Project 26: **Solid-state and micromeritic characterisation of pre- and post-spray dried systems: API, excipients, salts and co-crystalline forms** Date: **19/08/10**	Author: **Krzysztof Paluch** Strand: **The API/Formulation Interface** Institute: **Trinity College Dublin**

Title: Physicochemical characterisation and crystal structure elucidation of novel salt forms of model API compounds.

Principal Focus:

This project focuses on gaining an understanding of the implications of API-counter-(ion/compound) solid state interactions (ionic interactions, hydrogen bonds, Van der Waals forces) on modification of APIs' intrinsic properties and processability.

Principal Outcomes to Date:

Model (low aqueous solubility) APIs selected were: chlorothiazide (acidic, BCS IV) and salbutamol base (basic, BCS III). The counterparts chosen for chlorothiazide were strong, inorganic: sodium and potassium cations (Na^+<K^+). Salbutamol base interactions were investigated using weak organic acids: succinic and adipic (C_4<C_6).

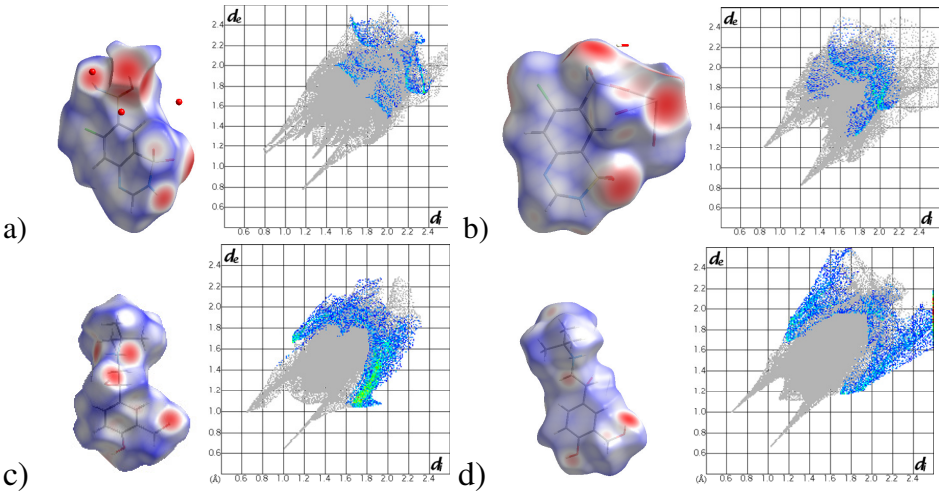

Fig. 1. Hirschfield surfaces with corresponding C…H interactions of:
a) chlorothiazide sodium dihydrate,
b) chlorothiazide potassium dihydrate, c) salbutamol adipate co-crystal,
d) salbutamol succinate hemiethanolate

Discussion:

Experiments resulted in the elucidation of new API compounds: hydrated intermolecular self-assemblies (ISA) of chlorthiazide sodium (CTZNa) and potassium (CTZK), co-crystal form of salbutamol adipate with adipic acid (SA) and solvated salt of salbutamol succinate (SSU) which are presented on Fig. 1. a-d.

ISA CTZK and CTZNA and their derivative forms presented a similar and nearly 400-fold enhancement in stoichiometric solubility over CTZ. Different water coordination capabilities for Na^+ and K^+ (Paluch at al., 2010) resulted in different stabilities of the hydrated forms when exposed to increasing relative humidity. Spray drying of CTZK and CTZNa resulted in amorphous dehydrated derivatives.

Analysis and comparison of Hirschfield surfaces of the crystal forms of SA and SSU showed evidence of stronger C…H interactions in SA, resulting in a nearly 4-fold reduction of intrinsic dissolution rate (IDR) for SA compared to salbutamol sulphate.

Future Work:

Despite preformulation studies of different solid-state and salt forms of APIs being widely investigated, the ability to predict salt, co-crystal, amorphous phase formation and behaviour remains poorly understood, largely empirical and requires further research.

References

Paluch, K.J., Tajber, L., McCabe, T., O'Brien, J.E., Corrigan, O.I., Healy, A.M., Salt or intermolecular self-assembly - physicochemical analysis of crystalline chlorothiazide and chlorothiazide sodium, *All Ireland Schools of Pharmacy 32nd Research Seminar*, Belfast, 2010

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