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INVESTIGATION OF THE PHARMACEUTICAL APPLICABILITY OF SOLVATES: SCREENING, CHARACTERIZATION, CRYSTALLIZATION

Summary of PhD Thesis

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1. INTRODUCTION, AIMS

Active pharmaceutical ingredients often exist in a variety of solid forms. The investigation of solid form diversity is an important step in pharmaceutical development, because inconsistencies in the solid structure may cause severe consequences. Understanding the properties and behaviour of pharmaceutical solids is fundamental to pharmaceutical discovery, development, processing, clinical studies, manufacturing and storage, thus throughout the whole lifecycle of the drug product. Interconversion between different solid forms may have a considerable influence on physicochemical properties that can consequently affect the bioavailability of the drug.

The scope of this research work is divided into three parts which follow the same scenario as a real pharmaceutical development project. The first part focuses on the methodology improvement on solid form screening with particular focus on solvated/hydrated solid forms. Five different model compounds with markedly different structures and solid form landscape were involved in the study in order to establish a comprehensive screening method which is universally applicable. The second part aimed to provide a deep understanding of the structure-property relationships of the investigated solvate structures. Various analytical techniques, including thermal analysis, dynamic vapour sorption, critical water activity investigation, stability testing, intrinsic dissolution rate measurement, variable humidity powder X-ray diffraction and single crystal X-ray diffraction, were utilised in an attempt to rationalize the propensity to solvate/hydrate formation and explore the stability boundaries of different forms. The third part focused on the crystallization method development of a selected hydrate candidate. By means of Process Analytical Techniques (PAT), such as Attenuated Total Reflection Fourier Transform Infrared Spectroscopy (ATR-FTIR), Focused Beam Reflectance Measurement (FBRM) and Particle Vision and Measurement (PVM) technology offered considerable insight into the crystallization process and helped develop a robust crystallization method.

2. LITERATURE REVIEW

Oral solid dosage forms are the most common way to deliver a drug substance to a patient, conventionally produced by the formulation of solid powders. This formulation is commonly selected due to the ease of handling and better chemical stability. Consequently, understanding the behaviour of different solid phases, as well as the rational selection of solid forms are crucial to enable efficient development of an active pharmaceutical ingredient (API).[1] Adequate control over solid forms is of paramount importance, as each phase can exhibit diverse properties including solubility, dissolution rate, physical and chemical stability and bioavailability.[2] Pharmaceutical solids are exposed to various organic and aqueous solvents during the course of a drug development upon crystallization, wet granulation, and dissolution, which may result in the formation of a solvate/hydrate deliberately or inadvertently.[3]

Solvate and hydrate formation is more frequent with increasing molecular size. The likelihood of hydrate formation decreases with the lipophilicity of the molecule, while solvate formation with organic solvates increases.[4] Large, branched molecules can improve their packing efficiency through incorporated solvent molecules, and the inclusion of a solvent is sometimes vital to build a stable crystal structure.[5] Water molecule's small size and ability to serve as both hydrogen bond donor and acceptor make it likely to be incorporated in the lattice either as space filler or as a stabilizing force.[6]

There is an observable trend in pharmaceutical development to move toward drug molecules that are more complex, more lipophilic and insoluble in nature, which might raise limitations in bioavailability.[2] One of the most common and effective approaches for increasing the solubility and dissolution rate of ionizable drugs is salt formation. Salt formation cannot only enhance bioavailability but may also improve physical and chemical stability.[4] Over 50% of the marketed drugs are administered as salts in oral formulation.[1] The observed higher prevalence of hydrates among salts can be attributed to the propensity of water to bind to ionic sites. As opposed to salts,

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[1] Y. Qiu, Y. Chen, G. G.Z. Zhang, L. Liu, W. Porter, Developing Solid Oral Dosage Forms: Pharmaceutical Theory and Practice, 1st ed. Burlington, MA, Academic Press, 2009

[2] H. G. Brittain, Polymorphism in Pharmaceutical Solids, 1st edition, Marcel Dekker, New York, 1999

[3] B. Rodríguez-Spong, Ch. P. Price, A. Jayasankar, A. J. Matzger, N Rodríguez-Hornedo, General principles of pharmaceutical solid polymorphism: a supramolecular perspective. Adv. Drug Del. Rev., 2004, 56, 241–274

[4] R. Hilfiker, Polymorphism in the Pharmaceutical Industry, Wiley-VCH Verlag GmbH, Weinheim, 2006

[5] A. J. Matzger,C. P. Price, G. D. Glick, Dissecting the Behaviour of a Promiscuous Solvate Former, Angew Chem Int Ed., 2006; 45(13), 2062-2066

[6] A. Y. Lee, D. Erdemir, A. S. Myerson, Crystal Polymorphism in Chemical Process Development, Annu Rev Chem Biomol Eng. 2011;2:259-80

non-charged molecules are more prone to form solvates and polymorphs.[6] The fact that the number of solvates/hydrates is increasing, underpin the need for a thorough understanding of the mechanisms of hydrate/solvate formation and the stability of these multicomponent systems, including the transformation pathways to other solid phases.

The differences between solvent-free and solvated forms are significant. An anhydrous crystalline form is a one component system, and its free energy is determined by temperature and pressure. On the other hand, a crystalline hydrate (solvate) is a two-component system and is defined by temperature, pressure and water (solvent) activity.[2] In general, hydrates are preferred over solvates, as the presence of water does not raise toxicity concerns, but more importantly, a hydrate can be the thermodynamically stable form at ambient conditions, while solvates are always metastable removed from their mother liquor. The significance of solvated forms has been further enhanced by their potential value in intellectual property.

Intellectual property (IP) protection is a critical element of pharmaceutical industry and have major economic implications. Different crystal forms are eligible for patent protection as they satisfy the criteria of novelty, non-obviousness and utility (industrial applicability). By definition, a new crystal form is novel and since crystal forms cannot be predicted, they are also not obvious.[7]

In general, innovator pharmaceutical manufacturers are trying to patent every relevant solid form of a drug molecule in addition to filing patents related to their indication, synthetic route or formulation to ensure exclusive rights to the invention and enhance product life cycle management. Nevertheless, in an attempt to reach earlier market entry, generic pharmaceutical companies constantly search for novel solid forms of a drug and challenge the originator's patents in order to circumvent the drug's intellectual property protection, and establish their own IP position and freedom to operate.[7,8]

As water is omnipresent, a hydrate is often the most stable form at ambient conditions and is therefore often the selected solid form for commercial drug products. But the judgement of solvates is changing: they are not anymore undesired by-products during the pharmaceutical development. As generic companies are seeking for new, non-infringing solid forms, solvates

[7] J. Bernstein, Polymorphism in Molecular Crystals. Oxford University Press, Oxford, 2002.
[8] H. Slowik, The Battle for IP, The Business & Medicine Report, 2003, 21(6)

offer an option to circumvent innovators' patents. Furthermore they have the potential to improve the in vitro dissolution kinetics.[9]

The goal of a rationally designed solid form screening is to generate all relevant phases of a compound that may be encountered during development, particularly the thermodynamically stable form, within the constraints of available time, material and resources.[10] Apparently, the most desirable crystalline form to develop is a stable solid form, as it has the lowest propensity to transform during scale-up, processing, formulation or storage.[1] At the same time, the identification of metastable polymorphs and solvated forms are also important as it allows the determination of key parameters for designing the final crystallization procedure and ensures to obtain the best possible intellectual property protection.[4]

Solvent-based techniques are certainly the standardly used methods for a traditional solid form screening due to the diversity of solvents and conditions that can be utilized.[10] Crystallization from solution is a particularly important process, as this is the primary means of purification during synthesis. Crystallization from solution might inherently favour metastable forms according to Ostwald's Rule of Stages. Depending on the crystallization conditions, a metastable phase might nucleate prior to the stable phase, meaning that kinetic factors prevail over thermodynamic factors, as the Ostwald rule of stages dictates. Solvent-mediated solid phase transformation (SMPT, competitive slurry experiment, maturation or aging experiment) is a commonly applied method to determine the relative thermodynamic stability of the solid phases generated during the screening, and to directly obtain thermodynamically stable forms.[11]

Thus the slurry technique can be considered as an extension of solid form screening, which – depending on the compound's characteristics – will result in stable anhydrous and/or solvated forms. These aging experiments rely on the fact that the most stable form of a compound is the least soluble, and thus a saturated solution of metastable form(s) is supersaturated with respect to the most stable phase. Given sufficient time, metastable phases will convert to the most stable form in order to establish thermodynamic equilibrium and relieve supersaturation.[12]

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[9] T. Threlfall, Analysis of organic polymorphs, a review, Analyst, 1995, 120, 2435–2460

[10] P. Augustijns, M. Brewster, Solvent Systems and Their Selection in Pharmaceutics and Biopharmaceutics, Springer, 2007

[11] C.H. Gu,; V. Young, Jr.; D. J. W. Grant, Polymorph screening: influence of solvents on the rate of solvent-mediated polymorphic transformation, J. Pharm. Sci. 2001, 90, 1878-90.

[12] C.H. Gu, V. Young, D.J.W. Grant, Identifying the Stable Polymorph Early in the Drug Discovery–Development Process, Pharm. Sci. 2001, 90, 1878.

Solid-state characterization is one of the most important elements of pharmaceutical development. A deep understanding of the properties of pharmaceutical compounds is essential to alleviate formulation problems in later stages of drug development as the stability of oral dosage forms may depend critically on the physicochemical properties of the selected solid form and on how thoroughly the solid form is characterized.[2]

Crystalline solvates/hydrates can be classified by either structure or stoichiometry. In terms of composition, they can be either stoichiometric (where a definite, but not necessary integer ratio of solvent to molecule exists) or non-stoichiometric (where the ratio of solvent to molecule may, but not necessarily vary continuously over a given range).[2] While the solvent in stoichiometric solvates is an integral part of the crystal structure and is essential for the maintenance of the molecular network, in the case of non-stoichiometric solvates it might be located in certain structural voids or channels and can act mostly as space filler. The desolvation of stoichiometric solvates always leads to a different crystal structure or results in a disordered or amorphous state, while in the case of non-stoichiometric hydrates the structure of the parent hydrate can be retained.[4] The idea of the structural classification scheme is to divide hydrates into classes that are discernible by commonly available analytical techniques.[3] The main advantage of this classification is that it can imply practical consequences on the ability of the solid form to maintain its integrity.

The following three categories of crystalline hydrates are recognized:

1) In *isolated site hydrates* the water molecules are isolated from direct contact with other water molecules by intervening drug molecules.

2) In *channel hydrates* the water molecules form channels through the crystal, where they can interact through weak interactions.

3) In *metal ion-associated hydrates* the water molecules are bound directly to a metal ion.[4]

This classification can be applied both on solvates and hydrates, with the exception of metal-ion coordinated hydrates. However, the behaviour of isostructural solvates is often analogous to metal ion-coordinated hydrates. The major concern with these classes is that they may exhibit considerably high desolvation temperature. There are also cases of so called mixed solvates in which more than one type of solvent is incorporated, usually of roughly comparable polarity.[2]

Crystallization of pharmaceutical active ingredients, particularly those that possess multiple polymorphic forms, is among the most critical pharmaceutical manufacturing processes. Controlling polymorphism is a major issue both for research and for industry, presenting

substantial scientific and economic challenges. Crystallization affects the efficiency of downstream operations such as filtration, drying, or formulation, furthermore the efficacy of the drug may be dependent on the final crystal form. To ensure consistent production of the desired polymorph, better control over the crystallization process is required. Strategies for obtaining the desired phase include seeding, choice of solvent, and crystal engineering.[13]

The key step towards a robust crystallization process is the knowledge of the solid form diversity and a detailed solid-state characterization and polymorphic investigation which provides an overview of the phase transformations, including the relative thermodynamic stability of the phases. Direct design approach can be used to determine and control the design space of the crystallization process. This approach follows a solution concentration trajectory as a function of temperature.[13] Due to the low depth of the IR beam which is about in the order of 1-2 μm,[14] the ATR-FTIR probe can be applied to acquire the spectra of liquid phase even in the presence of solid phase.

Various parameters must be taken into account during designing the seeding strategy, including seed size, seed loading and seeding temperature (supersaturation level). The solubility curve is a thermodynamic property of a given solvent-solute system, but the Metastable Zone Width (MSZW) is a kinetic boundary and can vary depending on process parameters such as cooling rate, agitation or scale.[15] The application of process analytical technology (PAT): FBRM, PVM and ATR-FTIR spectroscopy offer a great potential for process optimization and control.

[13] M. Fujiwara, Z. K. Nagy, J. W. Chew, R. D. Braatz, First-principles and direct design approaches for the control of pharmaceutical crystallization, J. Process Control, 2005, 15(5), 493–504

[14] F. M. Mirabella, Internal Reflection Spectroscopy, Marcel Dekker, Inc., New York, 1993

[15] A. S. Myerson Handbook of industrial crystallization, Butterworth-Heinemann, Boston, USA, 2011

3. MATERIALS AND METHODS

Five model compounds: sitagliptin L-tartrate, bosutinib, axitinib, idelalisib and sofosbuvir were selected for the research to maximize the diversity and the gained knowledge. These compounds exhibit markedly different structure, solid form landscape, indication and BCS classification.

Various analytical techniques were utilised for analytical characterization in an attempt to rationalize the propensity to solvate/hydrate formation and explore the stability boundaries of different forms.

Competitive slurry experiments: HLC thermoshaker (Ditabis, Pforzheim, Germany)

Differential Scanning Calorimetry: Mettler-Toledo 822e DSC (Mettler-Toledo, Greifensee, Switzerland)

Thermogravimetric analysis: NETZSCH TG 209 thermogravimetric analyser (NETZSCH-Gerätebau GmbH, Germany)

Dynamic Vapour Sorption: DVS Advantage 1 (Surface Measurement Systems, U.K.), Cahn D200 recording ultra-microbalance.

Variable Humidity X-ray Powder Diffraction: PANalytical X'Pert Pro diffractometer (X'Pert Pro PANalytical, Netherlands)

Rotating Disk Intrinsic Dissolution Rates: Sirius inForm platform (Sirius Analytical Instr. Ltd., Forest Row, UK)

Structure determination– single crystal: Xcalibur diffractometer, Atlas, Gemini ultra with a mirror-monochromator and a CCD detector

Structure determination from powder data: PANanalytical Empyrean powder diffractometer

Kinetic solubility data: Crystal^{16} crystallization system (Technobis Crystallization Systems, Alkmaar, the Netherlands)

Crystallization: Mettler-Toledo EasyMax workstation (Mettler-Toledo, Greifensee, Switzerland) and Radleys Reactor-Ready Lab Reactor (R.B.Radley Co. Ltd, Saffron Walden, UK)

***In Situ* Characterization Techniques**

Thermo Scientific™ Nicolet™ iS™10 FT-IR spectrometer (Thermo Fisher Scientific Inc., Waltham, MA, USA), FBRM probe: ParticleTrack G400 (Mettler-Toledo, Greifensee, Switzerland), ParticleView V19 probe (Mettler-Toledo, Greifensee, Switzerland).

4. RESULTS

A primary goal of this work was to achieve deeper understanding of solvated/hydrated crystal forms in terms of discovery, characterization and crystallization thereof.

The work presented in this thesis aimed to elaborate an extended screening methodology for exploring physical form diversity with particular focus on solvated/hydrated forms. Competitive slurry experiments were implemented in the conventional screening strategy. The experimental slurry parameters used in the screen were studied and optimized. The application of this extended screening methodology showed improved applicability, and led to the discovery of numerous (solvated) solid forms, manifested in two utility models.[U1,U2]

A screening strategy should take into consideration the solubility of the compound. In general, it is not practical to use solvents in which the solubility of the compound is so high that it would inhibit crystallization and provide amorphous, viscous outcomes. On the other hand, poor solubility may impede crystallization from solution and restrain the application of diverse crystallization conditions. Therefore, in order to save time and resources, a screening strategy was proposed (**Figure 1**) which takes into account the solubility of the substance.

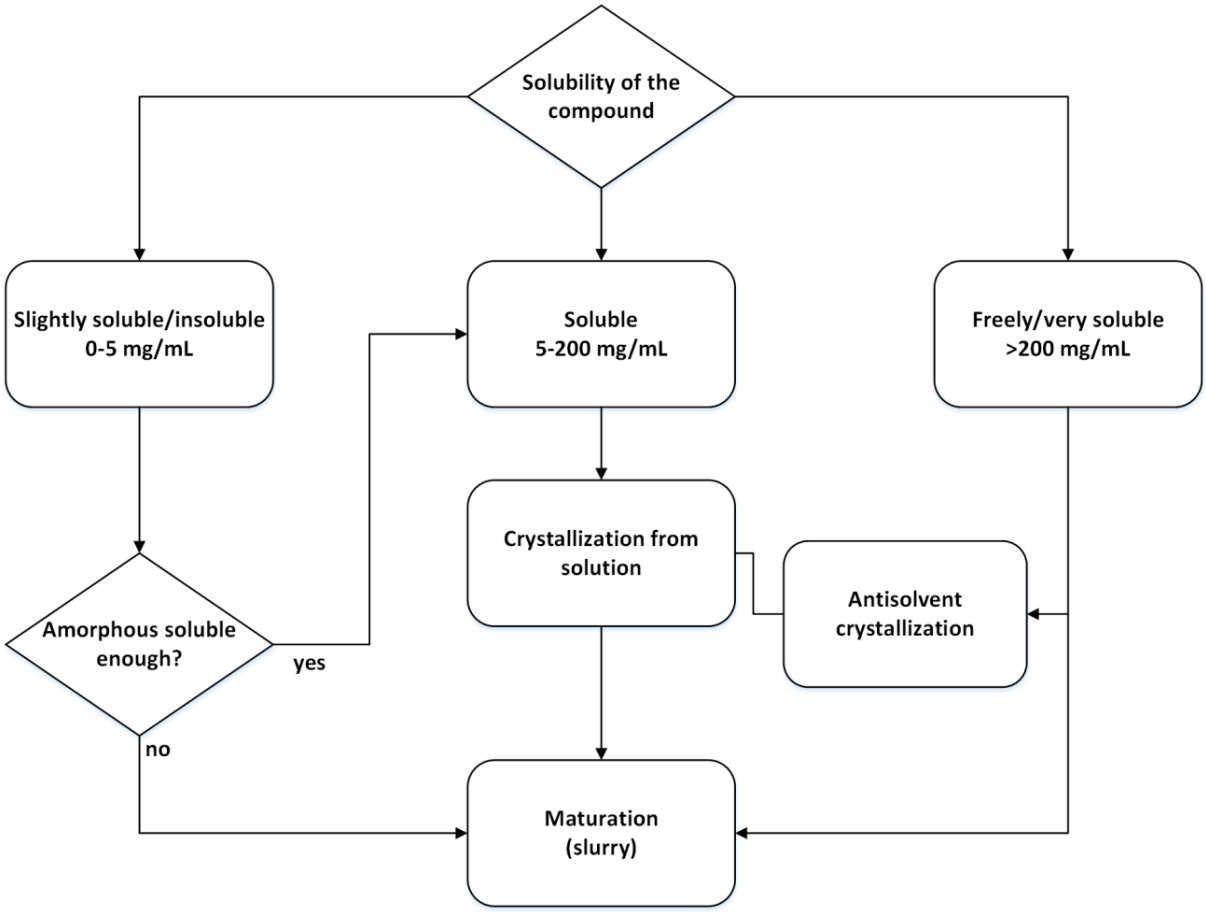

Figure 1 Solid form screening strategy

The range covered by the operating conditions is wider in the case of crystallization from solution than in slurry, thus these techniques should be viewed as complementary approaches, which enable to explore the entire solid form landscape and gain invaluable information about the behaviour of the compound of interest.

The reliability of solvent-mediated polymorphic transformation for generating stable forms (anhydrate/hydrate/solvate) is not without limitations. The presence of impurities, even in trace amounts, may inhibit nucleation of certain phases.[11] Lack of adequate solubility or inhibition of nucleation due to solvent-solute interactions, may also preclude transformation to the stable form.[A3] By the application of amorphous starting material, diverse set of solvents and temperature cycles to facilitate the dissolution-recrystallization mechanism leading to the stable form, one can significantly mitigate the risk of overlooking a relevant solid form.

Following the discovery of solid forms, a comprehensive characterization is required. Different model compounds with diverse properties and solid form landscape were investigated by various

analytical techniques including thermal analysis, dynamic vapour sorption, critical water activity investigation, stability testing, intrinsic dissolution rate measurement, variable humidity powder X-ray diffraction and single crystal X-ray diffraction to rationalize the propensity to solvate/hydrate formation and to assess their stability and pharmaceutical applicability with regard to the solvate classification.[A1,A2] The applied diverse set of analytical investigations provided considerable insight into the structure of the model compounds and contributed to the understanding of the structure-property relationships. Since the stability of a solvated form is governed by the role played by solvent molecules in the crystal structure, understanding the underlying factors affecting solvate formation and the thermodynamic and kinetic factors that dictate the stability of a solvated phase is essential in drug development to mitigate the risk of unexpected phase transformations and rationalize form selection.

The number and disposition of the hydrogen bond donors and acceptors in the structure of bosutinib do not enable strong hydrogen bonding in the solvent free structure. The stabilization effect of the solvents cannot be ascribed to decrease the void space in the structures, as the anhydrate is closely packed. The solvent molecules are utilised to satisfy the previously unused hydrogen bonding capabilities in the host molecule. The solvent selectivity of bosutinib is based on the solvents' functionality to provide strong intermolecular interactions.[A2] Multipoint hydrogen bonding is clearly a dominant factor that governs the inclusion of specific solvent molecules.

Numerous solvated forms were investigated by various analytical methods including thermal analysis, calculated binding energy, intrinsic dissolution rate, packing efficiency, critical solvent activity, physical stability under stress conditions and single crystal X-ray diffraction in order to assess their stability and behaviour.[A2] It was demonstrated that solvate stability is a really complex phenomenon, and the combination of various analytical techniques is required in order to select a suitable solid form. It was shown that analogous structure does not necessarily infer analogous stability and that even a kinetically preferred form can act as suitable candidate. Unambiguously, hydrates possess higher physical stability, compared to solvates, but mixed solvates might offer a rational compromise between physical stability and dissolution rate enhancement.[A2]

As opposed to bosutinib, axitinib displays indiscriminative solvate formation. The API forms a diverse set of solvated crystal structures, arising from the conformational flexibility of the molecule, including numerous isostructural solvates. Isomorphic solvate formation is driven by

the presence of specific solvent–host interactions. In the cases presented, the role of the solvent is to fill regular cavities in the lattice, resulting in multicomponent structures with extraordinary thermal stability.

A diverse set of analytical investigations provided considerable insight into the structure of the sitagliptin L-tartrate hydrates. The tunnel-like structure together with the ionic character provides optimal conditions for hydrate formation. The high affinity of water to the API framework is demonstrated by the fixed API/water ratio at ambient conditions and by the nearly vertical vapour sorption isotherm at low RH levels. The crystal structures showed that water molecules stabilize the crystal lattices by providing additional interactions between sitagliptinium cations and hydrogen tartrate anions.[A1] On the other hand, their non-stoichiometric character is evidenced by the VH-XRPD results and the superimposable sorption/desorption curves. The existence of isostructural dehydrates and the non-destructive process of the dehydration is an unambiguous proof of the non-stoichiometric nature of the studied hydrates of sitagliptin L-tartrate.[A1]

Once a solid form has been selected, a crystallization method is required to produce the desired form in a consistent and reproducible manner. In order to ensure robust crystallization of the selected candidate, it is essential to adopt process analytical techniques and to exploit the gathered analytical information and knowledge of transformation pathways between various forms. A systematic procedure was applied for identifying the operating conditions for a seeded, cooling crystallization process of sitagliptin L-tartrate Phase 1.[A3] This involved the determination of the solubility curve and metastable limit by a turbidity sensor and using the metastable zone as a guide, crystallization experiments with varying seeding protocols were conducted and monitored. FTIR calibration was established which allowed concentration monitoring of the API in the crystallization media (**Figure 2**).

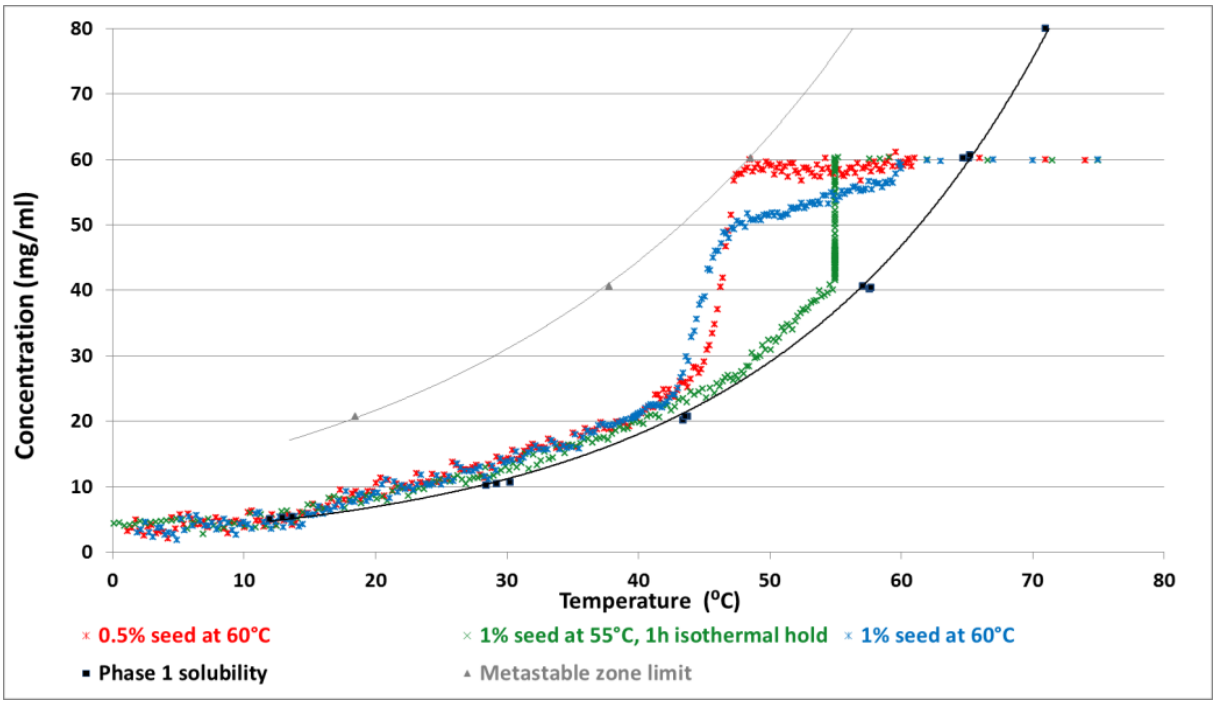

Figure 2 Solubility curve for SLT Phase 1 in 2-propanol-water 8-2 V/V mixture with overlaid concentration profiles

The evolution of the chord length distribution was monitored by FBRM probe, while the particle size and shape was followed by ParticleView V19 probe. A cooling, seeded crystallization process was developed which reproducibly provides the selected polymorph with 15% higher filtration rate.[A3]

The goal of the thesis work presented here was to provide an overview of the underlying factors that influence the screening, solid-state properties and stability of solvated/hydrated compounds and to highlight the complexity of solid state development. A deep understanding of the crystal form landscape, physicochemical properties, crystallization process parameters and their influence on the following unit operations contributes to a comprehensive overview of solid state development and facilitates pieces of the drug development puzzle falling into place.

5. THESES

1. An extended solid form screening methodology was elaborated aiming to explore the entire solid form landscape of an API, with particular focus on solvated forms. Crystallization from solution, the main technique used in conventional solid form screening was complemented by slurry (maturation) experiments in order to increase the hit rate of the screening. The experimental slurry parameters were investigated and optimized. A screening strategy, a decision tree was proposed, which takes into account the solubility of the API. The application of this extended screening methodology showed improved applicability, and led to the discovery of more solid forms, manifested in two utility models.[U1,U2]
2. I rationalized Bosutinib's high propensity to solvate formation. The number and disposition of the hydrogen bond donors and acceptors do not enable strong hydrogen bonding in the solvent free structure. The stabilization effect of the solvents cannot be ascribed to decrease the void space in the structures, the solvents are utilised to satisfy the previously unused hydrogen bonding capabilities in the host molecule. Discriminative solvate formation is clearly governed by multipoint hydrogen bonding established by the solvent molecules.[A2]
3. It was revealed by means of thermal analysis, calculated binding energy, intrinsic dissolution rate, packing efficiency, critical solvent activity and physical stability testing that analogous structure does not necessarily infer analogous stability, furthermore the main differences between stoichiometric and non-stoichiometric solvation and between individual solvate classes were highlighted. Unambiguously, hydrates possess higher physical stability compared to solvates, but it was revealed that mixed solvates might offer a rational compromise between physical stability and dissolution rate enhancement.[A2]
4. I elucidated that sitagliptin L-tartrate hydrates are by definition non-stoichiometric hydrates. Despite their fixed water content and high affinity to water, the existence of isostructural dehydrates and the non-destructive process of the dehydration is an unambiguous proof of their non-stoichiometric nature. Non-stoichiometric hydration is generally undesirable in the pharmaceutical industry, but I have demonstrated that in exceptional cases, non-stoichiometric hydrates can also act as suitable candidates for further development.[A1]
5. A systematic procedure and process analytical techniques (FBRM, PVM and ATR-FTIR probes) were applied for identifying the operating conditions for a seeded, cooling crystallization process of sitagliptin L-tartrate Phase 1, which reproducibly provides the selected polymorph with 15% higher filtration rate than the original, not optimized process.[A3]

6. POSSIBLE APPLICATIONS

The results of the present study have various practical implications, as it aimed to find solutions for real life problems in pharmaceutical development. Consequently, the findings have been already utilized in daily practice.

The comprehensive screening methodology developed is routinely used in screening strategies. As every compound exhibit diverse properties, there is no universal guideline how to conduct a solid form screening and one can never be confident that all relevant forms have been identified. The proposed decision tree and the application of slurry experiments are addressing the challenges associated with the diverse solubility of different APIs.

Understanding the underlying factors affecting solvate formation and the thermodynamic and kinetic factors that dictate the stability of a solvated phase is crucial in drug development. Non-stoichiometric hydration is generally undesirable in the pharmaceutical industry, but the term non-stoichiometric hydrate does not necessarily reflect continuously changing water content. I have demonstrated that in exceptional cases, however the hydrates are classified as non-stoichiometric hydrates, still they can act as suitable candidates for further development.

The research assessed the structure-property relationships of various solvated compounds with regard to the solvate classification. The results presented in this work contribute to the overall understanding of these multicomponent systems and facilitate solid form selection.

The systematic procedure applied for identifying the operating conditions for a seeded, cooling crystallization process may serve as a basis for the method development of other solid forms.

7. PUBLICATIONS

Publications that form the basis of this PhD thesis.

(The offprints of these publications are attached at the end of the thesis.)

Registered utility models:

U1. J. Richter, K. Jarrach, V. Kiss, E. Tieger, J. Havlícek, O. Dammer, Crystalline modification 2 of (3r)-3-amino-l-[3-(trifluoromethyl)-6,8-dihydro-5h- [l1,2,4]triazolol[4,3-]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one l-tartrate, CZ27898 (U1), 13.01.2015, International Application No.: PCT/CZ2016/000001

U2. J. Richter, K. Jarrach, V. Kiss, E. Tieger, J. Havlícek, O. Dammer, Crystalline modification 3 of (3r)-3-amino-l-[3-(trifluoromethyl)-6,8-dihydro-5h- [l1,2,4]triazolol[4,3-]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one l-tartrate, CZ27930 (U1), 13.01.2015, International Application No.: PCT/CZ2016/000002

Scientific articles:

A1. E. Tieger, V. Kiss, Gy. Pokol, Z. Finta, M. Dušek, J. Rohlíček, E. Skořepová, P. Brázda, Studies on the crystal structure and arrangement of water in sitagliptin L-tartrate hydrates *CrystEngComm,* **2016**, 18, 3819-3831. [IF: 3,849 (2015), I.:4 (3 independent)]

A2. E. Tieger, V. Kiss, Gy. Pokol, Z. Finta, J. Rohlíček, E. Skořepová, M. Dušek, Rationalization of the formation and stability of bosutinib solvated forms, *CrystEngComm,* **2016**,18, 9260-9274. [IF: 3,849 (2015), I.:2 (independent)]

A3. E. Tieger, V. Kiss, Gy. Pokol, Z. Finta, Crystallization of a salt hydrate with a complex solid form landscape, *CrystEngComm,* **2017**, 19, 1912-1925, [IF: 3,849 (2015)]

Poster presentation (in English):

1. E. Tieger, V. Kiss, Gy. Pokol, Z. Finta, M. Dušek, J. Rohlíček, E. Skořepová, Studies on the crystal structure and arrangement of water in sitagliptin L-tartrate hydrates, Summer School on Crystal Shape Engineering- ETH Zurich, Zurich, Switzerland, July 6-10, 2015.

Oral presentation (in English):

1. E. Tieger, V. Kiss, Gy. Pokol, Z. Finta, Pharmaceutical hydrates and solvates, XIIIth Conference of George Oláh PhD School, Budapest, February 11, 2016.