WHITE PAPER

Physical Stability of Agrochemical Formulations and Observation of Eutectics

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Technobis crystallization systems

1. Abstract

Physical stability of formulations is an important parameter during formulation development, especially when testing multiple phase systems (suspensions or emulsions). A broad temperature range needs to be observed in particular for agrochemical formulations. A model system of two active ingredients in solvent is investigated by storage at variable temperature and automated optical observation with the help of the ***Crystalline*** instrument. The phase transformation from a suspension to an emulsion can be easily detected with the particle view technology of the ***Crystalline*** instrument. Results based on the model system can be used for decisions on the path to the new formulation.

2. Introduction

2.1 Physical Stability of Formulations

A formulation is a mixture of active ingredient (AI) and formulation additives. It has the aim to bring an AI into an applicable form. Formulation additives are used to stabilize the formulation and to support the delivery to the application field. Pharmaceutical, agrochemical and nutrition AIs are mainly organic molecules or salts that shall be taken up by living organisms and interact e.g. with enzymes. Therefore, in the end the molecule needs to be in solution on a molecular level. However, important aspects favor solid AIs for formulation: chemical stability, AI loading, convenience for end-user, etc..

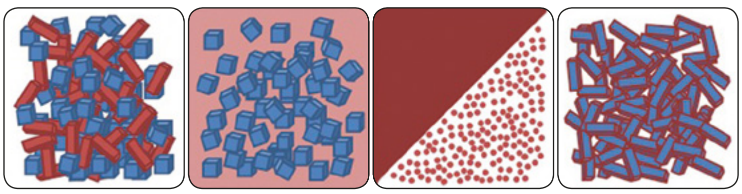
The formulation needs to be a stable formulation that when moved into a new system becomes instable and delivers the AI. A patient takes a stable solid tablet, which is dissolved in the intestinal tract (new system, instable as solid) and the AI permeates into the blood stream to reach the center of activity. The same applies to solid containing agrochemical formulations. A stable solid is delivered with or without liquid phase, the formulation is diluted with water to form a suspension, emulsion or solution and is applied on the plant where the finally dissolved molecule has to permeate into cells.

The physical stability of each formulation is crucial. In comparison to other applications, even harder temperature regimes are applied to agro formulations as they are stored in warehouses which are often not temperature controlled with temperatures potentially ranging from -20°C to well above 40°C. The rational investigation of physical stability of model systems shall be considered in this text to support decisions regarding formulation systems.

2.2 Agrochemical Formulations

A significant share of agrochemical formulations are sold as suspension concentrate (SC). The SC formulation consists of solid and liquid parts. In an easy view solids are the active ingredients (AIs), liquids are water, solvents and other formulants to stabilize the SC formulation and to support the uptake of the AI. This dosage form allows easy handling and mixing to a stable tank mix. However, in comparison to e.g. a wettable granule the presence of a liquid media increases probability of physical instability. The liquid medium facilitates re-crystallization, crystal growth or agglomeration. Therefore, beneath other stability test also extended physical stability investigations are performed during formulation development.

Figure 1: *Mixture of two actives as binary system and in liquid formulation.*



active 1 + active 2	**mixture of AIs**	**liquid plus solid (e.g. eutectic + excess solid)**	**eutectic melt**	**co-crystal**
active 1 + active 2 + formulants	**mixture of AIs in formulation (SC)**	**mixture of AIs in formulation (SC)**	**solution / emulsion**	**co-crystal in liquid formulation(SC)**

The majority of agrochemical formulations consists of mixtures of AIs. The application of more than one AI with different modes of action reduces resistance formation of fungi, insects or weeds. When two AIs are mixed in the SC formulation, they can have different interactions. They either can show no interaction, as two solids or as solid and dissolved, or they can interact by formation of a co-crystal, which is a new solid form, or in the melt, which leads to a lower melting point (eutectic). Possible interactions in the binary system and the formulation are listed in Figure 1.

Knowledge about interactions between two actives is necessary to define the target profile/specifications and the formulation system to be used. Testing of model systems in small scale can speed up and strengthen decisions regarding mixtures and formulation direction.

Stability testing of agrochemical formulations includes e.g. storage stability test for 2 weeks at 54°C. This accelerated shelf-life condition originates from chemical stability considerations, but are also routinely used to assess physical stability. With respect to real storage conditions of agrochemical formulations e.g. in warehouses or barns that are located in tropical areas and are not temperature controlled, these conditions might even occur.

3. Experiments and Results

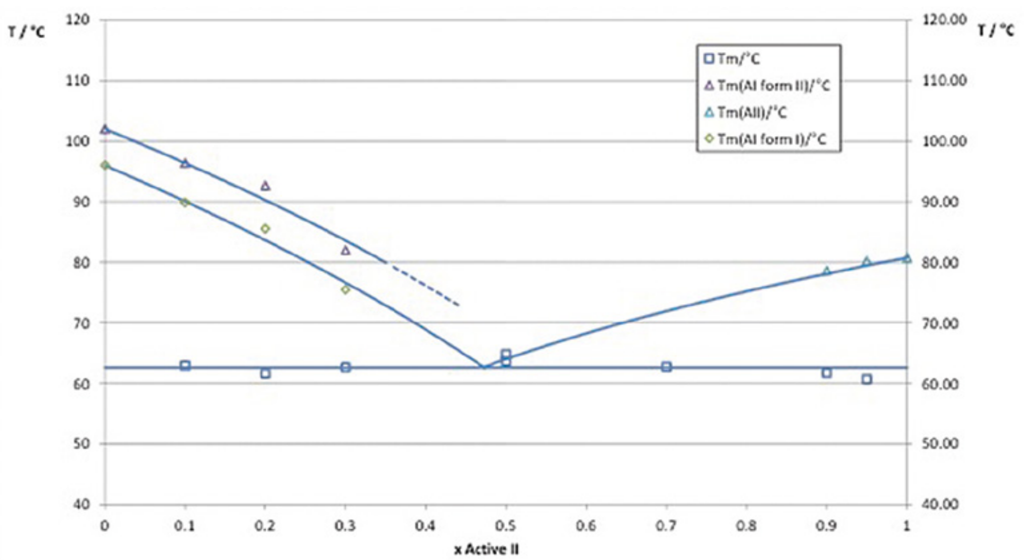
Stability tests need to be performed on the final formulation. However, a bottom up approach and investigations in applied systems and partial formulations allow a rational design of formulations. The knowledge of a sufficiently stable formulation is highly needed and not a short term stable formulation that might fail due to unknown/insufficiently investigated circumstances. Therefore, in case for active – active formulations, first investigations are always done in the simple binary system of actives, followed by the increase of excipients/solvents which allows a knowledge based design.

The importance of stability tests right from the first experiments shall be shown for an example of two active ingredients active 1 (AI1) and active 2 (AI2).

3.1 AI1 – AI2: Binary System

For two model actives, AI1 and AI2, co-crystal formation is not known. To investigate their joined behavior the binary system A1 – A2 is first investigated. Pure AI1 and AI2 and mixtures of both without further formulation additives are analyzed by DSC (Differential Scanning Calorimetry). Endothermal events are extracted and displayed in a phase diagram (Figure 2). Whereas both AIs melt well above 80°C, the mixtures show a melting peak at approx. 62°C. The two AIs form an eutectic mixture with approximately 1:1 molar ratio. These results show that a binary mixture of solid AI1 and AI2 is physically not stable above 62°C.

Figure 2: *Phase diagram of two active ingredients.*



3.2 AI1 – AI2 – Solvent: Ternary and Higher Systems

A physical instability at about 62°C is already quite low regarding real storage conditions encountered, but it might still be acceptable. However, this temperature is only valid for the binary system. Further formulants may further decrease this maximum temperature.

To investigate a possible SC formulation the addition of water or water solvent mixtures need to be tested.

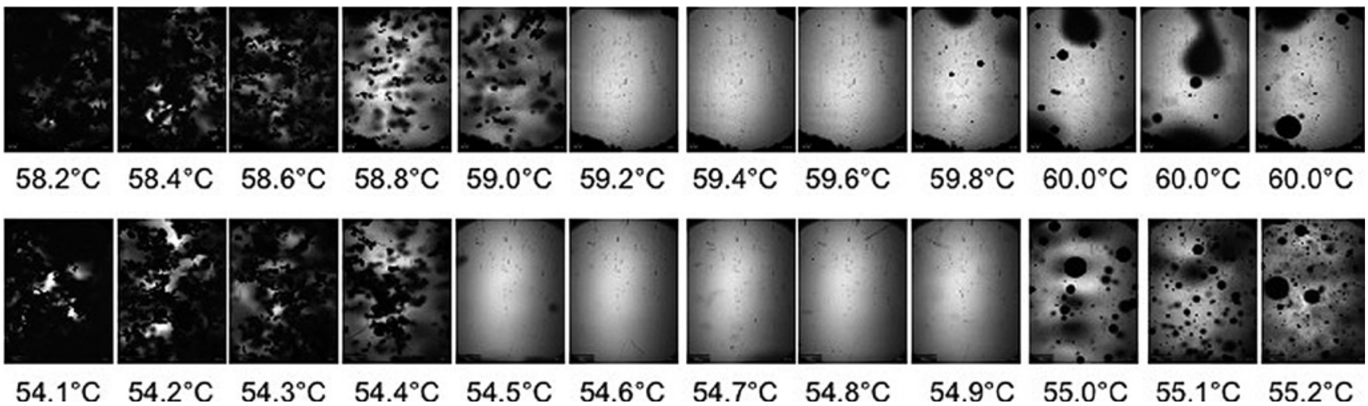
Temperature dependent suspension experiments of AIs in solvents were observed using the ***Crystalline*** instrument. Individual temperature ramps were performed and pictures of individual experiments taken. The pictures can be used for optical analysis: crystal growth, re-crystallization, dissolution or other phase transitions. A physically stable suspension needs to show none of the mentioned phenomena. Crystal growth or re-crystallization are not acceptable in a formulation. In general, a formulation is milled to obtain fine particles that could pass through fine nozzles when sprayed on the field. Dissolution due to elevated temperature would mean re-crystallization upon cooling with the same effect. Phase transition from suspension to emulsion can be observed in the discussed example.

Model formulations were prepared using crystalline AI1 and AI2 and solvent (water or water/solvent mixture). 3 mL were placed in the ***Crystalline*** instrument and stirred for mixing and observation. A temperature interval from 20° to 60°C with a heating rate of 1°C/min was investigated. Pictures were taken simultaneously every second during the experiment.

The picture series of two suspension experiments in water and water/solvent mixture is shown in Figure 3. The transformation of the suspension (solid in liquid) into an emulsion (liquid in liquid) can be observed. It can be seen that the eutectic melting temperature of the two actives in the binary system (62°C) is further decreased. Using water, the decrease is still small (59°C), but addition of co-solvent further decreases the melting temperature (55°C).

The physical stability of such a suspension prepared at room temperature cannot be guaranteed at 54°C when even a binary solvent mixture with water decreases the melting point to 55°C. Crystal growth, agglomeration and/or sedimentation have to be expected and actually can be observed in first "full formulation experiments". As a conclusion, the development of a SC formulation with these two actives can only be done with the limitation to mostly avoid formulation additives. Therefore other formulation types might be preferred, e.g. emulsion concentrate (EC), wettable granule (WG), and others.

Figure 3: *Picture series taken with the Crystalline instrument, of two temperature ramp experiments of AI1, AI2 and solvent (top: water, bottom: water/solvent mixture).*



4. Summary

Formulation development is the art of making stable formulations that become instable when they need to deliver the active. However, up to the application of the formulation, stability is crucial within the set specification. Physical stability seen in phase transition or crystal growth can greatly be observed using pictures of model formulations or full formulations. The ***Crystalline*** instrument offers the possibility to take pictures of small volumes (2-5 mL) of liquids, solutions, emulsions or suspensions. Model formulations or final formulations can be individually investigated at different temperature programs and stirring rates. Turbidity can be measured and pictures can be taken. Moreover, Raman spectroscopy can be also used on the ***Crystalline*** instrument giving additional information about the crystal form of an active ingredient.

The discussed example for the two model active ingredients shows the phase transition from a suspension to an emulsion. Decisions can be made at any stage of development, early exemplary model systems as shown here can allow extrapolation of stability for formulation systems. Final formulations can be investigated at various temperature cycles for fine tuning the complete formulation.

For more information on ***Physical Stability of Agrochemical Formulations and Observation of Eutectics*** please check our website for the ***webinar*** with the same title presented by Dr. Martin Viertelhaus and our publications database.

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