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A Rapid Screening Tool for Assessing the Utility of Amorphous Dispersions for Bioavailability Enhancement

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PURPOSE

Amorphous dispersions prepared by spray drying or hot melt extrusion can increase oral bioavailability of a wide range of drugs by leading to supersaturation in the upper intestine and sustaining that supersaturation long enough to increase the driving force for permeability. Recent work on amorphous dissolution has demonstrated the ability to readily detect amorphous phase separation in aqueous solutions.

Based on this work, we set out to develop a rapid assay for determining amorphous solubility and the ability of polymers and surfactants to prevent crystallization from the supersaturated state in biorelevant media.

In this work, we have measured the amorphous solubility in FaSSIF to understand how this more complicated case compares to the published work in simple buffers.

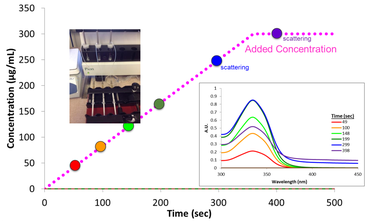
METHODS

Five model compounds (erlotinib, gefitinib, ketoconazole, and dipyridamole, and itraconazole) were tested as received. Concentrated stock solution of drug was added to fasted state simulated intestinal fluid (FaSSIF) using a syringe pump while simultaneously monitoring drug concentration and scattering using UV fiber optic probes (Pion). The experiment is set up and analyzed rapidly using a customized application.

Model Drug Properties

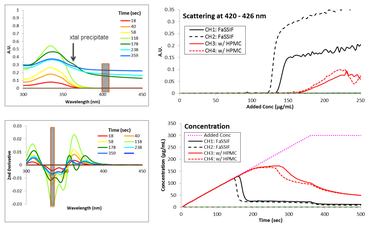
Property	Erlotinib	Gefitinib	Ketoconazole	Dipyridamole	Itraconazole
MW	393	447	531	505	706
pKa	5.4	5.3, 7.0	6.2	6.4	3.7
logP	3.0	4.1	4.3	3.9	5.9
Xtal Sol (FaSSIF) µg/mL	7.6	116	14	19	**0.07**
T_m (˚C)	**170**	**195**	**150**	**170**	**170**
T_g (˚C)	**37**	**64**	**43**	**31**	**54**
ΔH_{fus} (kJ/mol)	**44**	**31**	**53**	**32**	**64**
Structure					

Experimental Setup



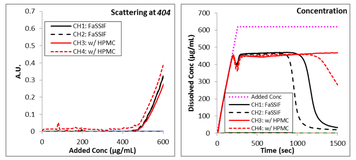
Drug isadded to the media of interest from a stock solvent solution using an 8-postion syringe pump

Amorphous Solubility of Erlotinib

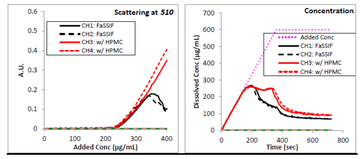


After amorphous phase separation, erlotinib precipitates to form UV-active nanoaparticles that can be quantified via deconvolution of the 2nd derivative of the UV spectra.

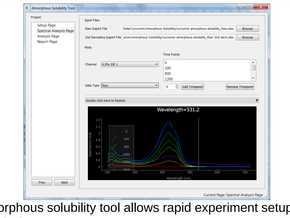
Ketoconazole



Dipyridamole



Specialized Data Visualization and Manipulation



The amorphous solubility tool allows rapid experiment setup and data analysis.

RESULTS

We have developed a rapid and reliable assay for measuring the amorphous solubility of compounds as well as the sustainment with potential dispersion polymers. To demonstrate the utility of this test, the amorphous solubility of erlotinib, gefitinib, ketoconazole, dipyridamole, and itraconazole in FaSSIF was determined:

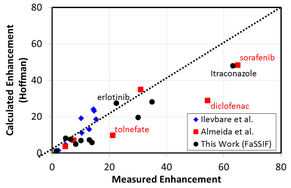
Property	Erlotinib	Gefitinib	Ketoconazole	Dipyridamole	Itraconazole
Amorphous Solubility (ug/mL)	170	740	490	265	7.2
S_{am}/S_{xtal}	22	6.4	35	14	63

. The “amorphous enhancement” is consistent with the predicted amorphous solubility[c] for all cases except dipyridamole and itraconazole. The discrepancies may be due to the fact that the predicted values are only applicable in the absence of micelle solubilization.

A specialized software application speeds up the analysis and visualization of the data.

$$\frac{C_{am}}{C_{xtal}} = e^{-1(a_2)} \cdot e^{\Delta G_{x\to a}/RT} \quad ; \quad \Delta G_{x\to a} = \frac{\Delta H_f (T_m - T) T}{{T_m}^2}$$

Experimental vs. Predicted Amorphous Solubility



Measured and predicted values of the amorphous enhancement factor are in good agreement. In this work, the activity of drug saturated with water was calculated using a linear regression of existing data with drug PK properties.

CONCLUSIONS

The amorphous solubility can be rapidly determined to predict the utility of amorphous formulations and the challenge in sustaining a supersaturated concentration. This capability can guide and speed up early formulation development for amorphous dispersions.

Despite the introduction of more complicated buffers such as FaSSIF, the amorphous solubility provides an estimated upper limit of enhancement that can be realized with amorphous formulations and is a rapid way to screen polymers for precipitation inhibition.

ACKNOWLEDGEMENTS

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