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Model Informed-Development of Amorphous Systems (MI-DAS) - an in-silico polymer selection tool for ASD development

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SUMMARY

Forming amorphous solid dispersions (ASDs) is one method for improving the solubility and subsequent absorption of poorly-water soluble drugs. An ASD is a matrix of a poorly water-soluble compound with a hydrophilic polymer carrier, which stabilises the drug in its amorphous form. The choice of polymer is often made based on previous success and precedence in other ASD products, and not on the suitability for the drug in development. A bespoke in-silico polymer selection tool (PST) has been developed which selects polymers based on their structural complementarity with the drug. Here, we demonstrate how use of the PST in early development of the Tacrolimus ASD would have identified a more optimal polymer with better API miscibility.

INTRODUCTION

Poorly water-soluble compounds exhibit suboptimal absorption in vivo which leads to low bioavailability. One approach to overcome low solubility is to form an ASD, whereby a poorly water-soluble compound is combined with a hydrophilic polymer carrier to form a homogeneously dispersed drug-polymer matrix. The dissolution rate of the drug-polymer matrix is much higher than drug alone, which results in a state of supersaturation. For an ASD to form, the drug and polymer must be miscible, and polymers should therefore be carefully selected.

The PST is utilised in the early stages of ASD development, and rapidly screens a large number of polymers to identify the most suitable for the active pharmaceutical ingredient (API) by using structural complementarity. The PST also predicts the glass transition temperature (Tg) of the drug-polymer matrix. This is important as a Tg of >80°C is preferred to ensure the ASD does not transition from the glassy to the rubbery state during downstream manufacturing. The use of the PST allows a rationalised focus onto a smaller polymer property space, negating the need for a trial-and-error approach which is labour and material intensive.

To investigate the utility of the PST, Tacrolimus was used as a case study. Tacrolimus is a BCS class II calcineurin inhibitor used in immunosuppressive therapy under the brand name Prograf®. It is formulated as an ASD with the widely used polymer hydroxypropyl methylcellulose (HPMC). HPMC is often the first-choice polymer as it has a good success rate and is present in many approved ASD products.

In this work we evaluated Tacrolimus using the PST to determine if HPMC is the optimum polymer, or if there are polymers which exhibit better miscibility.

MATERIALS AND METHODS

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The PST requires three inputs: 1) the Tg temperature of the amorphous form of the API, 2) the density and 3) the solubility parameter. The values used for Tacrolimus are shown in Table 1.

Table 1. *PST inputs for Tacrolimus*

Tg (°C)	True density (g.cm^{-3})	δ_T/MPa^(1/2)
79[a]	1.3[b]	19.7[a]

[a]*Values taken from Tsakiridou et al. (2019)*
[b]*Value estimated*

The PST uses these values to screen a database of polymers to determine A) the likelihood of miscibility of the API and each polymer, and B) the estimated Tg temperature of the drug-polymer matrices at various drug loads based on the Flory-Huggins Theory and the Gordon Taylor equation.

RESULTS AND DISCUSSION

The PST screening of Tacrolimus showed that a variety of polymers had better predicted miscibility with the API than HPMC, detailed in Table 2.

Table 2. *Miscibility and Tg temperature of Tacrolimus with various polymers, determined by the PST.*

Species	$\Delta\delta_T$/MPa^(1/2)[a]	Tg (°C)[b]
HPMC	9.0	151.8
Polyvinyl pyrrolidone K17	0.3	113.3
Polyvinyl acetate phthalate	1.9	108.6
Eudragit® E 12.5 / 100	0.5	51.9
Eudragit® L 12.5 / 100	1.2	138.4
Ethylcellulose	1.3	122.2

[a]*A $\Delta\delta_T$/MPa^(1/2) of <7 is indicative of miscibility between API and polymer, and the lower the value, the better the miscibility.*
[b]*Tg temperature for a 20% drug load ASD (typical drug load of ASDs).*

The miscibility value of Tacrolimus and HPMC is 9, which suggests a degree of immiscibility. Tacrolimus has better predicted miscibility with a variety of polymers, including Eudragit® E and Eudragit® L. Despite this, the Tg temperature of the Eudragit® E ASD is low (52°C) which is undesirable.

The PST screen suggests that HPMC is not the optimal polymer to use for Tacrolimus, and that other polymers may produce more stable and effective ASDs. Yoshinda et al. (2012) conducted a study looking at an ASD of Tacrolimus with Eudragit® E and found that an ASD using this polymer improved drug dissolution compared to the Tacrolimus ASD with HPMC. The dissolution results obtained from their study are shown in Figure 1.

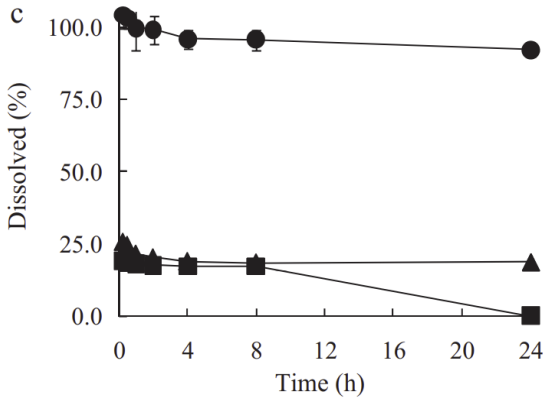

Fig. 1. *Dissolution of Tacrolimus in pH 6.8 buffer with Eudragit® E (circles), HPMC (triangles) and Tacrolimus alone (squares). Taken from Yoshida et al. (2012).*

The work by Yoshida et al. (2012) showed that Eudragit® E provided a greater uplift in solubility than the polymer currently used in the Tacrolimus ASD, HPMC. Using the PST has demonstrated that there may be an even more suitable polymer that is more miscible with Tacrolimus and unlike Eudragit® E, has a suitable Tg temperature: Eudragit® L. Future work could include an assessment of a Tacrolimus Eudragit® L ASD to investigate the solubility uplift.

CONCLUSIONS

This work demonstrates how the PST can provide value in early formulation screening to ensure the most suitable polymer is chosen to progress into ASD development. This focused approach enhances the development process by avoiding the need for a trial-and-error approach, reducing costs, time and API usage, and increasing the chance of success.

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