SSPC

Project 4: **The API/Formulation Interface**
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Title:

Quantification of the Amorphous and Crystalline Contents of Pharmaceutical Solids

Principal Focus: This study is focused on the quantitative analysis of mixtures containing amorphous and crystalline materials. Multivariate calibration models are developed for binary and ternary mixtures of amorphous sulfathiazole, sulfathiazole polymorphs and amorphous excipients. PLS regression models are constructed to predict the content of each component in unknown mixtures. Problems have been encountered in the preparation of amorphous sulfathiazole, where moisture is taken in from the atmosphere, hindering quantification analysis.

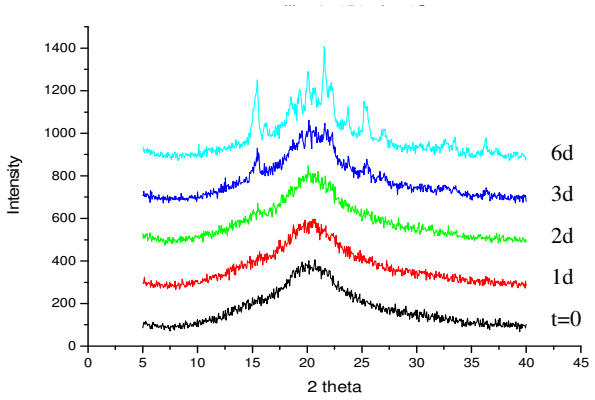

Fig 1. Stability of Commercial Sulfathiazole Cryomilled for 3hrs Monitored by XRPD

Preparation of Amorphous Sulfathiazole, Cryomilling:

1. ≈ 2g of commercial sulfathiazole placed in a stainless steel grinding jar, containing a grinding ball is cooled in liquid nitrogen for 3 minutes.
2. This is then run in a Retsch pulveriser, grinding for 7.5 minutes and then cooled in liquid nitrogen for 3 minutes.
3. The grinding and cooling is repeated for 3 hours.

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Preparation of Amorphous Sulfathiazole, Melt:

1. ≈3g of commercial sulfathiazole wrapped in aluminium foil is heated to 210˚C using a hot plate in a nitrogen filled glove bag.
2. After 1 minute the aluminium containing the sample of sulfathiazole is removed and allowed to cool.

Stability of Amorphous Sulfathiazole Obtained by Cryomilling:

This study is currently ongoing. XRPD measurements taken at different intervals suggest that amorphous sulfathiazole obtained by cryomilling is stable for the minimum of a day. Amorphous sulfathiazole obtained by cryomilling is significantly more stable than that prepared by other methods.

Multivariate NIR Method for the Quantification of Ternary Mixtures of Sulfathiazole form I, III and Amorphous PVP:

A study on the quantification of ternary mixtures of sulfathiazole form I and III and PVP by NIR spectroscopy in combination with chemometrics was carried out. Different data pre-treatment algortihms were compared.

Performance characteristics of the calibration models are shown in Table 1.

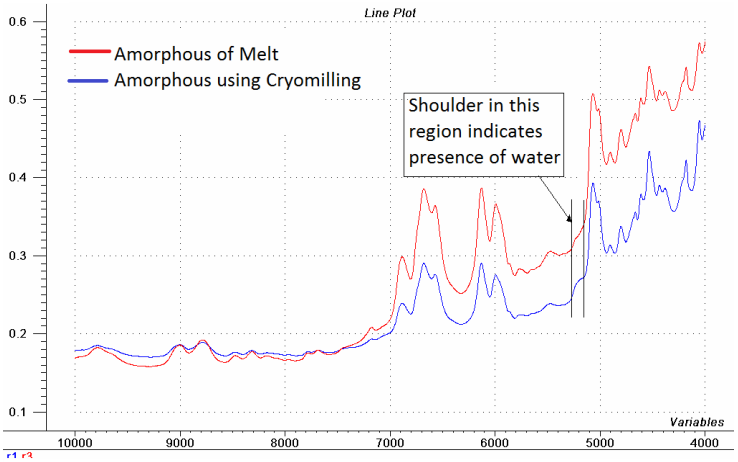

Fig 2. NIR spectrum of amorphous sulfathiazole prepared using cryomilling and melt method.

Table 1. Quantification of Ternary Mixtures of Sulfathiazole (stz) Form I, III and Amorphous PVP

	Quantification of PVP	Quantification of stz form	Quantification of stz form I
Pre-treatment	SNV	MSC	MSC
RMSEC	1.7180	1.691	2.196
RMSEV	2.090	1.984	2.587
RMSEP	1.800	1.324	2.471
Correlation_C	0.9993	0.9988	0.9976
Correlation_V	0.9988	0.9984	0.9967
Correlation_P	0.9997	0.9996	0.9997
PLS factors	2	2	2

Discussion: From the XRPD it can be seen that both methods produce amorphous sulfathiazole. However, NIR analysis reveals that moisture is absorbed during cryomilling. This in turn affects the stability of the amorphous sulfathiazole and hinders quantitative analysis using NIR and MIR. Amorphous sulfathiazole obtained from the melt does not contain moisture, but with further analysis (NMR) it is clear that some degradation occurs when melted in air.

Future Work: A method to prepare amorphous sulfathiazole containing as little moisture and degradation as possible will be finalised. This can then be used to develop regression models which can accurately predict low levels of amorphous content. This work along with further work on the quantitative analysis of quaternary mixtures containing the excipient PVP is relevant for studies carried out at TCD involving spray-dried sulfathiazole samples stabilised with PVP.