4-case chart to classify supersaturation and precipitation behavior

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Purpose

To provide a simple chart to allow users to classify supersaturation and precipitation to provide better understanding during drug formulation.

Methods

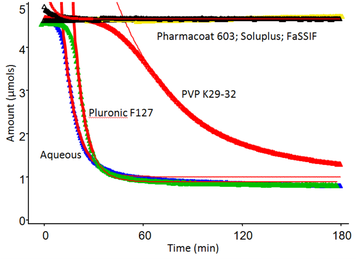
Hundreds of experiments of different types were run over a period of five years to investigate supersaturation and precipitation of small molecule drugs in aqueous solution. The results of this work have led to a better understanding of the types of behaviour that a drug can exhibit. The experiments undertaken comprised the following: solubility measurements by pH-metric methods; solubility by shake-flask; controlled supersaturation studies by pH-metric and UV methods; studies of the solid state using polarised light microscopy; aqueous dissolution under changing pH conditions; and biphasic dissolution.

Results

To help rationalize a complex set of behaviours, supersaturation and precipitation phenomena have been classified into four principal classes. Examples are provided of experiments and results that demonstrate the behaviour expected with each class. The first class comprises aqueous solutions in which a drug is supersaturated but no precipitate is present. The other classes comprise supersaturated solutions in which the drug is also present as precipitate in the LLPS (liquid-liquid phase separation) form, supersaturated solutions in which the drug is precipitated as a crystalline solid, and a fourth class comprising solutions in non-aqueous or partially non-aqueous media in which the concentration of drug dissolved is higher than the aqueous solubility; this behaviour is exemplified by drugs in lipid-based formulations.

Conclusion

A simple 4-case chart has been developed to classify the behaviour of drugs in supersaturated solution and during precipitation. It will provide a structured approach for evaluating the behaviour of compounds during formulation and in determining viable formulation strategies.



Solutions of bifonazole prepared by solvent quench. All solutions are super-saturated at time 0. Precipitation soon occurs in aqueous solution but is inhibited by additives.

1. API dissolves

Solution may be unsaturated.

Solution may be supersaturated.

It may precipitate (see 2) or crystallize (see 3).

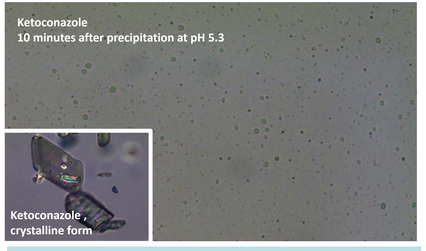
Additives may keep it in solution, e.g. Pharmacoat, Soluplus, FaSSIF.

2. Precipitates as LLPS*

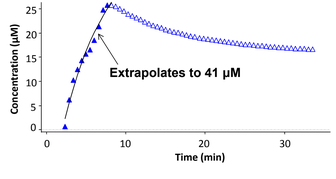
Concentration = LLPS solubility.
Reservoir of LLPS, may help absorption.

Drugs with melting point < 25°C can precipitate as liquids. Some drugs with higher MPt can precipitate as a LLPS, which may be regarded as a metastable, amorphous state with little or no long range order and a higher free energy than the crystalline equivalent.

*** LLPS = Liquid-Liquid Phase Separation**



Solution prepared by pH-shift. Ketoconazole precipitated from aqueous solution as LLPS. It can persist in this form for several hours.



Drug dissolving from nanoclay preparation. Concentration rises rapidly but drug soon crystallizes. In a better formulation, crystallization will not occur.

4. Dispersed in another phase

Solid form is not crystalline. Can be:

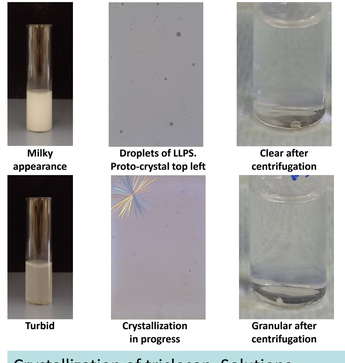
Amorphous
In lipid
In solid dispersion
In mineral, e.g. nanoclay, mesoporous silica

Capable of dissolving to achieve concentration higher than equilibrium solubility.

3. Crystallizes

Quickly (e.g. bifonazole in aqueous conditions).
Eventually (e.g. ketoconazole).

Due to the higher free energy of a LLPS, crystallisation will eventually occur. However, so long as a LLPS exists, an equilibrium with the solution phase will be maintained. Hence, the solution phase of drug will remain at a concentration of the LLPS solubility until the LLPS converts to the less soluble crystalline form.



Crystallization of triclosan. Solutions prepared by pH-shift. LLPS begins to crystallize after about 10 minutes.

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