Discovery and Applications of a Novel Solid-state arrangement: Water bridge Salt Form.

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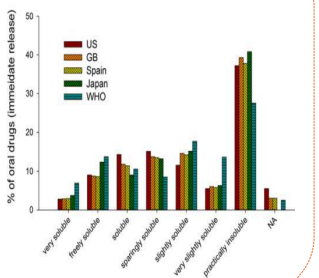
AIM: To build fundamental understanding of salt "water bridge" propensity, creation, stability, and structure-property relationships.

OBJECTIVE: Use data driven approaches to identify features that promote water bridge formation; characterize the structural features and mechanism of extended stability; discover and characterize new salt water bridge forms to confirm design approaches

Introduction:

Solid form diversity of pharmaceutical products plays a vital role during the discovery and development of drug.

85% of (API) exist in different polymorphic forms → *Select the right **Form** and **Formulation***



Key Challenge for many of the newly discovered drug molecule is
- Poor aqueous solubility
- Less bioavailability

About 40% of marketed drugs are practically insoluble (<0.1mg/mL)

Salt formation is a common technique to modify the properties and enhance aqueous solubility of API

~50-70% Approved API administered Salts form

- **Bioperformance** → Increase the solubility, dissolution rate; Enhance Bioavability
- **Manufacturing** → Optimize the formulation properties; Reduce hygroscopicity, enhance the crystallinity reduced toxicity; Limited polymorphic forms
- **Quality** → Improve stability/longer shelf life

However, the success of using these ionized species in tablets significantly depends on their stability both before and during drug release. There is a tendency for salts to convert back to its free (unionized) form under certain conditions via a reaction known as salt *disproportionation*. Here we seek to identify opportunities to extend the stability of salts through water bridge salt forms.

Case study: Miconazole Mesylate

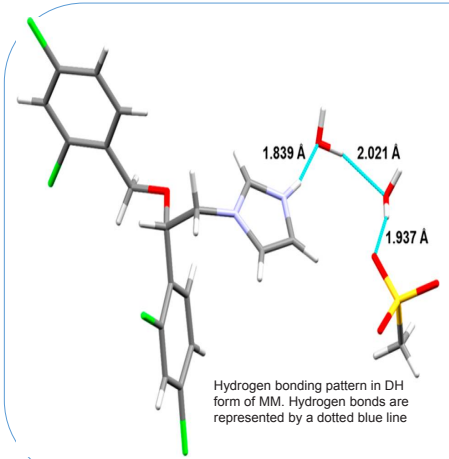
Different solid state forms of Miconazole Mesylate (MM) salt (amorphous AMO, anhydrous AH, dihydrate DH) were investigated and their disproportion tendency in the presence of excipient has been analzed.

Rate and extent of salt disproportionation for different solid forms of MM is significantly different.

AMO and AH form of the drug were found to be susceptible to disproportionation.

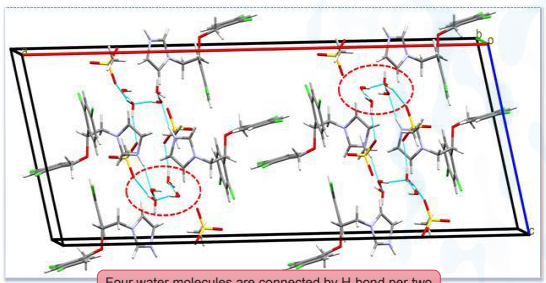
AMO and AH also undergo phase transformation to crystalline DH form.

DH form of MM was resistant over the time period studied.



Hydrogen bonding pattern in DH form of MM. Hydrogen bonds are represented by a dotted blue line

Miconazole molecule forms a hydrogen bond with a water molecule, which is bonded to another water molecule with a second hydrogen bond with another water molecule and this water molecule is then bonded with mesylate ion by a hydrogen bond.
This is the "water-bridge



Four water molecules are connected by H-bond per two molecules of miconazole mesylate

Phase 1
- Water packing arrangements in reported crystalline hydrate structures will be assessed to identify the propensity of specific molecular features and particular salts to adopt water bridge packing
- CSD structural search tool will be used to identify water bridge formation within the wider class of salt hydrates

Phase 2
- The study will explore the molecular features that favour water bridge formation in molecular salts, the factors that affect their formation from solution crystallization and the solubility, dissolution and stability of selected water bridge hydrate structures as a function of pH.
- Salt bridge formation on the selected system under wide range of temperature pH, and water activity will be analysed to investigate hydrate formation under thermodynamic and kinetic control.

Phase 3
- Study the structure property relationships in water bridge compounds.
- Study the relationship between molecular structure (functionality, pKa), crystal packing (intermolecular interactions, H_2O packing) and stability following dissolution under the effect of different prevailing solution pH.

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