of pre-formulation studies and proposes a generalised scheme for excipient screening in early stage formulation of amorphous solid dispersions (ASD). We used solubility, amorphization, and stabilisation of the active pharmaceutical ingredient (API) as key indicators to rank excipient suitability. Lumefantrine, an antimalarial active compound with both poor solubility and permeability, was used as a model API and solvent evaporation film casting was used to prepare the candidate ASD matrices in this work.

INTRODUCTION

Enhancing the solubility and oral absorption of poorly soluble drug compounds via development of amorphous solid dispersions (ASDs) usually requires a prudent choice of matrix excipients during the preliminary stages. However, there is a lack of systemic guidance regarding excipient selection for amorphous drug formulations, with many articles adopting a "trial and error" approach. Within this current work, we propose a general procedure to understand substance physicochemical properties and polymer drug enabling capabilities through a set of pre-formulation studies to support a rational polymer selection in ASD formulation development.

MATERIALS AND METHODS

Lumefantrine was purchased from Kemprotec (Carnforth, UK). Polymers were kindly supplied by BASF (Ludwigshafen, Germany). Chemicals were purchased from Sigma-Aldrich (Gillingham, UK). The methods and assessments for polymer screening in this study were summarised in Figure 1.

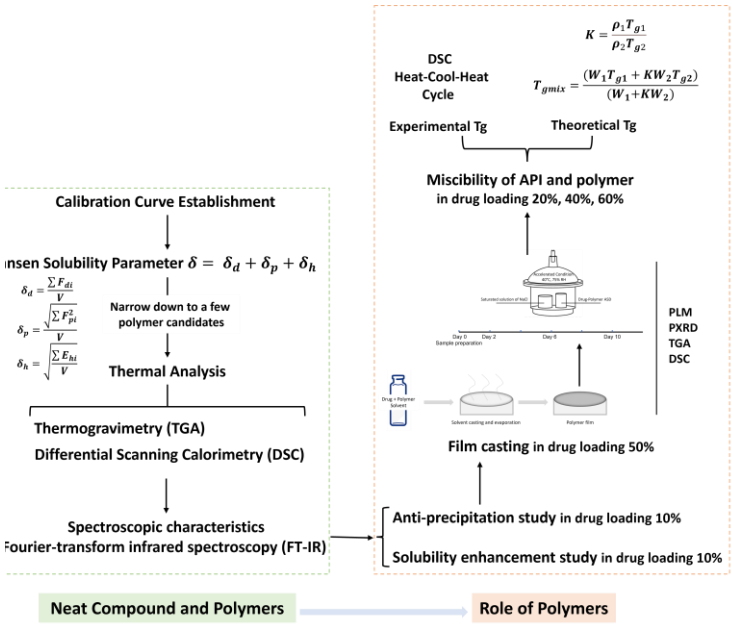

Fig. 1. *Polymer selection procedures in ASD development.*

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RESULTS AND DISCUSSION

Thermal analysis indicated the T_g of lumefantrine was 20.5 °C (± 0.5 °C, mid) and melting point was 128.9 °C (± 0.2 °C, onset; 135.9 ± 0.3 °C, peak). Lumefantrine was observed to exhibit a thermal behaviour of Class III according to a classification system developed by (Baird et al., 2010) during a DSC heat-cool heat cycle. This was characterised by the absence of recrystallisation on cooling, indicating good glass forming ability which can further resist devitrification upon reheating. The onset thermal decomposition temperature for lumefantrine was determined to be 271 °C (± 0.5 °C) where significant change was observed on the first derivative of the weight loss profile.

Amongst the polymers for which the HSP (δ) were calculated, Soluplus, PVP-VA64, PVP, and PEO with the Drug-Polymer Δδ below 2 $MP^{1/2}$ were promoted to the following experimental investigations. Characterisation, including PLM, PXRD and DSC, of drug loaded ASD films prepared through solvent evaporation film casting approach demonstrated that Soluplus and PVP were capable of transforming lumefantrine completely into amorphous form, whilst VA64 and PEO were not. However, lumefantrine recrystallised rapidly in the PVP based film during storage whereas Soluplus remaimed amorphous, confirmed by PXRD and DSC (Table 1).

Meanwhile, Solubility enhancement (Figure 3 (a)) and anti-precipitation tests (Figure 3 (b)) illustrated that Soluplus was able to improve the apparent solubility of lumefantrine up to 80.82 µg/mL compared to non-detectable dissolved drug concentrations in the control counterparts ($p<0.0001$) and prolonged the supersaturation period with a delayed drug precipitation exceeding 8 hours ($P<0.01$). Whereas other tested polymers either failed to enhance solubility, or were unsuccessful in maintaining the supersaturated concentration of lumefantrine for sufficient lengths of time. It is worth noting that the supersaturated state is also a prerequisite for the occurrence of LLPS phenomenon and drug-rich reservoirs, which may help enhance lumefantrine permeability (Xu et al, 2021). The T_g of Soluplus-lumefantrine mixtures were higher than the theoretical values calculated according to Gordon-Taylor theory at drug loadings of 20%, 40% and 60% w/w (Figure 3 (c)). The degree of miscibility between the drug and the excipient, particularly in fusion-based ASD manufacturing processes, significantly affects the amorphization of the drug and tendency to phase separate. Positive deviations from the predicted T_gs of polymer-drug blends could be attributed to stronger heteronuclear interactions resulting in a net expansion to form a more stable ASD binary system (Baghel, Cathcart & O'Reilly, 2016).

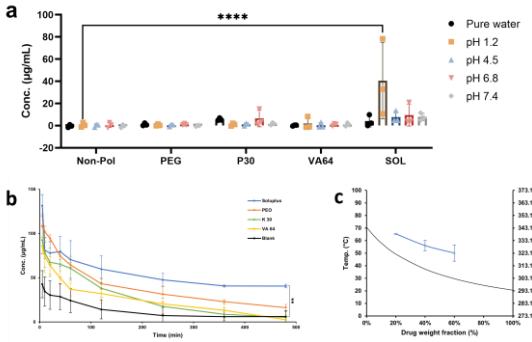

Fig. 2. *Suitability of Soluplus for lumefantrine ASD formulation, indicated by (a) Solubility enhancement assay and (b) anti-precipitation test (c) D-P miscibility by DSC.*

Table 1. *The melting enthalpy of recrystallised lumefantrine in different polymer films during storage.*

Polymer type	Melting Enthalpy (J/g)			
	Day 0	Day 2	Day 4	Day 10
Soluplus	0	-0.72	-0.91	-19.12
VA64	-17.72	-19.23	-22.19	-75.25
PVP	0	-17.89	-20.42	-82.65
PEO	-90.06	-15.86	-21.96	-69.30

CONCLUSIONS

Soluplus is the most appropriate polymer carrier for lumefantrine among the candidates, as indicated by HSP with the best performances in terms of supersaturated behaviour, solubility enhancement, amorphization ability, amorphous stabilisation ability and miscibility.

REFERENCES

Baghel, S.; Cathcart, H.; O'Reilly, N. J. Polymeric Amorphous Solid Dispersions: A Review of Amorphization, Crystallization, Stabilization, Solid-State Characterization, and Aqueous Solubilization of Biopharmaceutical Classification System Class II Drugs. J. Pharm. Sci. 2016, 105 (9), 2527–2544.

Baird, J. A.; Van Eerdenbrugh, B.; Taylor, L. S. A Classification System to Assess the Crystallization Tendency of Organic Molecules from Undercooled Melts. J. Pharm. Sci. 2010, 99 (9), 3787–3806.

Xu, S.; Zhang, H.; Qiao, B.; Wang, Y. Review of Liquid–Liquid Phase Separation in Crystallization: From Fundamentals to Application. Cryst. Growth Des. 2021, 21 (12), 7306–7