



## **A Review on Significance of Identifying an Appropriate Solid Form During Drug Discovery and Product Development**

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### **Abstract**

In recent years, solid form screening has become an integral and mandatory part of drug development. Solid form screening typically involves producing and characterizing maximum possible solid forms of a potential drug candidate. Different types of solid forms for future drug product development includes salt screening, co-crystal screening, crystallization process development, polymorph screening as well as amorphous solid dispersion screening. Screening studies of a solid form is a set of carefully designed experiments that requires use of advanced analytical techniques to collect analytical data followed by a thoughtful data analysis. This solid form screening studies guide an important decision-making of lead solid form which is likely to play a vital role during the pharmaceutical product development lifecycle. The selection criteria include pharmaceutically relevant properties, such as therapeutic efficacy and processing characteristics as well as role of physico-chemical properties (i.e. solubility, dissolution rate, hygroscopicity, physical stability and chemical purity) in drug product development. A selected solid form, if thermodynamically unstable, it may undergo solid form changes upon exposure to environmental conditions such as temperature and relative humidity as well as manufacturing stress during the pharmaceutical unit operations. In the present work, fundamentals of solid form screening are discussed, including the experimental screening methodologies as well as characterization and analysis of solid forms. The importance of drug product risk assessment pertaining to the desired solid form are also discussed here.



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### **Introduction**

Identifying a thermodynamically stable and acceptable solid form is an essential part that

follows drug discovery. In past, overall goal of finding appropriate solid form was achieved by selecting low energy crystalline forms such as

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salts and polymorphs.<sup>1-5</sup> However, the discovery of more poorly soluble drugs has obligated the scientists to explore more solid forms which can be used to improve therapeutic efficacy as well as minimal risk during manufacturing of the drug substance as well as the drug product. Co-crystals and amorphous solid dispersions (ASD) have been emphasized upon in past two decades. Hygroscopicity, physicochemical stability and drugability are other important challenges that needs to be overcome using a solid form with desirable properties.

The dispersal of research activities from early stage to marketing approval depends on several factors. However, cost effectiveness and short time frame are limiting factors for the researchers in the early stage research and development to identify a relatively stable solid form.<sup>6</sup> These challenges often require an effective solid form selection strategy which may explore various aspects of the physicochemical properties of a new chemical moiety.<sup>7</sup>

Solid form selection requires a multi-testing process. The screening activities in early stage have become more promising through the availability of automated screening machines, advanced solid-state characterization techniques, and availability of computational approaches.<sup>7</sup> However, the time-sensitivity during early development only allows a limited screening experiments with a complete focus on searching for an appropriate solid form and swift transition to the next stage of pharmacokinetic and pharmacodynamic studies, toxicity studies followed by a preformulation studies.<sup>8</sup> Once the clinical efficacy is established during the later developmental phase, material availability improves due to scale-up of materials as well as availability of other resources. At this stage, a more comprehensive screens have become more promising through the availability of automated screening machines, advanced solid-state characterization techniques, and availability of computational approaches.<sup>9</sup> This exhaustive screening not only allows finding all possible polymorphs, but also provide intellectual property protection and demonstrate readiness of optimal solid form for large scale production through a robust crystallization process.<sup>10-11</sup>

One of the major challenges with newly discovered drugs is their poor solubility. Poorly soluble drug

in early drug development poses may lead to incomplete optimization along with increased timelines.<sup>12-13</sup> Application of an appropriate solid form screening supported with predicted as well as experimental results expands the possibility of identifying a more soluble form with confidence. Solubility of a drug molecule in aqueous conditions mimicking bodily fluids is an important requirement to determine molecule's success with increase bioavailability.<sup>1-3,14</sup> If the solubility of a newly discovered solid form is high then it can speed up the preclinical as well as clinical studies. Furthermore, highly soluble drugs may not require time-consuming and complicated advanced enabling technologies to develop a drug product.

Advanced technologies and automation globally have also benefitted solid form screening approaches which not only supports the preparation of samples but also enable in-situ characterization of the sample.<sup>15-16</sup> Accessibility of these technologies has made evaluation of different solid forms efficient and less time consuming with availability of very limited material in early developmental stages. These activities can be executed in parallel with pharmacokinetics (PK) studies of multiple compounds during lead optimization and enables a rapid decision-making process.<sup>2</sup>

The overall goal of this review work is to emphasize on a rational that supports a "fit-for-purpose" strategy to employ a successful solid form screening and selection. Furthermore, it is important for a pharmaceutical company to be able to advance a drug candidate to the next stage in cost-effective manner right from the discovery stage → pre-clinical stage → clinical stage → regulatory approval → marketing authorization. In addition to this, the key considerations such as cost, timelines, and product quality and their impact are highlighted during solid form selection.

### **Physicochemical Properties of A New Drug Candidate**

The performance of a drug candidate is largely dependent on its solid form. The physicochemical properties of a solid form such as melting point, solubility, stability, hygroscopicity, and bulk density can have a major influence of its *in vivo* behavior. Therefore, in the early developmental stage, majority of the efforts are focused on improving the physical

properties to enhance the drug processibility, improve absorption, and optimize delivery options.<sup>17</sup>

Generating pH solubility profile and kinetic as well as equilibrium solubility measurement in different biorelevant media are among the important data that a researcher needs to obtain during the preformulation stage. *In-vitro* permeability studies using CaCO<sub>2</sub> cell membrane is also another important piece of information in early developmental stage. Solubility and permeability data are then used to determine the projected doses for toxicity, pre-clinical and clinical studies.

In addition to the experimental studies, computational results also provide some insights on the physicochemical and *in vivo* behavior of a drug candidate:

- Determine possibility of salt formation by calculating the acid-base dissociation constant (pK<sub>a</sub>) value(s)
- Based on solubility and permeability assigning a Biopharmaceutics Classification System (BCS) to a drug candidate
- Calculate the dose number
- Predicting the possibility of improved physical and chemical stability followed by solid form selection
- Drug product risk assessment strategies during formulation development
- Design solid form screening and formulation strategies<sup>18</sup>

### Biopharmaceutical Considerations

In recent years, 90 % of the newly discovered small molecules suffers from limited solubility. With the detailed understanding of biopharmaceutics, pharmacokinetics and pharmacodynamics of the newly discovered drugs, different classification systems have evolved over the period of time.

- Biopharmaceutics Classification System (BCS)<sup>18</sup> (Figure 1),
- Developability Classification System (DCS)<sup>19</sup> (Figure 2) and
- Biopharmaceutics Drug Disposition Classification System (BDDCS)<sup>20</sup> (Figure 3).

Most of the newly discovered drugs fall into the BCS 2 or 4 category (Figure 1). The poorly soluble compounds have non-linear dose proportionality, limited toxicological coverage, and inter-subject pharmacokinetic variabilities. These challenges may often affect human dosing prediction and future studies.

Therefore, the application of enabling technologies to improve solubility and permeability via extensive solid-form screening and novel drug delivery systems becomes very important to achieve an overall goal of getting complete toxicological information, followed by a consistent exposure in different animal species as well as humans as the molecules progresses during the drug lifecycle.

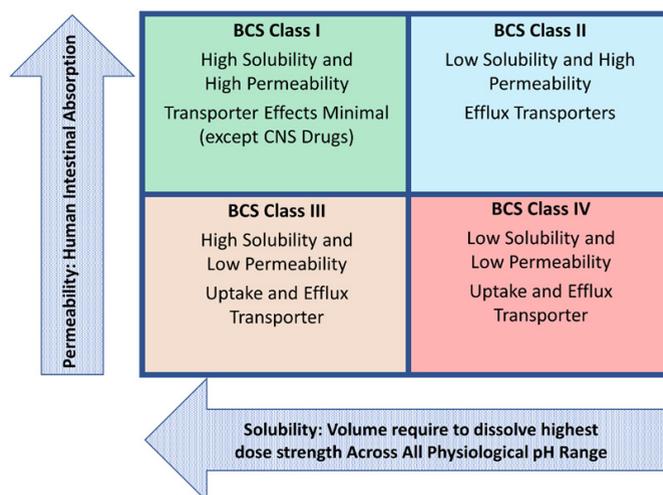


Fig.1: Biopharmaceutics Classification System

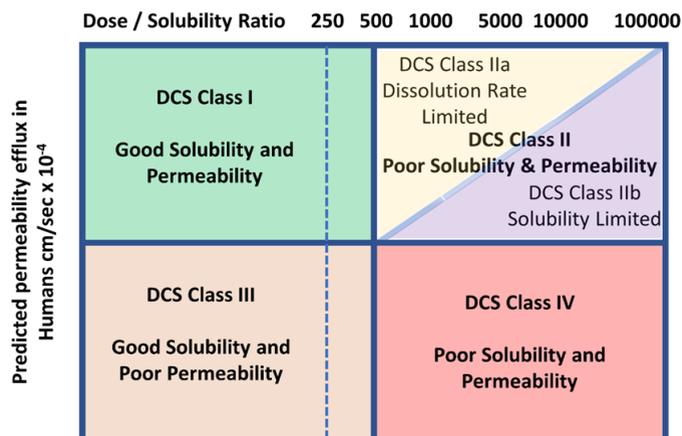


Fig. 2: Biopharmaceutics Developability Classification System

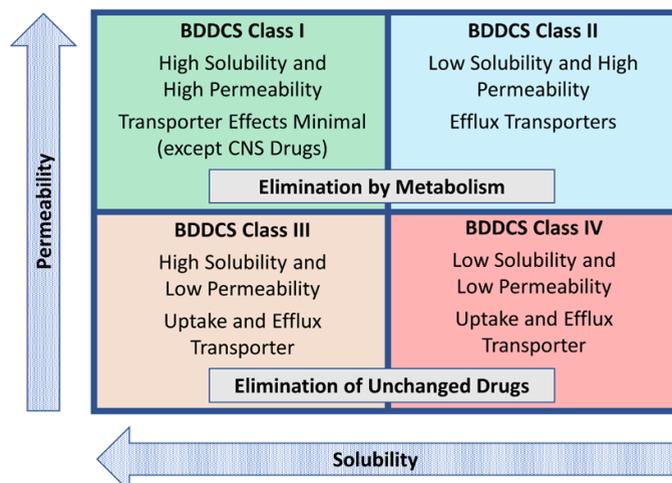


Fig. 3: Biopharmaceutics Drug Disposition Classification System

**Solid form Screening**

Researchers’ main goal is to identify a promising drug candidate for further study in the lab and in animal models, and then in people. Therefore, it is very critical to identify and select a crystalline form that is reproducible, easily processable, as well as chemically pure. These three characteristics will ensure the availability of drug substance with desired physical properties with a robust process. The availability of drug substance will expedite formulation research to support preclinical and clinical studies.

**Salt Screening**

As compared to a free form a drug candidate, forming salt using a suitable counterion via salt screening is by far the most effective approach to

enhance the solubility of a molecule. Salt formation occurs when a compound is ionized in solution which forms a strong ionic interaction with an oppositely charged counterion.<sup>21</sup> From the literature, the pKa difference of more than three between a drug molecule and a counterion may be an underlying mechanism for salt formation.<sup>1, 22</sup> The quantum mechanics and interaction between a drug molecule and a counterion are extensively studied even today.<sup>9, 23</sup> The salt formation phenomenon improves crystallization of a particular drug candidate. It is well known that salts readily undergo crystallization which further aids in the subsequent processing. 50 % drug products available on market comprises of salt forms. One of the reasons for salt selection included solubility improve as well as other physical properties including stability, hygroscopicity and

manufacturability.<sup>24-26</sup>  $pK_a$  can be calculated by Henderson Hasselbach equation (eq. 1)

$$pH = pK_a + \log \frac{[A^-]}{[HA]} \quad \dots(1)$$

Where,  $K_a$  is acid dissociation constant,  $[A^-]$  is concentration of the conjugate base of the acid and  $[HA]$  is a concentration of chemical species HA.

For example, levothyroxine sodium, indicated for hypothyroidism, is available for several delivery methods in order to achieve the necessary pharmacokinetic profiles.<sup>27</sup> However, levothyroxine sodium is narrow therapeutic index drug which is rate limiting step to achieve desirable therapeutic efficacy. While the sodium salt has a relatively higher solubility than the free acid, this molecule exhibits physico-chemical instability. The drug maker developed a tablet and with the efforts from regulatory agency to control the dose variability from dose to dose, the assay specifications have been tightened so as to prevent *in vivo* variability of levothyroxine sodium.<sup>28</sup> While levothyroxine sodium is one example demonstrating the importance of thorough investigation during drug product development. Metformin hydrochloride is another example which has higher solubility as compared to its free form, but it exhibits poor compressibility profiles which available as both immediate release as well as extended-release tablets, which allows the controlled release of a molecule to improve patient compliance.<sup>29</sup> Therefore, if a salt exhibits high solubility than the other parameters like physical-chemical instability as well as processability should also be taken into consideration and evaluated accordingly during the developmental stages to prevent any complications during the commercialization phase.

If a poorly soluble compound is ionizable and has potential for salt formation, an extensive salt screening should be employed. A highly soluble and stable salt will aid in minimizing PK variations (inter-subject, inter-species, and dose-to-dose) as it would increase *in vivo* exposure as well as toxicological coverage. Simple formulations, such as powder in bottle (PiB), powder in capsule (PiC), and suspensions can be easily prepared using a salt form for preclinical and clinical studies. The salt screening of compounds with solubility limitations might be focused on finding a more soluble salt using

counter-ions, acetic acid, methanesulfonic acid, citric acid and other such counterions may be preferred ones due to their low molar mass and hydrophilic nature. While improving solubility is a primary goal from salt screening, it also important to recognize more studies may be required as bioavailability also depends on dissolution, precipitation kinetics, and PK studies.<sup>30-33</sup> It should be recognized that salt formation requires a carefully designed dissolution method to predict the *in-vivo* performance of the drug.<sup>31-32, 34-35</sup> Overall scientific considerations leads to an appropriate decision making in selection of a right salt.

### Co-Crystal Screening

Co-crystal is a multi-component system that includes a drug and one or more co-formers crystallized into a single crystal lattice.<sup>36-37</sup> Co-crystal formation can occur between a free form and a co-former, or a salt and a co former. Contrary to the salt formation, co-crystal formation is usually possible between a drug and conformer with a  $pK_a$  difference less than three. Co-crystallization extends a promising crystal engineering approach to modify a crystal structure and improve physical properties of a given drug.<sup>38-39</sup> There are numerous examples drug formulation and manufacturing wherein co-crystallization has offered solutions to the existing problems.<sup>38, 40</sup> Due to these advantage, co-crystallization have become an attractive alternative to develop and advance a new chemical entity to the next developmental stage. Novartis' Entresto® is a co-crystal of two different drugs (i.e. sacubitril and valsartan). This co-crystal not only offers a combination therapy but also exhibits more efficacy than administered individually.<sup>40-42</sup> Recent investigations also demonstrate the cocrystals also have improved physical stability as well as mechanical properties, which improves the tabletability of a drug.<sup>43-45</sup> Furthermore, size reduction of a tablet is also achievable by use of cocrystal.<sup>46-47</sup>

Co-crystal screening and salt screening exhibits similarity in multiple ways.<sup>48-50</sup> However, at molecular level, co-crystal formation is driven primarily by the H-bonding and other molecular ( $\pi - \pi$ ) interactions between drug and co-former.<sup>39, 51-52</sup> These interactions are relatively weak compared to ionic interactions observed in salts. Successful co-crystal screening is dependent on 1) in-depth understanding of structure-property relationship, b) solubility of both API and

co-former, and c) specialized screening methods, such as solvent-drop grinding (SDG), homogenous crystallization and thermal methods.<sup>37, 53-54</sup> At the same time, insufficient knowledge base and limited screening technologies probes challenges for further use during early developmental stage.<sup>42, 55-56</sup>

Discovery and identification of few co-crystals, commercial scale production and formulating these co-crystal into drug products may be relatively straight forward as compared to its salt counterpart.<sup>57-59</sup> Like any other crystalline material (free form or salt), most co-crystals also require significant efforts in terms of crystallization process development at large-scale followed by stability assessment and biopharmaceutical characteristics assessment in drug products.<sup>50, 60-61</sup> Approved co-crystal drug products are a clear demonstration of how co-crystal formation can be rewarding, despite the associated challenges for specific compounds that have limited solubility, poor compressibility and difficult to crystallize out as a free form.<sup>62-63</sup> With a thorough understanding of co-crystal at molecular level and carefully designed efficient screening methodologies will certainly allow co-crystal to be a more imperative tool during drug development.<sup>53, 64-66</sup>

### Polymorph Screening

Polymorphs are often defined as crystalline forms that have same chemical formula but diverse molecular arrangements and/or conformations within the same crystal lattice.<sup>67</sup> Different polymorphs are anticipated to have different physico-chemical properties including solubility, stability, micromeritic and mechanical properties.<sup>68-69</sup> The goal of polymorph screening is to identify different polymorphs, hydrates and solvates.<sup>70-71</sup> Importantly, from the polymorph screening studies, it is expected to come up with a form phase map to determine their thermodynamic relationship.<sup>72-73</sup> Towards the end of screening studies, the researchers must recommend the most suitable and thermodynamically stable polymorph closer to ambient environmental conditions for further development.<sup>6, 11, 74-75</sup> Polymorphs screening experiments are generally conducted using small amounts of materials (~30 mg per experiment). An effective screening experimental design should include using different solvents (polarity, H-bonding donor and acceptor), aqueous solvent mixtures of different water activities, slurry ripening,

crystallization conditions, such as temperature and cooling rate, anti-solvent addition, liquid vapor diffusion, solid vapor diffusion, slow evaporation, polymer induced crystallization experiments as well as computational tools which should be able to investigate various parameters influencing nucleation and growth kinetics of different crystalline forms.<sup>7, 76-78</sup> Ideal mole fraction solubilities of a given crystal form can be calculated using the ideal solubility equation (eq 2) using  $T_m$  and enthalpy values from DSC measurements.

$$\ln X = \Delta H/R (1/T_m - 1/T) \quad \dots(2)$$

Where, X is the mole fraction,  $\Delta H$  is the change in enthalpy, R is the gas constant,  $T_m$  is the melting point and T is the temperature at which the ideal solubility needs to be calculated.

While conducting a polymorph screening, it is very important to include the real-time conditions during process chemistry, crystallization as well as drug product process in the screening design so as to identify any risks that may be encountered during drug isolation as well as formulation prior to selection of an optimal polymorph proposed for preclinical and clinical studies. Process-induced solid form transformation is equally important during drug product unit operations including API micronization, wet granulation, tableting, and solid-state interaction with excipients.<sup>79-81</sup>

Polymorphs can be divided into two categories, enantiotropic polymorphs and monotropic polymorphs. The relatively stable form can be determined by Berger-Ram Berger Rule using enthalpy of fusion and melting temperature results from differential scanning calorimetry (DSC), competitive slurry experiments and Van't Hoff plot by obtaining solubility at different temperatures.

The heat flow (dq) in the DSC heating a sample is equal a change in enthalpy. A change in enthalpy is further related to the heat capacity  $C_p$ , as described in eq. 3,<sup>82</sup>

$$dq = dH = \int_{T_2}^{T_1} C_p dT \quad \dots(3)$$

Where, dq is the heat transferred,  $C_p$  is the heat capacity, T is the temperature.

Researchers can imagine how difficult it can be to switch to a different polymorphic form at a later stage.<sup>83-84</sup> These changes at a later stage will likely invite additional work. These activities may include crystallization process development, reformulation, as well as possibly bridging toxicology and PK studies. This could lead to significant delays in drug product life cycle as well as high costs.

The International Conference on Harmonization (ICH) guidelines mandates polymorph screening for a new drug molecule to be included in the chemistry, manufacturing, and controls (CMC) section of a regulatory submission. Polymorph screening gives confidence in the robustness of drug substance as well as drug product manufacturing processes. Selecting a stable polymorph at ambient conditions can avoid associated risks with drug product and guarantee that the drug product is stable, efficacious, and safe for patients.

As the drug candidate advances to a later stage in drug development, a more comprehensive screening may be required depending on the route of administration and drug delivery system which may include amorphous material.

#### **Crystallization Process Development**

Once a desired solid form is selected a robust crystallization process is required to isolate the solid form at a commercial scale with a potential for impurity rejection.<sup>84</sup> This step becomes even more critical especially for high-volume drug products, wherein, cost of a drug substance contributes to the overall cost of drug product.<sup>85-87</sup> A successful final drug crystallization process requires finding solvents system through series of metastable zone width solubility experiment to determine a phase boundary within practical ranges of critical processing parameters.<sup>88-91</sup> Finally, a developed and optimized process should meet requirements and specifications of particle attributes with controlled particle size distribution (PSD), crystal morphology or shape, bulk density and offers yield maximization with thorough understanding of the thermodynamics and kinetics of a specific (polymorphs/solvents) system.<sup>10</sup> With recent advances in crystallization process development, a real-time in-process information can be continuously monitored and analyzed using *in situ* process analytical technologies

(PATs).<sup>10,86,92</sup> This will provide a better understanding and control of crystallization processes. Some of PATs used nowadays include Focused beam reflectance measurement, Blaze Metrics®, process Raman, and ReactIR applied by scientist during process development.<sup>10,93-94</sup> A suitable crystalline form of a drug candidate is important in determining the success of manufacturing on a large commercial scale due to the aforementioned benefits a crystalline form can offer by ensuring product quality and safety.<sup>10</sup>

#### **Amorphous Solid Dispersion Screening**

The drug candidates for which it is challenging to obtain a stable crystalline form with acceptable solubilities will require enabling technologies to improve solubility studies. Amorphous solid dispersions (ASD) are often explored and used to improve solubility for compounds with limited solubility. Like salts, co-crystal and polymorph selection, an amorphous dispersion also required a detailed screening protocol to search a suitable amorphous dispersion with desirable properties. The main goal of amorphous solid dispersions is to improve a higher kinetic solubility for better drug absorption compared to its crystalline counterpart. The expected solubility improvement of an amorphous solid typically ranges from approximately 2 to 1,000 folds.<sup>25</sup> Although, the presence of disorder in the amorphous solids complicates the system, the crystalline lattice energy and H-bonding donors and acceptors in a molecule do offer insights on the predicted physico-chemical properties improvement.<sup>95-97</sup>

The ASD requires optimization of polymers and surfactants which can inhibit precipitation and re-crystallization of the drug in supersaturated solutions.<sup>98-100</sup> Different methodologies are employed to prepare ASD, such as rapid solvent evaporation, spray drying (SD) of solutions, freeze-drying (FD), or hot melt extrusion (HME).<sup>25,101-103</sup> With the increase in demand of ASDs due to discovery of poorly soluble compounds have forced the equipment manufacturers to provide machineries which can be used to test these technologies at very small scale (as low as ~10 g material). These technologies can be easily scaled up to suffice large scale production requirements during commercialization state.<sup>104</sup> One of the most challenging problem

associated with ASD is its physical stability and risk of recrystallization to the most stable form. Efforts have been made to study and predict the stability of ASD. Zografis et al has reported that if the ASD is stored at a temperature 50°C below glass transition temperature then the recrystallization kinetics can be slowed down significantly. The physical stability of ASD is dependent on maximum enthalpic recovery (eq. 3), extent of relaxation (eq. 4) and relaxation time (Eq. 5).<sup>105</sup>

$$\Delta H_{\infty} = (T_g - T) \cdot \Delta C_p \quad \dots(3)$$

$$\phi_t = 1 - (\Delta H_t / \Delta H_{\infty}) \quad \dots(4)$$

$$\log \tau_s = \log \tau_0 + (D T_0) / T - T_0 \quad \dots(5)$$

Where,  $\Delta H_{\infty}$  is the maximum enthalpic recovery,  $T_g$  is a glass transition temperature at a given temperature  $T$ ,  $C_p$  is the heat capacity,  $\phi_t$  is the extent of relaxation,  $\tau_s$  is structural relaxation time,  $D$  is the fragility parameter and  $T_0$  is the initial temperature. The ASD formulation requires screening in early development that includes testing solubility of drug in organic solvents suitable for solid dispersion, drug-polymer miscibility, and drug interaction with surfactants. Drug loading plays a major role in deciding the formulation for ASD preparation. Advanced solid-state characterization techniques including polarized light microscopy, X-ray powder diffraction, differential scanning calorimetry, thermogravimetric analysis, dissolution profiles, and accelerated stability assessment are required to characterize ASD formulations. The promising leads among ASD formulations are further tested for PK studies in animal to gain confidence on the selected ASD for further development.

### Formulation Strategy & Drug Delivery

Solid form selection is directly dependent on various drug product development aspects including route of administration, dose, dosage form, and release profile of a drug. Early product development support highlights the role of solid form selection for preclinical and clinical studies. A relatively stable solid form is typically moved on to the final stage to achieve robust manufacturing of commercial formulation. A highly soluble salt is a preferred choice for a formulation meant for oral delivery. Contradictorily, a free form which is unionized

may be chosen for topical applications wherein permeability of a drug is more important parameter as compared to solubility. Each drug delivery system may have a specific preference in terms of physico-chemical properties as well as desired solid form. Solid-state stability, adequate solubility and dissolution rate, drug-excipient compatibility, bulk density, micromeritics, and compressibility are few among the important considerations for an oral drug delivery system. It should be noted that highly soluble salt in aqueous systems is not a direct outcome for bioavailability. A relatively stable salt form in solid-state may undergo precipitation as well as disproportionation *in vivo*, which might hamper the bioavailability for that particular drug.<sup>35, 106</sup> In such cases, polymeric excipients as well as surfactants must be included in the formulation to inhibit the nucleation and crystallization of the free form. This should be thoroughly investigated during the early developmental stages to avoid patient-based failure modes in future.<sup>33</sup> As in the inhalation formulations, physico-chemical compatibility with excipients as well as device components, hygroscopicity, and milling are specifically important. Liquid formulations such as solutions or suspensions are conventionally used to carry out toxicological studies. The similar approach is used for parenteral formulations, intranasal, and pulmonary delivery systems. In these drug delivery systems, the drug is in direct contact with formulation vehicle either solubilized or suspended which is also crucial while selecting the solid form. While considering salt as a solid form for parenteral dosage, the pH of the salt solution at the desired concentration in the biorelevant medium should be investigated to assess the acceptability of pH compatibility with physiological fluids. In addition to this, solubilized formulations need a pH solubility profile knowledge database so to ensure the drug concentration is well below the equilibrium solubility of the most stable form in the formulation vehicle to maintain the under-saturated without triggering self-nucleation or crystallization.<sup>8</sup> In addition to the important aspects discussed above, the solid form selection becomes even more challenging for pediatric formulations.<sup>107-109</sup>

### Solid Form Screening & Selection Strategies

Each newly discovered drug candidate has a specific physico-chemical and quantum-mechanical properties which requires careful application of solid-form

strategy, which typically varies from molecule to molecule during the drug development life cycle. Table 1 delineates the application of solid form investigations aligned with developmental stages to achieve phase-specific developmental goals.

**Table 1: Solid form investigations at each developmental stage during drug product life cycle**

Drug Product Lifecycle Stage	Key Development Objective	Solid Form Investigations
Discovery (lead to candidate selection)	Selection of a crystalline form for isolation and purification purposes (anhydrates, hydrate and solvates) <sup>110</sup>	Crystallization, salt / co-crystal screening
Early Development (PK, Tox, Phase 1 and 2a)	Assess polymorphism and chose the most stable solid form at ambient conditions ASD to the exposure of poorly soluble drugs	Polymorph screening and selection  Revisit salt/ co-crystal screening  ASD screening
Late Development (Phase 2b and 3, Launch)	The optimal solid form to support pivotal study till commercial launch  Finalize drug substance as well as drug product manufacturing process	Comprehensive polymorph screening  Process risk assessment and mitigation  Drug product risk assessment
Life Cycle Management (New Indications & formulations)	Comprehensive solid form knowledge  Optimal form of new drug manufacturing, new indications, and novel formulations	Comprehensive salt / co-crystal screening

Early developmental stages focus on searching a suitable crystalline form. Crystalline solid form enables availability of improved isolation process as well as chemically pure drug substance. Highly soluble and physico-chemically stable drug substance can be further used in preclinical, toxicity and clinical studies. As the drug substance progresses further with supportive data from toxicity studies, further studies are carried out during the later stages to evaluate the solid form risks associated with drug substance and drug product manufacturing. These studies may include an extensive polymorph screening to establish a form phase relationship map. This would maximize opportunities to advance the molecule with new indications and novel formulations to the final and commercial stage of drug product lifecycle.

### **Bridging Drug Discovery & Formulation Development**

Drug product lifecycle is generally divided into two stages. First stage involves discovery of drug with the help from medicinal chemists whose focus is to develop a chemical moiety with desired therapeutic effect through multiple organic reactions as well as structure activity relationships knowledge. Once the molecule is deemed effective against a specific biological target that is important in a disease, it progresses to the next stage. Stage two involves the placement of a drug molecule into a drug delivery system by formulation scientists to investigate the safety and efficacy of the newly discovered molecule. The transition from stage one to stage two can sometimes be very challenging.

Medicinal chemists invest their knowledge and time towards optimizing a lead molecule with best selectivity and *in vitro* potency. At the discovery stage, the focus of the studies lies on *in vitro* potency of candidate molecules, which typically has poor physicochemical and biopharmaceutical properties. There is neither any understanding on non-clinical as well as clinical dosing nor the formulation and dosage form technologies that may be needed in future.

Therefore, it is vital to transition the lead molecule from the hands of medicinal chemists to the preformulation and formulation scientists who understands the physicochemical as well as biopharmaceutical importance of a potential drug candidate. The role and involvement of introducing formulation scientists during discovery stage to next stage is very diverse among different companies. In general, it is towards the late discovery stage, where in, a particular salt and desired polymorph has been decided.

A disconnect in the transition of lead molecule is clearly observed in this approach conventionally that most biotech companies follow. The primary focus emphasizes on resolving the solubility issues, wherein other important parameters could be ignored, instead of putting all resources to get a 360° view on the overall characteristics of a potential drug molecule.

A recent review work demonstrated that salts were selected in the early developmental stages due to ease of synthesis and crystallization and economic viability. The same salt forms had no or minimal understanding on the down stream processes (physical and chemical stability, processability into dosage forms, solubility, and dissolution rate at different pH conditions). Hypothetically, if the lead salt form does not have desired solid-form properties, it may become very difficult to alter the salt form during the later stages. If at all, a different salt is selected for further development then it would significantly increase the timelines as well as costs. All the important studies such as biological, toxicological, formulation, and stability tests may need to be revisited using a new salt form. This ultimately led to longer timelines and increased costs.<sup>24</sup>

## Conclusion

The solid form of a potential drug candidate might have a deep impact on the physicochemical properties and drug developmental activities. The solid form selection strategy is outlined in this review work. The current work highlights the fundamental consideration of molecule's physicochemical properties, the role of different solid forms in rejecting undesired impurities, physical properties, as well formulation approaches. This can provide a framework to develop an appropriate solid form selection strategy of small molecule drug candidates wherein the drug candidate advances to the next developmental stage rapidly. Importantly, it should be noted that the lack of detailed understanding of a solid form at molecular level has resulted in a drug product recall due to pharmaceutical quality concerns. This can be very well exemplified by the most recent drug product recall of levothyroxine sodium tablets manufactured by Acella Pharmaceuticals from the US market on Apr 29<sup>th</sup>, 2021.

Lastly, the researchers should acknowledge that discovering a soluble solid form using an enabling technology to improve the solubility and dissolution of a candidate is just the first step in drug development. The later steps include determination of doses, dosing strategies, devising a drug delivery system and drug product risk assessment which will ensure the complete drug absorption occurs without chemical degradation, physicochemical instability or disproportionation of the drug in physiological fluids. The safety and efficacy of a drug product can be ensured by availability of new prior knowledge.<sup>11</sup>

## Expert Opinion

Solid form screening has been explored extensively by the researchers in drug product development and it is very well established. The drug properties of a potential new chemical entity can only be understood if the solid-state structure of drugs molecules have been thoroughly studied by itself as well as its impact on the future drug formulation. Each researcher has their own screening workflows, thoughtful strategies, and availability to advanced analytical tools to help choose a stable solid form at ambient conditions. However, the pharmaceutical industry and the regulatory agencies are familiar with the fact that the drug product recalls have happened in past

and it has led to evolution of regulatory guidance to streamline the research activities pertaining to solid form selection and enable a possibility of robust drug product on market. This manuscript has summarized different examples that aid the development programs at pharmaceutical companies for a newly discovered molecule.

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