Doctoral (PhD) Thesis

Anti-Tuberculosis Multi-Drug Cocrystals and Nano-Sized Cocrystals: Formation Prediction, Polymorph Control and Pharmaceutical Advantages

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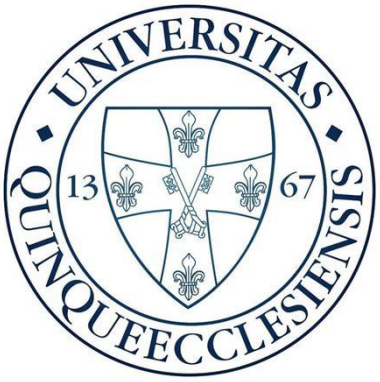

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1. Introduction

1.1. Active pharmaceutical ingredient solid forms

Active pharmaceutical ingredients (APIs) are mostly solid in nature and could exist in many forms varying significantly in their properties. This leads to different biopharmaceutical, chemical, physical and mechanical properties [1]. Solid pharmaceuticals are classified as amorphous and stable crystalline forms [2]. The crystal structure assumed by a molecule affects numerous solid state properties, greatly affecting its use. This represents both a challenge and an opportunity, as the ability to formulate new forms of crystal, like salts or cocrystals, with enhanced properties is highly desired [3]. Discovering new crystal multicomponent forms of available medications is important, since they signify a straightforward path to considerably impact the solid-state drug properties [4] and the delivery of an efficacious, safe and cost-effective drug to the patient largely depends on the physicochemical properties [5].

1.2. Pharmaceutical Cocrystals

Pharmaceutical cocrystals have been used to enhance the physical and chemical properties of APIs. The bioavailability, solubility, dissolution rate, physical stability [6, 7] and hygroscopicity [6, 8] can be modified by cocrystallization.

Cocrystals are crystalline entities formed by weak intermolecular interactions between an API and a pharmaceutically acceptable co-former molecule in stoichiometric ratio. Cocrystallization has been successfully used to improve API properties, without necessitating the existence of drug ionisable groups [9]. Generally, the accepted current definition of cocrystals is “single phase crystalline solids composed of more than one molecule in a stoichiometric ratio that are neither simple salts nor solvates” [10].

A suitable molecule that forms a cocrystal with an API is termed a co-former. Selection of a co-former is done on bases of safety and pharmacological inertness [11]. The proper co-former selection aids in the effective and efficient development of a pharmaceutical cocrystal of the desired pharmacokinetic and physicochemical properties [12]. Co-formers are pharmaceutically acceptable molecules. Nonetheless, a co-former can also be an API (drug-drug cocrystal) [13].

In an aim to develop fixed dose combination (FDC) [14], pharmaceutical drug-drug cocrystals, offers a convenient approach when a specific disease is treated by a combination of APIs [15]. Therefore, a main aim of formulating drug-drug cocrystals is not only to modulate the API physicochemical properties, but the possibility of producing a combined medication as well, resulting in a reduced pill burden and minimizing medication errors [16].

Drug-drug cocrystals are more challenging to rationally design compared to pharmaceutical cocrystals, because the APIs are chosen on the basis of therapy rather than with specific strategies of crystal engineering. Crystal engineering offers useful insights into drug-drug cocrystals design by supramolecular synthon investigations [15].

1.2.1. Nano-cocrystals

Aiming for API dissolution rate improvement, grinding or milling is performed typically to reduce the particle size [17]. Nano-sized crystals have gained substantial attention in medicine, mainly because of their exceptional physicochemical properties like high surface area and low density [18]. Generally, nano-crystals adjust the pharmacokinetic properties, also enhance penetration and distribution. With the rapid development of cocrystal and nano-crystal technology, nano-cocrystals, that are multi-component nano-sized crystals, seem to enhance API properties via combining the benefits of both nano- and cocrystals. Unfortunately, nano-cocrystals have been reported in a limited number of publications related to the pharmaceutical formulation, perhaps due to their complex preparation techniques. Despite the promising opportunities of nano-sized cocrystals, however the research at the interface of nano-technology and cocrystals has been described to be at its infancy [19, 20].

1.2.2. Cocrystal polymorphism

Polymorphic forms refer to distinct crystal structures of the same chemical compound. However, polymorphism can vastly affect API properties, like melting point, stability, solubility, hygroscopicity and bioavailability. Therefore, investigating API polymorphic behavior is a critical part in drug development [21, 22]. Nonetheless, the number of reported polymorphic cocrystals is limited, despite polymorphism of crystalline APIs being a common phenomenon [23].

Polymorph formation prediction and control is regarded among the greatest challenges in physical chemistry [24]. The control of polymorph nucleation is considered among the most primary approaches in obtaining a desired crystal form. A widely utilized method to

control polymorph nucleation, in solution crystallization, is through the use of different solvents [25].

1.3. Cocrystal preparation

Cocrystals can be prepared by many techniques. These methods have been classified as either solid-state cocrystal formation [26] or liquid-assisted cocrystallization including solvent evaporation (SE) and ultrasound crystallization [27] and high-pressure homogenization (HPH) [28]. Ultrasound assisted cocrystallization is an advantageous novel method in screening cocrystals [29]. HPH is a widely employed top down technology [28].

Many parameters influence liquid-assisted or solution crystallization, including supersaturation and the solvent choice. Appropriate solvent selection can aid cocrystal design [30]. Organic liquids are characterized by physical and chemical properties such as polarity and ability to form hydrogen bonds. The hydrogen bond donation (HBD) ability is termed α, while β is its hydrogen bond acceptance (HBA) or electron pair donation ability. The polarity/polarizability parameter is given the term π^* [31]. These solvent properties can be estimated using the Hansen solubility parameters (HSPs).

1.3. Hansen solubility parameters

HSPs is an approach where the liquids total cohesion energy is split into contributions from atomic dispersion (δ_d), dipole-dipole/polar interactions (δ_p) and hydrogen bonding (δ_h). The δ_h contribution in the HSPs is divided into hydrogen-bond donor (δ_{hDon}) and acceptor (δ_{hAcc}) values. For a given liquid pair, the closer are the HSP values in the three dimensional HSP space, the greater is their similarity, and consequently their affinity is stronger [32].

As cocrystals can form by eutectic melt, miscibility as a concept has been considered in a similar sense as cocrystal formation prediction tool by Mohammad et al. in 2011 [32]. HSPs were used to successfully predict and guide cocrystal formation and screening of indomethacin with different co-formers. However the criterion used for this prediction according to Greenhalgh et al. that "$\Delta\delta_t$ value of less than 7 $MP_a^{0.5}$ is predictive of miscibility", might not be accurately used with HSPs as it was devised for Hildebrand

solubility parameter rather than the HSP [33] (**Figure 1**). One advantage of HSPs is that it is a simple theoretical approach, requiring knowledge of a molecules chemical structure only [34].

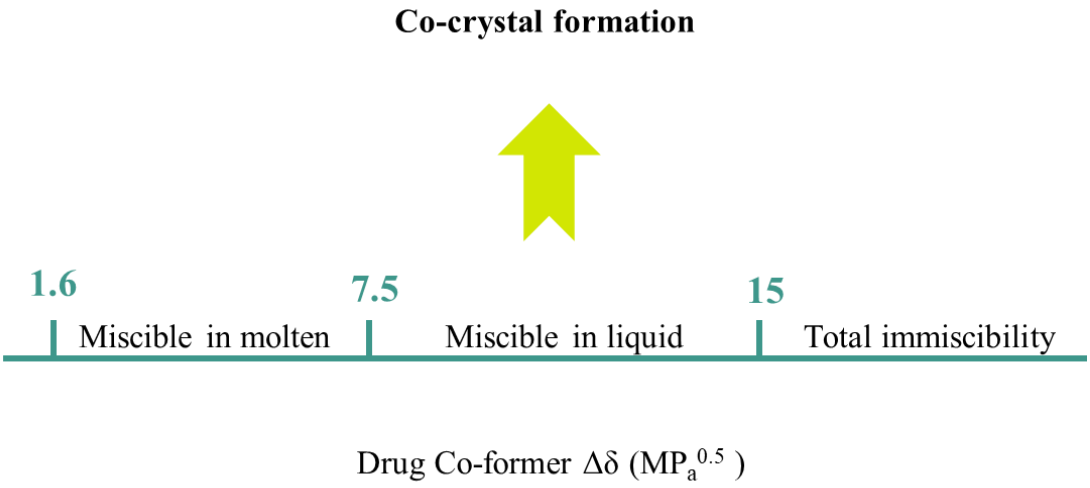


Figure 1 HSP value interpretations in cocrystal formation prediction

1.4. Tuberculosis

Cocrystals can offer many opportunities for enhancing the stability of tuberculosis (TB) FDCs. TB, the infectious disease usually caused by *Mycobacterium tuberculosis* [35], remains a main cause of mortality globally [36]. The treatment of TB necessitates the use of multiple medications for long periods of time. The standard regimen consists of isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA) and ethambutol (EDH) for two months followed by INH and RIF for four additional months [37]. However, control of multidrug-resistant TB (MDR-TB) is failing [38, 39] and treatment outcomes remain poor [40], while treatment has advanced very little [35]. Prevention through vaccination with the only available vaccine, Bacillus Calmette-Guérin (BCG), can decrease the risk of infection by 20% in vaccinated children and decreased the risk of turning the infection into active by 60% [41].

Patients failing multiple first-line TB medications, have to use expensive second-line TB drugs, these include aminoglycosides, polypeptides, fluoroquinolones, cycloserine, and 4-aminosalicyclic acid (4-ASA) [42]. Many of these antibiotics have been developed decades ago and suffer from toxic side-effects, administration difficulty and poor activity against *Mycobacterium tuberculosis* [35]. It is recommended to manage MDR-TB with at least four

effective antibiotics for 18 to 24 months [37, 43]. Meanwhile trials are set to find shorter and less debilitating regiments for MDR-TB [40, 44].

Cocrystals have been utilized to enhance classic FDCs of TB antibiotics. INH-caffeine/vanillic acid cocrystals were reported to have greater stability compared to the classical drug combination [45]. Cocrystals of 4-ASA with isonicotinamide have been shown to have improved solubility and stability [46]. Moreover, cocrystals of 4-ASA with INH were reported to be more thermally stable [47]. The combination of 4-ASA and sulfamethazine (SMT) in cocrystals was proposed to exploit an anti-TB synergistic effect [48].

2. Aims

The overreaching thesis aim is to prepare pharmaceutically advantageous cocrystals of anti-tuberculosis medications.

First, Hansen solubility parameters as theoretical cocrystal formation prediction tool:
Aims to validate the use of HSPs as cocrystal formation prediction tool and establish calculated molecular descriptors cut-off values for co-former selection.

Second, solvent dependent cocrystal polymorph control:
Aims to identify key solvent parameters that play a role in cocrystal polymorph generation, through the preparation of different 4-aminosalicylic acid-sulfamethazine cocrystal polymorphic forms, the study aims to control cocrystal polymorph generation by solvent selection.

Third, nano-sized cocrystals of 4-aminosalicylic acid-sulfamethazine:
Aims to prepare and characterize nano-sized cocrystals. Examine the benefits from combining the technologies of nano-sizing and cocrystallization on solubility enhancement. Compare high-pressure homogenization and high-power ultrasound and the effect of preparation conditions on the generated cocrystals.

Finally, anti-tuberculosis cocrystals:
Aims to prepare a stable FDCs with two cocrystals of the four first-line anti-TB medications, evaluate the physicochemical advantages brought about to the fixed dose combination dosage form by cocrystals.

3. Experimental methods and results

3.1. Hansen solubility parameters as cocrystal formation prediction tool

HSPs in theoretical cocrystal screening, once validated using a scope of APIs and co-formers, can be a promising method to confirm miscibility as cocrystallization prerequisite. Cut-off values reassessment and refinement is needed before this method can become routine in screening of pharmaceutical cocrystals. The aim of this study was to evaluate the reliability of HSPs in formation prediction of published cocrystals of different APIs, compare different calculation methods in solubility differences, and finally identify the limitations of using HSPs in cocrystal screening. The established cut-off values were refined using a set of test co-formers to accurately predict the formation of cocrystals. Furthermore, cocrystals were compared to eutectics to establish the possibility of HSPs to differentiate between these closely related pharmaceutical forms.

3.1.1. Methods

109 reported co-formers of carbamazepine, theophylline and caffeine were used as a training set to evaluate HPS cocrystal formation prediction. HSP values were calculated using Hansen Solubility Parameters in Practice (HSPiP) software version 5.0.11. Sixteen descriptors were calculated. Statistical analysis was performed to conclude the effectiveness and cut-off values of the different calculation approaches. The parameters' ability to predict the formation of cocrystals was described in terms of statistical measures of performance; specificity, sensitivity, fall-out and miss rates, precision and accuracy. Lastly, forty-four published co-formers of piroxicam and twenty seven co-formers of nicotinamide were used as a test set to evaluate the cut-off values and compare the different approaches.

3.1.2. Results and discussion

HSPs as a tool for pharmaceutical cocrystal formation predict was evaluated. Co-formers of three APIs were used and the results were tested using two other APIs co-formers. The previous cut-off value of $\Delta\delta$ ($7MP_a^{0.5}$) has been validated, as the cut-off value found ($8.18MP_a^{0.5}$) was not statistically difference in terms of specificity and sensitivity. Using data of 16 calculated descriptors, the use of $\Delta\delta_t$ and Ra with cut of values of 16.87 and $17.64MP_a^{0.5}$, respectively, was suggested. A simple yet efficient selection of plausible co-formers was obtained with 73.8-85% efficiency for the test set with these approaches.

Nevertheless, this method may exclude plausible co-formers that were predicted as immiscible. These, however, did form cocrystals with the API. The miss rate was found to be 13.64% using $\Delta\delta$. However, $\Delta\delta_t$, had a lower miss rate (9.09%) and even lower using Ra (0%) for test group co-formers (**Figure 2**). This may limit the use of HSP in cocrystal formation prediction, yet it may be useful for screening large numbers of co-formers. The statistical data quality is influenced by insufficient number of experiments, particularly the limited reports on failed cocrystallization. The quality of the results was further influenced by the nature of reported experiments, as co-former selection is done on chemical intuitive or synthon basis.

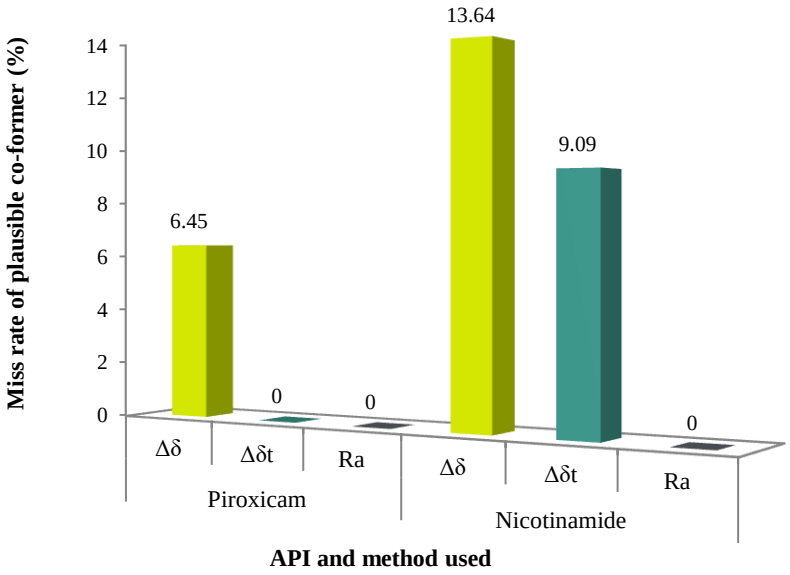


Figure 2 Percent miss rate for each of the methods

3.2. Solvent dependent cocrystal polymorph control

Multi-drug cocrystals represent a convenient approach when a specific disease is treated by a combination of APIs, such as tuberculosis [49]. There have been two reported polymorphic forms of 4-ASA-SMT cocrystals. These cocrystal forms, prepared by different methods, were found to have different thermodynamic stabilities, where form I was found to be thermodynamically more stable than form II in aqueous solution [48]. However, no further details were published on selective polymorph cocrystallization of this cocrystal pair to the best of our knowledge, and an attempt to control the generated cocrystal polymorph using solvent parameters has never been reported.

This study aims to study the effect of different solvents on the production of cocrystal polymorphs of the two APIs by fast solvent evaporation. For this aim, HSPs were calculated to select solvents based on hydrogen bonding (δ_h) contributions, as this is the most relevant cocrystal forming parameter. Further, we have attempted to explain the effect of solvents in terms of hydrogen bonding and polarity. The principal hypothesis of this investigation is that systematic variation in HSPs between the solvent and cocrystal constituents will affect the cocrystallization process and influence the formation of different cocrystal polymorphic forms, given that this difference is within the limit which permits the formation of cocrystals. As APIs crystallization by solvent evaporation is influenced by saturation [50], knowledge of solubility by HSPs could therefore aid in cocrystal design.

3.2.1. Methods

Eight different solvents were selected based on δ_h HSPs, having low boiling points and being non-toxic. The cocrystals were prepared by fast solvent evaporation; briefly 4-ASA and SMT in 1:1 molar ratio were dissolved in 60 ml of the solvents. After complete dissolution, solutions were transferred into a round-bottom flask and attached to a rotatory evaporator with a vacuum pump at 90rpm rotation speed. Solvent evaporation was carried out at 55 and 23°C (room temperature). Finally, a 1:1 molar ratio physical mixture was prepared by mixing the APIs manually using a mortar and pestle, avoiding excessive grinding as to reduce the risk of phase change.

Solid state characterization was carried by powder X-ray diffraction, differential scanning calorimetry, Fourier-transform infrared spectroscopy and Micro Raman spectroscopy (μRaman), Scanning electron microscopy images were taken and finally long term stability of the cocrystals was evaluated.

3.2.2. Results and discussion

The influence of systematic solvent variation based on HSPs on the cocrystallization process, as an initial hypothesis, has resulted in a new 4-ASA-SMT cocrystal polymorph. The main roles of the solvent in solvation of a solute molecules and desolvation are the fundamental steps in solution crystallization. HSPs derived descriptors like Ra, δ_d, δ_p, δ_h, δ_{hDon}, δ_{hAcc}, obtained by simple calculations, can offer insight into the nature and strength of the interactions between a solvent and a solute molecules. This can directly influence the process

of crystallization and therefore, the crystal structure produced. Hydrogen bond acceptance ability (δ_{hAcc}), of a solvent, seemed to influence polymorph generation more than hydrogen bond donation ability. The solvents with higher δ_{hAcc} were found to influence the acidic properties of 4-ASA, which may have induced the SMT amidine-imidine tautomeric transformation. Structural examination of the new form by Raman spectroscopy showed changes in the vibrational bands ratio assigned to C=N and C=C in the SMT pyrimidine ring. This supported the assumption that SMT tautomerisation have occurred. However, further structural examinations of the new polymorphic form have to be conducted to confirm this assumption. More studies are needed to assess the effect and extent of the different solvent parameters on forms generation in association with thermodynamic parameters of the generated polymorphs. The results suggest that solvent selection based on HSPs can be an effective tool in polymorph screening and can play a significant role in cocrystal polymorph generation.

3.3. Nano-sized cocrystals of 4-aminosalicyclic acid-sulfamethazine

Nano-sized cocrystals present promising opportunities, however, research at the interface of cocrystals and nano-technology was described to be “at its infancy” [19, 20]. Nano-cocrystals seem to enhance API properties by combining benefits of both nano-crystals and cocrystals [51]. A “synergistic effect” was achieved when cocrystallization and nano-technology were combined. Furosemide-caffeine nano-cocrystals have been reported to have a dissolved concentration that was more than three times that of the furosemide nanocrystals. The nano-cocrystals had a higher dissolution rate than the unmilled cocrystals [52]. Likewise, baicalein-nicotinamide nano-cocrystals showed enhancement in dissolution compared to cocrystals and baicalein nanocrystals [53]. Phenazopyridine-phthalimide nano-cocrystal have significantly enhanced the release rate of phenazopyridine [18]. By knowing the benefits of these strategies, their use can further enhance fixed-dose combinations, as the number of suitable co-formers and the field of their properties enhancement is limited. Application of both techniques can be used for further enhance the dissolution rate of poorly water-soluble APIs when one strategy does not provide adequate enhancement [54]. The potential for nano-cocrystals, after production challenges are overcome, includes prolonged and localized drug delivery when incorporated into complex delivery systems [20]. The aim of this study is to prepare and characterize nano-sized multi-drug cocrystals. Moreover, to establish the effect

of homogenization and high power ultrasound parameters on the size distribution, degree of crystallinity and polymorphic cocrystals form prepared. To examine the effect of method parameters, different HPH pressures and cycles were used. On the other hand, cocrystallization by high power ultrasound was conducted with different process times and amplitudes.

3.3.1. Methods

A 2% w/w water suspension containing 1:1 molar ratio of 4-ASA and SMT was prepared with 0.4% polyvinyl alcohol as a stabilizer. The suspension was then homogenized with lab scale high shear dispersing emulsifier for 10 mins at 17500 rpm. The water-based suspension at room temperature was consequently passed through the HPH using three different pressures (300, 600 and 900 bar) and homogenization cycle numbers (c) (1, 3 and 5). The sane suspension was used to prepare the cocrystals by high power ultrasound, using 50, 70 and 90% of 20 kHz amplitude for 10 mins, while the 70% amplitude was further used for 20 and 30 mins. Pulses were set at 5 sec with a one second separation gap. Filtered samples from both methods were then allowed to air dry before moving to a desecrator to further dry, at room temperature, before further analysis. While a non-micronized control of the cocrystals was prepared by fast solvent evaporation using ethanol as a solvent.

Samples were characterized by transmission electron microscopy, powder X-ray diffraction and differential scanning calorimetry. While particle size determination was conducted using dynamic light scattering and image analysis of the transmission electron microscopy. Finally the dissolution of SMT from the different samples was studied.

3.3.2. Results and discussion

Nano-sized 4-ASA and SMT cocrystals were prepared by HPH. On the other hand, high-power ultrasound resulted in micro-sized cocrystals. Regarding process parameters, five HPH cycles at 900 bar resulted in smaller sized cocrystals with narrow size distribution. However, high-power ultrasound produced wide particle size distribution cocrystals. The cocrystal morphology was affected by the preparation method, as those prepared by high-power ultrasound were of various habits and morphologies, contrary to the needle shaped cocrystals observed by TEM when prepared by HPH. Cocrystals prepared by both methods were of the stable polymorph I, Triclinic, P-1. Furthermore, the nano-sized cocrystals prepared by HPH

significantly improved the dissolution rate of SMT compared to the micro-sized cocrystals and even more compared to the pure API (**Figure 3**). The nano cocrystals were stable for 6 months without change in size distribution.

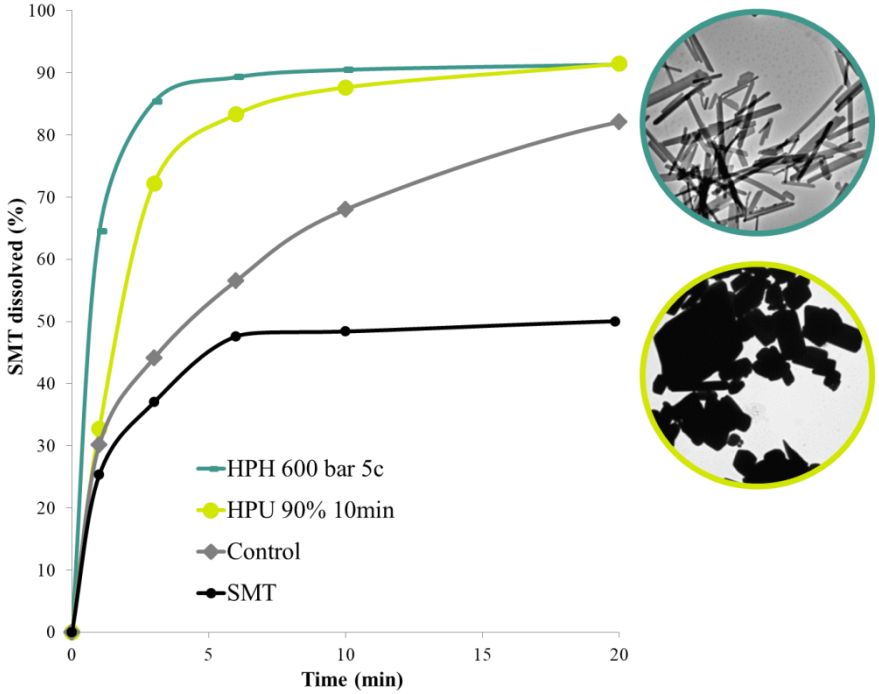
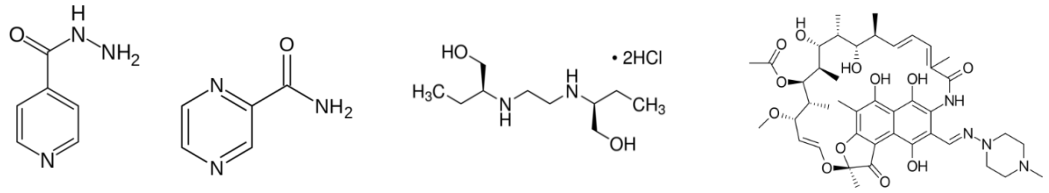


Figure 3 TEM images of the cocrystals and dissolution profiles

3.4. Anti-tuberculosis drug cocrystals

The treatment of TB necessitates the use of multiple medications for long periods of time. The standard regimen consists of isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA) and ethambutol dihydrochloride (EDH) (**Figure 4**) for two months followed by INH and RIF for four additional months [37]. However, control of multidrug-resistant TB (MDR-TB) is failing [38, 39] and treatment outcomes remain poor [40], while treatment has advanced very little [35]. Fixed dose combinations (FDCs) are recommended over the use of single drug tablets to enhance patience compliance, manage drug supply as well as prevent MDR-TB [55]. The aim of this study is to formulate anti-TB cocrystals that have advanced pharmaceutical properties that can minimize drug-drug interactions and represent optimized FDC formulations.



INH PZA EDH RIF

Figure 4 First line anti-TB medication
(**INH**) Isoniazid; (**PZA**) Pyrazinamide; (**EDH**) Ethambutol dihydrochloride; (**RIF**) Rifampicin

3.4.1. Methods

HSPs were calculated to screen the potential cocrystal formation of the APIs and select appropriate solvents. INH-PZA cocrystals were prepared by fast solvent evaporation in acetone at rotation speed of 90rpm and 45±1°C. EDH-RIF cocrystals were prepared similarly in acetonitrile. A physical mixture, FDC and other samples were also prepared to allow comparison.

Samples were analysed by scanning electron microscopy, powder X-ray diffraction, differential scanning calorimetry - thermogravimetric analysis, Fourier-transform infrared spectroscopy and high-performance liquid chromatography. Rifampicin dissolution studies were conducted and accelerated stability studies were used to establish the effect of cocrystals on anti-TB FDC.

3.4.2. Results and discussion

The treatment of TB necessitates the use of multiple medications for long periods of time. The standard regimen consists of INH, RIF, PZA and EDH. FDCs are recommended over the use of single drug tablets to enhance patience compliance, manage drug supply as well as prevent MDR-TB. However FDCs of the four ant-TB drugs is unstable and INH degrades. Cocrystals have been reported to decrease the hygroscopicity of APIs. HSPs were used to theoretically screen the APIs and select suitable solvents. The drug-drug cocrystals were paired so that INH-PZA would protect INH from degradation and also to reduce the hygroscopicity of EDH by cocrystallization with RIF (**Figure 5**). FDCs formulated with INH-PZA and RIF-EDH cocrystals had less drug-drug interactions and represented optimized

FDCs that are more stable. These advantages are brought about by reduction of EDH hygroscopicity in the cocrystals and reducing the RIF triggered degradation of INH by cocrystallization. Furthermore, the FDC with cocrystals had comparable RIF dissolution rate to that of the classical FDC.

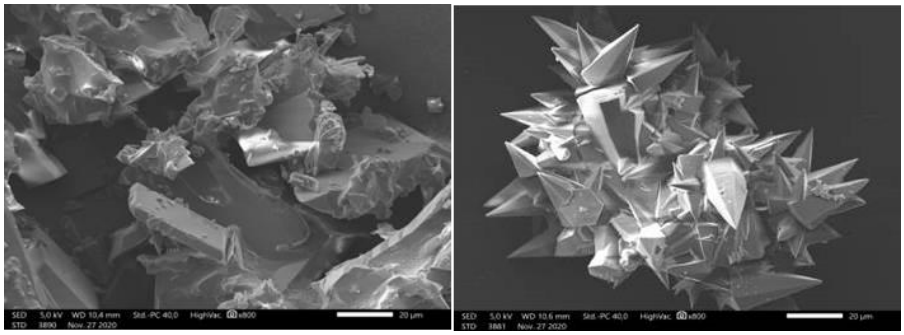


Figure 5 TEM images of (**a**) INH-PZA and (**b**) RIF-EDH cocrystals

4. Conclusions

The importance of pharmaceutical cocrystals in general and drug-drug cocrystals in particular has gained increasing interest in many fields. Multi-drug cocrystals are used to enhancing physicochemical API properties and also as drug combination formulation possibility. It is more evident that collaborative multi-disciplinary research is crucial for the development and design of novel and clinically superior drug formulations. Spanning from crystal structure engineering and design, passing through screening processes, including cocrystal structure and formation prediction and scale up characterization. Further studies are required in this growing field to formulate drug-drug cocrystals of enhanced pharmaceutical properties with less time and cost consuming processes.

Collectively, the results presented in this thesis aid in rational pharmaceutical cocrystal generation. First, the use of HSPs as an effective tool in screening plausible co-formers has been validated. The new cut-off values obtained were used further in solvent selection and cocrystal polymorph control. Furthermore, Nano-sized cocrystals of 4-ASA-SMT were produced and the effect of process parameters was reported. The properties of the nano-sized cocrystals in terms of size, morphology, polymorphic form and dissolution were also described. Finally, the results obtained from the preliminary studies were used to guide the preparation of two novel cocrystals of particular usefulness in the management of TB. Pharmaceutical advantages offered by the INH-PZA and EDH-RIF cocrystals were highlighted.

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List of publications and communications related to this thesis

Research papers

1. **Salem A**, Nagy S, Pál Sz, Széchenyi A. Reliability of the Hansen solubility parameters as co-crystal formation prediction tool. *International Journal of Pharmaceutics*, **558** (2019) 319-27 (IF: 4.845)

2. **Salem A**, Hagymási A, Vörös-Horváth B, Šafarik T, Balić T, Szabó T, Gősi F, Nagy S, Pál Sz, Kunsági-Máté S, Széchenyi A, Solvent dependent 4-aminosalicylic acid-sulfamethazine co-crystal polymorph control, *European Journal of Pharmaceutical Sciences*, **156** (2021) 105599 (IF: 3.616)

3. **Salem A**, Takácsi-Nagy A, Nagy S, Hagymási A, Gősi F, Vörös-Horváth B, Balić T, Pál Sz, Széchenyi A, Synthesis and Characterization of Nano-Sized 4-Aminosalicylic Acid-Sulfamethazine Co-crystals, *Pharmaceutics*, **13** (2) (2021) 277 (IF: 4.421)

Oral presentations

1. Multi-drug co-crystal polymorph control by solvent parameters, MedPECS 2019, Pécs-Hungary, 09/11/2019

2. Solvent dependent multi-drug co-crystal polymorph control, 8th BBBB Conference on Pharmaceutical Sciences, İzmir-Turkey, 14-16/10/2019

Poster presentations

1. Nano-sized anti-tuberculosis multi-drug co-crystals, 6th Nano Today Conference, Lisbon-Portugal, 16-20/06/2019

2. Validation of the Hansen Solubility Parameters as Co-Crystal Formation Prediction Tool, 3rd International Symposium on Scientific and Regulatory Advances in Biological and Non – Biological Complex Drugs: A to Z in Bioequivalence, Budapest-Hungry, 12-14/11/2018

Awards

1. JEOL image contest winner for the month of March; “Alien Crystals” SEM image of cocrystals of Ethambutol and Rifampicin, 3/2021

2. Second prize in the II Research Pitches Contest of the CGU; Crystals: the path towards better drugs, 6/2018

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