Amorphous solids - Pharmaceutical technology and drug formulation.

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Abstract:

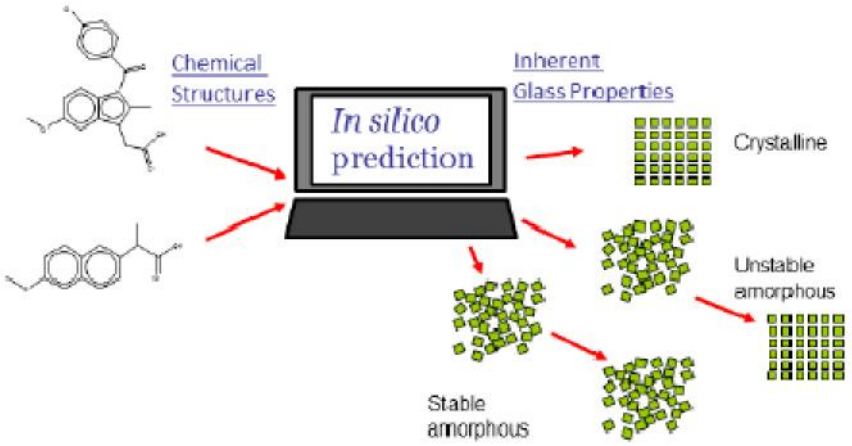
The physical properties of materials are to a high extent influenced by its solid state. For instance, poorly soluble drugs may attain higher dissolution rate if made amorphous, i.e. transformed into a disordered, non-crystalline state. The mechanical properties, such as elasticity and hardness, of many excipients are also a function of the degree of molecular disorder. Characterization, prediction and control of the solid state of drugs and excipients are hence crucial components of pharmaceutical technology and drug formulation.

Key words: amorphization, Rotary Evaporation, Spray Drying, Hot Melt Extrusion .active pharmaceutical ingredient (API); Amorphous solid dispersions (ASDs)

INTRODUCTION

- Properties of amorphous composites

Composites are formed by incorporation of nano-particles into spray-dried powders. The incorporated particles can give the solid advantageous properties, e.g. improved stability of an amorphous compound. We produce and utilize amorphous composites as model to find out how inclusion of various material components affects the properties of the amorphous state. Our focus is to incorporate micro- to nano-sized filler particles into spray-dried amorphous disaccharides and to find out how this affects the material properties of the formed composite in terms of physical stability, particle agglomeration behavior and mechanical properties**.**



Prediction of disordering propensity of solids different materials have different propensity to become amorphous when exposed to manufacturing operations such as drying, mixing and compaction. We are developing prediction tools which give us the opportunity to predict the disordering potential and amorphous stability of drug-like solids in the dry state and in aqueous dispersions. Since disordering leads to large alterations in material properties, predictions could help

Alerting problematic compounds that are intended to be included in a formulation. Also it can highlight the possibilities to utilize amorphization to improve material properties, such as poor solubility. The over all aim is to better understand the fundamental properties that govern the ability of a solid material to become a stable amorphous solid

It is frequently reported that the percentage of drug candidates that are limited by poor solubility is increasing [1,2]. These poorly soluble compounds typically require enabling formulations, and this trend creates challenges for teams in discovery and development who must drive *in-vivo* exposures high for animal toxicology studies and deliver robust dosage forms for clinical evaluation. Many enabling technologies are available for the formulator to consider, including lipids, co solvents, surfactants, nano particles, cyclodextrin complexes, amorphous solid dispersions, and others. The suitability of the particular formulation approach depends largely on the physicochemical properties of the active pharmaceutical ingredient (API). Amorphous solid dispersions (ASDs) are particularly attractive for many poorly soluble drug candidates because these formulations offer many of the advantages of more conventional solid oral dosage forms but they also provide faster dissolution rates and higher drug concentrations in the gastrointestinal milieu [3]. Further, typical excipients utilized in production of ASDs are commercially available and they have proven to be well tolerated *in vivo*. We have successfully employed ASD technology to drive high plasma exposures in toxicology studies as well as to deliver challenging molecules in clinical studies. In this article we will discuss approaches for preparing, screening, characterizing, and dosing ASDs in preclinical and early development.

Methods of Preparation

Rotary Evaporation

Rotary evaporation is a desirable method for preparation of ASDs for early stage (pre-clinical efficacy/toxicology, Phase I) studies. This approach is fast, material sparing, relatively inexpensive, and readily available. Moreover, a wide range of batch sizes from mg to kg quantities may be prepared with high yield. ASD preparation by rotary evaporation is carried out by first dissolving the API and formulation components (polymers, surfactants) in a pharmaceutically acceptable solvent. Typical solids load in the solvent is 5% to 25% by weight, and this is generally dictated by API/polymer solubility. The solvent is then removed in a rotary evaporator using heat (typically 40 to 80 oC) and vacuum. Total time for solvent evaporation can range from minutes to hours.

Because of the relatively long evaporation time, the compound must have adequate chemical stability in the solvent at elevated temperatures. Longer evaporation times may lead to physical

instability, so care must be taken to avoid API crystallization during solvent removal. This issue can be mitigated to a large extent through optimization of the temperature, vacuum, rotation, and total solids load. After removal of the solvent, the resulting ASD is isolated, dried, and milled to the desired particle size. Secondary drying in a vacuum oven or tray dryer is often employed to remove any residual solvent that remains in the final ASD powder.

Polymer	Tg (°C)	Solvent Solubility	Hygroscopicity	Amenable Methods of Manufacture
Copovidone	106	Dichloromethane Ethanol Methanol Water Acetone	<10% @ 50% RH	Rotary Evaporation Spray Drying Hot Melt Extrusion
Polyvinyl caprolactam-polyvinyl acetate-polyethyleneglycol copolymer	70	Water Ethanol Methanol Acetone	~5% @ 50% RH	Rotary Evaporation Spray Drying Hot Melt Extrusion
PVP	130 (K17) 168 (K30)	Chloroform Ethanol Methanol Water Acetone	~15% @ 50%RH	Rotary Evaporation Spray Drying Hot Melt Extrusion
HPMC	170	Cold Water Dichloromethane: Ethanol Dichloromethane: Methanol Water: Alcohol	<10% @ 50% RH	Spray Drying
HPMC P	133 - 137	Acetone: Methanol Acetone: Ethanol Methanol: Dichloromethane	2 – 5% @ 50%RH	Spray Drying
HPMC AS	110 - 130	Acetone* Ethanol:Dichloromethane* *clear or turbid viscous solution	~3% @ 50%RH	Spray Drying
Methacrylate/ methacrylic acid copolymer	110 - 150	Ethanol, Methanol, Acetone, Acetone with 3% water	<5% @ 50% RH	Rotary Evaporation, Spray Drying, Hot Melt Extrusion

The polymers that may be employed for ASD preparation by rotary evaporation are limited to those that can be easily isolated in high yield after solvent removal (Table 1). Hydroxypropylmethyl cellulose (HPMC) based polymers are typically not amenable to rotary evaporation, as these polymers often result in a glassy film that is difficult to isolate.

While preparation of ASDs by rotary evaporation is ideal for the early stages (pre-clinical to Phase I) of drug development, it is not well suited for later stage development, manufacturing, and commercialization. The process is not readily scalable beyond quantities on the order of 10 kg because solvent volumes become too large, leading to very long and unrealistic evaporation times. Therefore, bridging to larger scale spray drying or hot melt extrusion (HME) processes is required if the drug candidate progresses into later stage development.

Spray Drying

Spray drying is another method that is commonly utilized for the preparation of ASDs of poorly soluble compounds [4]. The method is readily scalable from gram-sized batches during discovery and early development to kg and metric ton quantities during later stage manufacturing and commercialization. The first step in the spray drying process is to prepare a feed solution of the API and formulation components (polymers, surfactants) in a pharmaceutically acceptable solvent. The total solids load in the feed solution is typically 5% to 25% by weight, and this is generally dictated by API/polymer solubility as well as viscosity of the solution. The feed solution is then pumped into a spray nozzle along with inert, hot (typically 60 to 100 ^{o}C) drying gas where it is atomized and sprayed into a drying chamber. The solvent quickly evaporates during this process, leaving behind spray dried dispersion particles. These particles are collected in a cyclone with attached bag house filter. Secondary drying in a vacuum oven or tray dryer is often employed to remove any residual solvent that remains in the final ASD powder. Because solvent evaporation time is extremely fast (on the order of seconds), spray drying is particularly advantageous for preparing ASDs of compounds with poor thermal stability.

There is no limitation to the types of polymers that may be employed for preparation of ASDs by spray drying. In particular, spray drying enables the preparation of ASDs in HPMC based polymers, which is often difficult, if not impossible, to achieve using rotary evaporation or HME processes. Spray drying also offers the opportunity to optimize particle size and bulk powder properties through process parameter optimization and also through the type of spray nozzle (e.g. two-fluid, ultrasonic, rotary, and pressure nozzles) [4]. In general, particle size increases with equipment scale, as a result of larger droplet sizes and longer drying residence times. This may present difficulties during development, as particle size of the spray dried powder is inherently changing as the formulation is scaled. This can be especially challenging during discovery and early development, because smaller batch sizes lead to inherently small particles (~10 μm) which can lead to issues with flow and compressibility during downstream processing. Issues with particle size can be largely mitigated via dry granulation of the spray dried powder, however this adds another relatively complicated unit operation to the overall process. Another challenge to employing spray drying during discovery and early stages of development is that the currently available lab scale spray dryers suffer from poor yield and generally cannot work on mg quantities of material.

Hot Melt Extrusion

Hot melt extrusion (HME) is the most widely used method of preparation for ASDs for commercial products, because it is particularly well suited for large scale manufacturing [5, 6]. The preparation of ASDs by HME typically involves the use of twin screw extruders to mix multiple materials (API, polymer, and surfactant) into a melt which is extruded through a die. The extrudate is then cooled and either shaped by calendaring or pelletized and milled to a desired particle size.

The final milled extrudate is then typically blended with additional excipients and compressed. Direct shaping to a final dosage form is also possible with calendaring or injection molding technology. HME is advantageous for commercial manufacturing because it is a continuous and easily scalable process. Unlike rotary evaporation and spray-drying, HME does not require the use of organic solvents, thus it is a "green" process that reduces cost and alleviates safety/environmental concerns. Processing must be performed at temperatures above the Tg of the polymer and high enough for the API to either melt and/or dissolve into the polymer matrix. HME can be limited in the ability to process heat sensitive and/or high melting point drugs and it is generally not amenable for manufacturing small (mg to g) quantities needed in preclinical development.

Selection of Excipients

Polymers

Polymers are critical components in ASDs because they act as carriers for the drug and they inhibit crystallization in both the dosage form and *in-vivo*. By remaining in an amorphous state during dissolution, the drug can achieve super saturation and potentially greater absorption, when solubility is the limiting factor. In addition to *in-vivo* performance considerations, polymer properties such as the glass transition temperature (Tg), solubility in organic solvents, and hygroscopicity must be considered in order to make the ASD stable and manufacturable.

The properties of some commonly used polymers for preparation of ASDs are summarized in Table 1. The polymer Tg is an important property to consider when preparing and selecting an ASD formulation. Polymers with higher Tg have less mobility, lending to better inhibition of drug crystallization. Additionally, the polymer Tg is particularly important for hot melt extrusion, as the process must be carried out above Tg to sufficiently mobilize the polymer. Organic solvent solubility of the polymer is a critical factor when manufacturing by rotary evaporation or spray drying to ensure that the polymer can be fully dissolved at the required concentration. The hygroscopicity of the polymer must also be considered, because an increase in moisture content can negatively affect physical and chemical stability, and proper packaging may be needed for ASDs composed of hygroscopic polymers.SurfactantsTable 2 - Properties of Surfactants Commonly Used in ASDs [7]

Surfactants are often used as solubilizers or emulsifying agents in ASDs. Their primary purpose is to increase the apparent aqueous solubility and bioavailability of the drug. The properties of some common surfactants used in ASDs are listed in Table 2. As with polymers, solubility in organic solvents is an important consideration when preparing ASDs from solvent. In the case of hot melt extrusion, surfactants can have a plasticizing effect, which allows processing at lower temperatures.

Polymer	Tg (°C)	Solvent Solubility	Hygroscopicity	Amenable Methods of Manufacture
Copovidone	106	Dichloromethane Ethanol Methanol Water Acetone	<10% @ 50% RH	Rotary Evaporation Spray Drying Hot Melt Extrusion
Polyvinyl caprolactam-polyvinyl acetate-polyethyleneglycol copolymer	70	Water Ethanol Methanol Acetone	~5% @ 50% RH	Rotary Evaporation Spray Drying Hot Melt Extrusion
PVP	130 (K17) 168 (K30)	Chloroform Ethanol Methanol Water Acetone	~15% @ 50%RH	Rotary Evaporation Spray Drying Hot Melt Extrusion
HPMC	170	Cold Water Dichloromethane: Ethanol Dichloromethane: Methanol Water: Alcohol	<10% @ 50% RH	Spray Drying
HPMC P	133 - 137	Acetone: Methanol Acetone: Ethanol Methanol: Dichloromethane	2 – 5% @ 50%RH	Spray Drying
HPMC AS	110 - 130	Acetone* Ethanol:Dichloromethane* *clear or turbid viscous solution	~3% @ 50%RH	Spray Drying
Methacrylate/ methacrylic acid copolymer	110 - 150	Ethanol, Methanol, Acetone, Acetone with 3% water	<5% @ 50% RH	Rotary Evaporation, Spray Drying, Hot Melt Extrusion

Organic Solvents Table 3 - Properties of Organic Solvents Commonly Used for Preparation of ASDs[8]

Polymer	Tg (°C)	Solvent Solubility	Hygroscopicity	Amenable Methods of Manufacture
Copovidone	106	Dichloromethane Ethanol Methanol Water Acetone	<10% @ 50% RH	Rotary Evaporation Spray Drying Hot Melt Extrusion
Polyvinyl caprolactam-polyvinyl acetate-polyethyleneglycol copolymer	70	Water Ethanol Methanol Acetone	~5% @ 50% RH	Rotary Evaporation Spray Drying Hot Melt Extrusion
PVP	130 (K17) 168 (K30)	Chloroform Ethanol Methanol Water Acetone	~15% @ 50%RH	Rotary Evaporation Spray Drying Hot Melt Extrusion
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HPMC AS	110 - 130	Acetone* Ethanol:Dichloromethane* *clear or turbid viscous solution	~3% @ 50%RH	Spray Drying
Methacrylate/ methacrylic acid copolymer	110 - 150	Ethanol, Methanol, Acetone, Acetone with 3% water	<5% @ 50% RH	Rotary Evaporation, Spray Drying, Hot Melt Extrusion

Solvents are necessary when preparing ASDs by rotary evaporation or spray drying. The properties of some common solvents used for ASD preparation are listed in Table 3. Solubility of the drug typically drives the solvent selection process, but all components should be completely dissolved to produce a homogeneous feed solution and a consistent final ASD powder. The solubility of the components in the chosen solvent must be high enough to manufacture at a reasonable throughput (typically > 5% weight of the total solids load). Water is often employed as a co solvent for drugs (e.g. hydrates) that exhibit maximum solubility in a water-organic solvent mixture. The boiling point of the solvent is used as a guideline to set process temperatures in both rotary evaporation and spray drying processes. Sometimes a system with multiple organic solvents can be used to improve the solubility of various components. For GLP/GMP manufacturing, the ICH limit of the chosen solvent must be considered and secondary drying is often necessary to remove residual solvent.

Small-Scale ASD Screening

When conducting a screen for ASDs, the primary objective is to identify a formulation that enables *in-vivo* exposure of a poorly water-soluble compound and one that is also stable, both chemically and physically. For this, a wide range of polymers and polymer-surfactant systems can be screened. In addition, the drug and surfactant loading in the ASD can be evaluated for its effects on release behavior and *in-vivo* performance, as well as physical and chemical stability. If multiple combinations of polymers, surfactants, and drug/surfactant loads are screened, the number of samples can easily range into the hundreds.

For early stage screening, a centrifugal solvent evaporator can be used to quickly prepare a large number of samples, in parallel, using mg quantities of material. Samples can be prepared using 96-well plates for small (mg) scale screening or gram-scale quantities can be prepared using scintillation vials or small beakers [9].

Small samples allow for larger, more comprehensive screens to be carried out quickly while still providing enough material for meaningful characterization. Potential lead formulations can then be manufactured on a larger scale for further evaluation, including physical and chemical stability studies, *in-vitro* release characterization, and *in-vitro* studies in animals.

Characterization

Characterization of an ASD is a critical requirement following preparation in order to be confident in the performance of the formulation. Characterization should include analyses of both solid form and *in-vitro* API release in aqueous media.

Numerous methods are available for characterization, the more common of which are described in the following sections and in Table 4.

Table 4 - Common Techniques Employed for ASD Solid Form Characterization

Polymer	Tg (°C)	Solvent Solubility	Hygroscopicity	Amenable Methods of Manufacture
Copovidone	106	Dichloromethane Ethanol Methanol Water Acetone	<10% @ 50% RH	Rotary Evaporation Spray Drying Hot Melt Extrusion
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Solid Form Evaluation

Of primary importance is the identification of residual crystalline character as this signals potential long-term physical instability of the amorphous API. Polarized light microscopy (PLM) and powder X-ray powder diffraction (PXRD) are rapid, non-destructive techniques employed as an early screen for crystalline. Individual crystals may be identified via microscopy while PXRD diffractograms provide information regarding the gross amorphous or crystalline character of the solid. Data from both methods provide greater insight when combined with more sensitive thermal methods such as differential scanning calorimetry (DSC).

DSC is employed to study transitions in the solid state as a function of temperature. Most often, ASDs are evaluated for the presence of melt endotherms and Tg. Observation of melt endotherms confirms the presence of crystalline components. Tg is an important descriptor that can provide insight into the long term stability of the ASD. Since a higher Tg generally indicates better stability, a single, high Tg value is desired for a particular ASD. Tg generally decreases with increased moisture uptake, which makes the API more prone to crystallization at higher RH conditions. Multiple Tg values indicates heterogeneity in the system and an increased potential

for phase separation within the solid leading to crystallization. Thermogravimetric Analysis (TGA) is a thermal method that is complementary to DSC. TGA is employed to study weight loss from an ASD as a function of temperature and this technique is typically employed to roughly quantitate amounts of residual water or organic solvent present in the ASD. It is possible to determine the identity of materials lost during heating by coupling the TGA to a mass spectrometer (TGA-MS). These data may then be utilized to adjust processing or storage parameters to minimize the amount of plasticizing solvents which may lead to physical instability for the ASD. Dynamic vapor sorption can also be performed to understand the hygroscopic tendencies of the ASD powder.

Many other analytical methodologies are available to further characterize ASDs, although these are typically less common. Some of the other techniques include solid-state NMR spectroscopy [10], Raman spectroscopy [11], infrared spectroscopy [12], and isothermal microcalorimetry [13].

Long term stability of ASDs should be evaluated due to the increased risk of both physical and chemical instability associated with amorphous solids. Accelerated stability studies should be conducted under stressed conditions (e.g. open dish at 40°C/75% RH, 60°C/75% RH, etc.) to understand both the physical stability of the ASD and any increased risk of chemical reactivity in the presence of excipients. Photostability should also be examined to determine whether special packaging is required to prevent photochemical reactions in the amorphous state. Understanding the stability of an ASD allows one to reformulate as necessary by varying drug load, by adding antioxidants, or by selecting alternative polymers/surfactants to maximize stability.

In-vitro Release

Release of API from an ASD may be studied by a variety of in-vitro methods. One way to evaluate release from ASDs is by simple powder dissolution. This is performed by transferring a known mass of material into a known volume of biologically relevant dissolution medium (e.g. simulated gastric/intestinal fluid) under constant stirring. Solution concentrations are measured as a function of time to generate a concentration versus time release profile for the API. Solution concentrations in significant excess of the equilibrium API solubility in the particular medium should be targeted to test the ability of the ASD to achieve and maintain super saturation.

However, it is desirable to be as biorelevant as possible to predict *in-vivo* performance. More dynamic techniques, such as the artificial stomach duodenum, and other multicompartmental dissolution/ release methods, should be employed to understand API release from ASDs [3,14]. These methods are used to understand complex release phenomena and to begin building *in-vitro/in-vivo* correlations. A dynamic dilution scheme was recently shown to provide valuable inputs for predictions of pharmacokinetics (PK).

Dosing Considerations

Since ASDs are inherently Meta stable systems, it is important to consider the implications of the dosage form and dosing conditions on physical/chemical stability, manufacturability, and *in-vivo* performance. Aqueous suspensions enable dosing of higher ASD amounts and they are therefore

ideal for dosing to animals for toxicological evaluation. Care must be taken to ensure that the ASD does not crystallize in the aqueous suspension during preparation and dosing, which could compromise *in-vivo* performance. Gelling and/or foaming can occur when suspending an ASD in aqueous solution. This issue may be overcome through optimization of the ASD loading in the suspension and/or addition of anti-gelling/foaming agents. When dosing smaller animals by oral gavage, the particle size of the ASD in aqueous suspension must be small enough to pass through the gavage tube.

Hard gelatin capsules (HGC) are ideal for dosing of the dry ASD to larger animals and humans. If long term stability is required, the physical and chemical compatibility of the ASD with the capsule shell must be considered, especially for hygroscopic polymers which may dry out or cause the HGC to swell depending on the RH conditions. Tablets are generally the preferred dosage form for ASD formulations of commercial products. Formulation of the ASD intermediate with secondary excipients (e.g. fillers, disintegrates, lubricants, glidants) is typically required in order to optimize the flow and compressibility of the ASD formulation to enable manufacturability of the finished tablet. Thus, the ASD intermediate must be physically and chemically compatible with the API/ ASD powder. The particle size of the ASD powder is also an important consideration for tablet formulations, as the particle size can affect the manufacturability (i.e. flow and compressibility) as well as the dissolution/release rate of the API from the tablet matrix. ASDs made by HME or rotary evaporation processes are typically milled to the optimal particle size for tableting. The desired particle size of spray dried ASDs may be obtained through process optimization, especially on large scale spray dryers. Spray dried powders made on a smaller scale during early development tend to have inherently small particle size, thus these powders may require dry granulation (roller compaction, milling) in order to obtain the desired particle size for optimal tablet properties.

Key drug properties vital to the development of a quality drug product are the bioavailability. and solid-state stability. Solubility and dissolution rate are physical characteristics that are directlyrelated to the bioavailability. It has been reported that the solubility ratio between polymorphic

Chemical	Kinetic	Mechanical
• Chemical reactivity/stability • Photochemical reactivity	• Rate of dissolution • Solid-state reaction kinetics • Stability • Rate of crystal growth	• Compactability • Hardness • Powder flow • Tableting • Tensile strength
Packing/physical	**Surface**	**Thermodynamic**
• Conductivity • Density (or molar volume) • Hygroscopicity • Refractive index • Color • Particle morphology	• Interfacial tensions • Surface area • Surface free energy	• Chemical potential, free energy, and solubility • Enthalpy and entropy • Heat capacity • Melting and sublimation temperature • Vapor pressure

DISCUSSIONS

PERVASIVENESS AND SIGNIFICANCE OF POLYMORPHISMIN DRUG DEVELOPMENT

The strong interest in crystal polymorphism within the pharmaceutical landscape can be attributed to its frequent occurrence and the fact that significant differences in chemical and physical characteristics may arise with changes in the solid-state form, thus affecting the manufacturability, performance, and/or quality of the drug product. Some have suggested that virtually all chemical compounds have more than one crystalline form. The prevalence of polymorphism is often linked with McCrone's statement "that every compound has different polymorphic forms and that, in general, the number of forms known for a given compound is proportional to the time and money spent in research on that compound." Others have made similar suggestions, including Buerger & Bloom, who commented in 1937 that "polymorphism is an inherent property of the solid-state and it fails to appear only under special conditions," and Kuhnert-Brandstatter, who more recently noted in 1975 that "probably every substance is potentially polymorphous.

The only question is, whether it is possible to adjust the external conditions in such a way that polymorphism can be realized or not." These comments likely are a bit exaggerated, as isolation of new polymorphs is most often a result of chance or serendipity. Moreover, for some small molecules such as naphthalene, only one crystalline form exists even though the molecule has been crystallized many times, and for others such as dibenzylidene sorbitol, a nucleating agent or clarifier used in polymer manufacturing, a crystalline phase is unattainable.

Examination of the polymorphs and solvates of the top ten best-selling small-molecule drugs in 2009 (**Table 1**) and common over-the-counter (OTC) drugs (**Table 2**) would suggest that most drug molecules exist in multiple polymorphic and/or pseudo polymorphic forms. This inconsistent with an earlier review on polymorph screening in which he noted that out of 245 small-molecule organic compounds screened for polymorphs, approximately 90% of these showed evidence of multiple crystalline and noncrystalline forms, with approximately half of these exhibiting polymorphism. An earlier survey of 62 drug compounds revealed a higher frequency of polymorphism, as four out of five molecules were polymorphic. Regardless of the statistical percentages, polymorphism is a widespread phenomenon and may strike all typesof compounds including salts, cocrystals, and those that are chiral and racemic

Similarly, formation of solvates is frequently encountered with organic molecules. Given the Ubiquities of water, hydrates are the most common solvates found. A survey of the Cambridge Structural Database (CSD) Version 5.26 by Motherwell and coworkers showed that approximately6.5% (6,558) of the crystal structures of organic compounds in the database (101,244) are in the hydrated form. Interestingly, pharmaceutical salts, in particular hydrochloride and sodium salts, formed hydrates more frequently than non-salts. This can be attributed to the propensity of water to bind to ionic sites. In contrast, non-salts are more prone to form solvates and polymorphs.
(**Table 1**)

Rank	Brand name	Companies	Active pharmaceutical ingredient(s)	Indication	Sales ($ in billions)	Minimum number of solid phases[b]	Reference
1	Lipitor	Pfizer, Astellas	Atorvastatin calcium	High LDL cholesterol	12.5	41	108
2	Plavix	Bristol-Myers Squibb (BMS), Sanofi Aventis	Clopidogrel bisulfate	Atherosclerosis	9.3	6	109, 110
3	Advair	GlaxoSmithKline	Fluticasone propionate Salmeterol xinafoate	Asthma	7.8	2[c] 2[d]	111, 112
4	Diovan	Novartis	Valsartan	Hypertension	6.0	10	113
5	Abilify	Otsuka, BMS	Aripiprazole	Schizophrenia	5.6	9	114
6	Nexium	Astra Zeneca	Esomeprazole magnesium	Ulcer	5.0	4	115
7	Zyprexa	Lilly	Olanzapine	Schizophrenia	4.9	25	6
8	Seroquel	Astra Zeneca, Astellas	Quetiapine fumarate	Schizophrenia	4.9	2	116
9	Crestor	Astra Zeneca, Shionoggi	Rosuvastatin calcium	High LDL cholesterol	4.7	3	117
10	Singulair	Merck	Montelukast sodium	Asthma	4.7	4	118

[a]Sales data according to Reference 119.
[b]Includes both anhydrates and solvates.
[c]Minimum number of fluticasone propionate solid phases.
[d]Minimum number of salmeterol xinafoate solid phases.

Table 2 Solid-state forms of common over-the-counter (OTC) drugs

Brand name	Active pharmaceutical ingredient	Indication	Polymorphs/solvates/hydrates	Reference
Tylenol	Acetaminophen (paracetamol)	Pain	Forms I, II, and III; monohydrate; trihydrate; dioxane hemisolvate; methanolate	120, 121
Bayer	Aspirin	Pain, arthritis	Forms I and II	122
Tagamet	Cimetidine	Ulcer	Forms A, B, C, and D; hydrated Forms M1, M2, and M3	123
Pepcid	Famotidine	Ulcer	Forms A and B	124
Advil, Motrin	Ibuprofen	Pain	Forms I and II	125, 126
Imodium	Loperamide hydrochloride	Diarrhea	Forms I, II, and III; tetrahydrate	127, 128
Claritin	Loratadine	Allergy	Forms I and II	129
Aleve	Naproxen sodium	Pain	Form 1; monohydrate; dihydrate Forms I and II; tetrahydrate; methanolate; ethanolate; 1-propanolate; 2-propanolate; 1-butanolate; isobutanolate	130, 131
Zantac	Ranitidine hydrochloride	Ulcer	Forms 1 and 2	132

There are many types of organic solvate-forming solvents including alcohols, aromatics, esters, ethers, and ketones. Nangia & Desiraju searched the CSD and elegantly showed that after applying a usage correction, the organic solvents most likely to form solvates are *N*,*N*dimethylformamide.(DMF), dimethyl sulfoxide (DMSO), and 1,4-dioxane. This is probably because all three solvents may participate in hydrogen bonding with the solute molecules. It is quite common to encounter cases in which a particular molecule is prone to form multiple solvates.

One classic example of a promiscuous solvate former is sulfathiazole, a potent antibacterial sulfonamide compound, which has been described in more than 100 solvated forms . In some Instances, the solvent molecules simply fill the channels (or cavities) and are innocuous bystanders, thereby forming iso structural solvates; in other cases the solvent molecules play an integral role in stabilizing the crystal lattice.

Variations in the solid form will most likely lead to alterations in the material's chemical and physical properties. **Figure 1** summarizes properties that may be affected in crystal polymorphs.

One of the most apparent differences in physical properties is polychromism (i.e., differentcolors). The synthetic intermediate to olanzapine, 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophene carbonitrile, also known as ROY, is a classic example of polychromism . ROY refers to the red, orange, and yellow crystals that can be crystallized. The difference in colors is a result of the conformational differences among the polymorphs .Key drug properties vital to the development of a quality drug product is the bioavailability and solid-state stability. Solubility and dissolution rate are physical characteristics that are directly related to the bioavailability. It has been reported that the solubility ratio between polymorphic

pairs is generally less than two, although in certain cases, higher ratios were observed . In the simplest form, differences in solubility are a reflection of the free energy differences between polymorphs. The most famous example of polymorphs influencing the solubility and dissolution profile of a pharmaceutical is the antiretroviral drug ritonavir (Norvir) . In 1998, a more stable, less soluble crystalline phase appeared in the formulation vehicle that resulted in dissolution failures of the soft gelatin capsules. Ultimately, the pharmaceutical product was withdrawn from the market because the manufacturing process was no longer able to reliably produce the desired polymorph. Eventually the product was reformulated with the most stable polymorph and re launched .A timeline of events involving solid-state polymorphism over the past 25 years is shown in **Figure 2**. In most of the cases, the products were recalled owing to ambiguous product performance and quality as a result of a phase conversion. There are probably many more events, most of which have not been reported in the public domain, in which crystal polymorphism has occurred and led to manufacturing troubleshooting, batch rework, and delays in project or clinical timelines.

SUMMARY POINTS

1. The existence of multiple solid phases is inevitable foremost small-molecule drugs.Knowledgeof the solid-state properties of all solid phases is necessary to judiciously select the optimal phase.

2. Solid form screening is a critical activity initially carried out at the drug discoverydevelopmentinterface. It enables the discovery of all potential crystalline phases and includes the evaluation of the solid-state properties of these phases. The phase selection process involves a cross-functional team from various scientific disciplines, as the selection of a developable phase depends on the solid-state stability, solubility, dissolution, hygroscopicity, process ability, and manufacturability of the drug substance.

3. Polymorphic control in a crystallization process requires understanding the kinetics and thermodynamics of the polymorphic system. Establishing phase diagrams or maps is beneficial in identifying thermodynamic stability regions to selectively crystallize the most stable phase.

4. Phase transitions not only are solution mediated but may also occur in the solid state as response to variations in humidity, pressure, and temperature. The solid-state behavior of the drug substance must be thoroughly investigated to understand the risks associated with process-induced stresses (e.g., heat, pressure, and shear).

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