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Review Article

Theme: Team Science and Education for Pharmaceuticals: the NIPTE Model
Guest Editors: Ajaz S. Hussain, Kenneth Morris, and Vadim J. Gurvich

Predictive and Accelerated Formulation Design Using Synchrotron Methods

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Abstract. Predictive formulation design and accelerated formulation design can lead to the discovery of useful formulations to support drug clinical studies and successful drug approval. Predictive formulation design can also lead to discovery of a path for commercialization, especially for poorly soluble drugs, when the target product profile is well defined and a "learning before doing" approach is implemented. One of the key components of predictive/accelerated formulation design is to understand and leverage the material properties of drug substance including solubility, BCS classification, polymorphs, salt formation, amorphous form, amorphous complex, and stability. In addition, utilizing synchrotron-based PDF (pair distribution function) analysis can provide important structural information for the formulation. This knowledge allows control of physical and chemical stability of the designed product. Finally, formulation design should link to process development following Quality by Design principles, and solid-state chemistry should play a critical role in many of the steps required to achieve Quality by Design, which can lead to successful product development.

KEY WORDS: formulation; quality; synchrotron; x-ray; accelerated.

INTRODUCTION

Is it possible to predict the best formulation for a drug? NO! However, this review is intended to explore strategies to assist in the design of a formulation utilizing approaches that can accelerate the discovery of useful formulations. This review also focuses on solid oral formulations of poorly soluble drugs. This is because poorly soluble drugs constitute as much as 60% of drugs under development. This review will especially focus on the utilization of synchrotron X-ray studies to assist in formulation design and the strategy of utilizing amorphous complexes to ensure high exposure in preclinical studies.

To develop a predictive/accelerated formulation strategy for a poorly soluble solid oral drug requires the establishment of the following steps:

1. Define the target product profile
2. Learn before doing
3. Leverage material properties of the drug substance
4. Prepare amorphous complexes
5. Utilize predictive tools and synchrotron X-ray studies to anticipate/predict stability and provide structural information
6. Link to process development with Quality-By-Design principles again using synchrotron X-ray studies to provide sameness analysis of clinical supplies

This review addresses approaches to gaining the knowledge required to understand the material properties of the drug substance and model formulation design studies that would lead to a well-defined strategy for formulation development.

TARGET PRODUCT PROFILE

The goal of drug formulation is to develop a quality drug product to meet the defined target product profile, which describes a high-level summary of product concepts and forms the basis of product design.

The target product profile (TPP) for a drug was originally proposed in a 1997 FDA document as a platform to facilitate the discussions about a drug development program between the product sponsor and the FDA in terms of labeling concepts. The TPP is gradually evolving into a planning tool and serves as a strategy document to guide drug clinical development and product development in the pharmaceutical industry. The TPP bears the strategic thinking of beginning with the goal in mind and defines the overall intent

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of a drug development program. The TPP is commonly organized according to the key sections in the intended drug labeling as listed in Table I.

The target product profile is often developed through a substantial evaluation of the pharmacology, pharmacokinetics, safety profile, physical and chemical properties, and the patient group. The poor solubility and the need for amorphous complexes are identified during the establishment of the target product profile. In addition to the quality attributes and desired features for a drug product, the sponsor should also evaluate the commercial viability including the following assessment:

- Market analysis
- Cost of goods
- Target price
- Commercial strategy

The TPP is also critical to the strategic focus of the development goals for the drug, usually also as major milestones of developing a drug, including efficacy, safety, drug dosage form and delivery, and cost.

The target product profile should evolve as the newly obtained clinical information is gathered, while significant modification should be carefully evaluated since it may significantly shift development paradigm and timeline. For example, change from an oral dosage form to other routes of administration, due to poor oral bioavailability, possibly leads to a total restart of formulation and process development. In comparison, readjusting of dose strength based on early clinical studies only results in a certain degree of change in formulation composition while the manufacturing equipment train and process can stay the same.

LEARNING BEFORE DOING

In many respects, drug product development, including formulation design and development, are a learning process. The learning not only leads to a full understanding of the goal, the target product profile, but also to knowledge about the materials and the processes required to make the product.

Table I. Sections for the Target Product Profile of a Drug

Section
Indications and usage
Dosage and administration
Dosage forms and strengths
Contraindication
Warnings and precaution
Adverse reactions
Drug interactions
Use in specific populations
Drug abuse and dependence
Overdosage
Description
Clinical pharmacology
Nonclinical toxicology
Clinical studies
References
How supplied/storage and handling
Patient counseling information

Pisano, who carried out an extensive study of the drug development process, described the development process as a learning process since knowledge of the molecule and its properties must be gathered in order to develop a drug product (1). Importantly, formulation design starts with an analysis of the molecular structure of the drug. Of particular importance is knowledge of the structure, the functional groups, the solubility, the octanol-water partition coefficient, the molecular weight, the ionization coefficient, the permeability, the chemical stability, and the solid-state properties of the drug. This approach, termed "Leaning before Doing" by Pisano was suggested to be the best way to do drug development, which is also applicable to formulation design and development.

Pisano's research showed that doing it right the first time is the greatest single factor in mitigating risks and reducing time to market. Specifically, learning before doing (LbD) is approached by gaining the following:

- Knowledge of the system using theory, algorithms, and if possible computer-aided simulations
- Knowledge of the underlying causal variables and their relationship to performance especially as they relate to solid-state chemistry
- Knowledge of the future manufacturing environment and the new variables introduced by that environment
- Knowledge of how those variables affect process performance and behavior

Pisano showed that LbD enhances performance and productivity.

Under the traditional approach, formulation development is empirical and random. It focuses on taking various lots of API and relies on the preparation of numerous prototype formulations, which are tested for quality, stability, and pharmacokinetics. In many cases, additional runs of optimization are needed to obtain an appropriate formulation to support clinical development, regulatory approval, and commercialization. An LbD strategy puts emphasis on the design phase, learning by thinking or modeling, instead of depending fully on the execution of experiments and data interpretation, *i.e.*, the development phase. The LbD approach uses simplified formulations and focuses on formulation design by using solid-state chemistry. In the case of poorly soluble compounds, utilizing amorphous complexes to increase exposure is recommended. A drug powder with desired solid-state properties, such as improved solubility and good flowability, is placed in a capsule, if possible. Multivariate experiments guided by knowledge of solid-state chemistry are used to find the solid form/complex with the best properties. Multivariate experiments are also used to control the formation of that solid form/complex in the last step of API synthesis using crystallization/spray drying/evaporation/ *etc.* and during the drug manufacturing processes. The LbD approach prefers creating the solution upfront instead of solving problems in real time. For example, to design a formulation for a poorly soluble compound, modeling by using a simulation tool such as GastroPlus or calculation of the dose number, per LbD approach, would indicate that the

drug product may have a solubility-limit or dissolution-limited absorption. This would dictate the selection of an amorphous formulation approach. LbD should lead to more efficient formulation development compared to the empirical approach relying on empirical experimental results.

MATERIAL PROPERTIES OF THE DRUG SUBSTANCE

Knowledge of the material properties of the drug substance is perhaps the most important factor in development, which forms the basis of LbD. Understanding these properties at the molecular level keys the strategy for the design of the amorphous complex to meet the target product profile.

First, it is important to determine the drug solubility and then the various possible solid forms of the drug substance. These can be determined by utilizing a polymorph screen, a salt screen, an amorphous solid dispersion screen, or an amorphous complex study. Next, the polymers and other components of the amorphous complex are selected. Finally, a few trial formulations are developed and analyzed by dissolution and synchrotron X-ray pair distribution function (PDF) methods to provide structural information.

SOLUBILITY

It is possible to develop a general prediction of solubility, although there are numerous exceptions. Furthermore, solubility prediction typically requires input of measured parameters such as logP, the octanol/water partition coefficient, reflecting lipophilicity and melting point, and indicating the crystal lattice energy. Prediction of drug solubility begins with Yalkowsky's seminal book, where a general solubility equation was developed (2). Utilizing this equation requires measurement of the logP, the octanol/water partition coefficient, and the melting point of the drug in degrees Celsius. In some cases, it may be faster to experimentally estimate the solubility and proceed to develop the amorphous complex formulation. It is helpful to do a small solubility screen to discover solvents that the drug and the complex formers are soluble in to aid in preparation of the amorphous complex.

BIOPHARMACEUTICAL CLASSIFICATION SYSTEM AND DOSE NUMBER

Amidon, in his ground-breaking papers, has outlined the concepts of the Biopharmaceutical Classification System (BCS) and dose number (3). Knowledge of these two factors plays an important role in strategies for formulation design. The BCS divides drug substances into four classes as described in Table II. Of particular interest for formulation design is BCS class II. For this class, the formulation generally determines the bioavailability because the drugs in this class are poorly soluble and highly permeable. This means that the solubility/dissolution of the drug is the rate determining step in the absorption, since absorption or permeability is high. Ku demonstrated that BCS can serve as a useful tool for decision-making in early product development of new drugs to support clinical studies (4).

Amidon and coworkers defined the dose number (D_o = mass of dose/solubility × Volume of GI tract) as the number of stomach volumes required to dissolve a specific dose (3). When the dose number is greater than 1, there is a risk of incomplete solubilization of the drug in the GI tract and some solubility enhancement strategies will typically be required for the most successful formulations.

AMORPHOUS COMPLEX STUDY

In most cases, the material properties of crystalline polymorphs are such that alternative solid forms are needed. This is because many of the solid forms for most drugs under development have low solubilities and a dose number greater than 1 so that they will likely have poor bioavailability.

Figure 1 shows the strategy for amorphous complex formation and early development. The goal is to obtain a complex that has high bioavailability as quickly as possible in order to move into toxicology studies quickly. As shown in this figure, the first step is to determine the initial API properties of the solid provided. Next is complex formation based on the studies outlined below. The basis of this idea is that most compounds under development are poorly soluble and it is fastest and most direct to immediately make amorphous complexes. Salts would fall into this category and could be crystalline. Next is a solubility study of the complex. This study will indicate the degree of solubility enhancement achieved by the complex. Then, a structural study of the complex is carried out. The structural information is important for interpreting the stability and dissolution data. Finally, if further information is desired during this early development stage, an optional PK study in animals can be carried out.

It is important to consider the possibility of using the amorphous complex formulation of the API, which usually can produce high levels of supersaturation in water relative to that of the crystal, thus having the potential for greater dissolution and bioavailability. For purposes of this review, an amorphous complex is described as any two-component mixture of drug and excipient that is amorphous and contains a complex. Amorphous solid dispersions of drug and polymer fall under the category of amorphous complexes but special emphasis is placed on mixtures where the drug is specifically complexed to the excipient forming a complex. In this review, we also consider amorphous salts formed with polymers and co-amorphous systems with multiple components as amorphous complexes. To form amorphous complexes, drugs are generally combined with various polymers and additives to produce miscible mixtures known as amorphous complexes. Amorphous complexes are advantageous over amorphous mixtures because they have less tendency to crystallize. This term, amorphous complexes, is derived from the original publications of Higuchi and coworkers on complexes of drugs and the definition of the FDA for an API (5). Higuchi introduced solid complexes many years ago as a means of improving properties of drugs. The code of federal regulations defines an active moiety as "the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance." In this regard, salts as well as complexes meet the

Table II. Biopharmaceutics Classification System

BCS class	Permeability	Solubility	Absorption rate control step	Formulation strategy
Class I	High	High	Gastric emptying	Simple capsule or tablet
Class II	High	Low	Dissolution	Micronized API and surfactant, nanoparticle technology, solid dispersion, liquid- or semisolid-filled capsule
Class III	Low	High	Permeability	Simple capsule or tablet, absorption enhancer
Class IV	Low	Low	Case by case	Combination of BCS class II and absorption enhancer

definition of an active moiety. Enhancing solubility, dissolution rate, and bioavailability of the API provides a drug substance that can be simply and easily developed. The goal of an amorphous complex study is to prepare amorphous complexes using a variety of methods utilizing polymers or other excipients to produce the complex that is most soluble and most stable. Preparation methods used include flash evaporation of a mixture of drug substance, polymers, and other components from a variety of solvents under several conditions including evaporation and spray drying. Solvent-based methods are advantageous since they can be easily scaled up using spray drying and can be easily studied using "lab on a drop" synchrotron-based analytical methods.

Amorphous complexes have recently seen a resurgence of interest. Laitinen *et al.* described co-amorphous systems containing a drug and multiple low molecular weight materials (6). These formulations are described as supersaturating drug delivery systems. They suggested that these systems could inhibit crystallization/precipitation of poorly soluble APIs. They specifically described co-amorphous salts as a type of system that is supersaturating. Chaven *et al.* described a product development approach to amorphous complexes (7). Again, they described amorphous systems prepared from the drug and two or more small molecules. They suggested that these multicomponent systems would overcome the miscibility problems of drug polymer complexes. They further defined co-amorphous systems as systems with small molecules only. Kasten and coworkers described a screen for amorphous complexes of several poorly soluble drugs including indomethacin, mebendazole, and carbamazepine (8). In this study, they used amino acids as the amorphous complex formers. They co-milled 20 amino acids with various drugs and measured the decrease in crystallinity using conventional X-ray methods. They suggested that the neutral amino acids were good first choices in some cases and that basic amino acids were good choices for acidic drug perhaps because they formed salts or weak complexes. Dengale and coworkers summarized recent advances in the co-amorphous field, again defining co-amorphous formulations as formulations that contain the drug and two other small molecules (9). They suggested that the structure of this blend was a single phase containing all three molecules. They also suggested that this approach can overcome some of the issues with solubility of drugs in amorphous polymers in conventional amorphous dispersions. Many multicomponent small molecule systems had low glass transition temperatures suggesting these systems can have substantial molecular mobility. Interestingly, tryptophan, with its high glass transition temperature was especially useful in stabilizing these multicomponent systems. These workers also emphasized the intermolecular interactions that exist in these systems. Finally, they showed dissolution data for lurasidone HCl saccharin compared to crystalline lurasidone showing a 5.6-fold increase in dissolution. They also showed ritonavir-indomethacin system with a 4.3 increase in dissolution. Of course, these increases were in a specific dissolution medium (9). Our perspective suggests that amorphous complexes can include drug

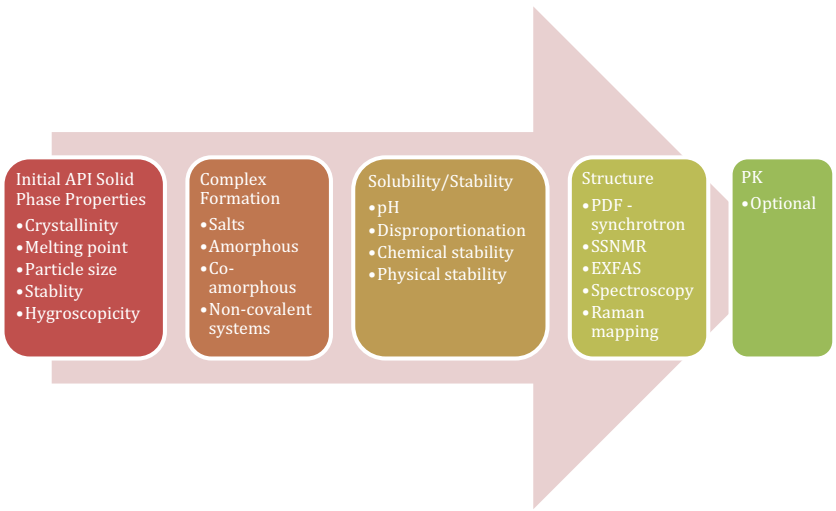

Fig. 1. Amorphous complex strategy for accelerated formulation development

and polymer and small molecules such as the well-known commercial product—ritonavir.

In some cases, amorphous complexes could even extend to solid self-emulsifying drug delivery system (SEDDS) formulations. A typical SEDDS study begins with a determination of the solubility of the drug in a range of SEDDS-related solvents or surfactants: distilled water, dehydrated ethanol USP, polyethylene glycol 400, dimethylsulfoxide, cremophor EL, polysorbate 80, polyethylene glycol, propylene glycol, glycerin, vitamin E polyethylene glycol 1000 succinate, medium chain triglycerides (*e.g.*, miglyol 810), oleic acid, and other acids including fumaric acid, Labrasil, Gelucire 44/14, and possibly other compounds. Acidic excipients such as oleic acid are of particular interest for basic drugs since they would be expected to form salts with enhanced solubility. Since solubility in solvent mixtures can be quite different from a linear extrapolation of the solubility of the pure compounds, some mixtures need to be investigated. Based on the solubility data, the solubility in SEDDS type formulas composed of (1) water miscible solvent (*e.g.*, dehydrated ethanol, (2) non-ionic surfactant (*e.g.*, polysorbate 80), and (3) medium chain triglyceride need to be investigated.

For solid SEDDS formulations, a solid carrier like dextran should be evaluated following the procedures of Yi et al (10). In this study, the nifedipine SEDDS formulation suspended in dextran was amorphous by X-ray diffraction and showed two to six times higher blood levels than conventional nifedipine tablets in rabbits. The solid carrier Aerosil 2000 should also be evaluated following the procedures of Balakrishnan et al. (11). In this study, they first determined the formulation by construction a ternary phase diagram with labrasol, labrafilm, and a co-surfactant capryol-90. This information provided the best ratio of components to mix with Aerosil 200 and spray-dry to form a solid SEDDS formulation. The spray-dried solid SEDDS formulation showed two times higher blood levels in rats and a five times faster dissolution rate. Additional polymeric solid carriers including celluloses (such as HPMC and HPMCP) and methacrylates may also be investigated. These solid formulations can be manufactured using laboratory-scale spray dryers or evaporation. In these studies, the solution of drug and carrier is spray-dried and further dried under vacuum with or without mild heat, if required. Bulk density and excipient compatibility studies for powder-filled capsule formulation can also be carried out. The trial formulations should also be evaluated for stability/interaction (appearance, assay, and impurities/degradants) at 2°–8°C, 25°C 60% RH, and 40°C /75% RH for 2, 4, and 8 weeks.

One of the best examples of amorphous complexes is the ritonavir product currently on the market. This product is amorphous and contains ritonavir, copovidone, anhydrous dibasic calcium phosphate, sorbitan monolaurate, colloidal silicon dioxide, and sodium stearyl fumarate. The paper by Tho shows that only the formulations containing both copovidone and sorbitan monolaurate formed nanosuspensions in solution (12,13). Thus, the solid ritonavir formulation appears to contain an amorphous complex of ritonavir, polymer, and surfactant.

SYNCHROTRON STRUCTURAL STUDIES OF AMORPHOUS COMPLEXES

In recent years, a powerful new method of analysis of amorphous complexes has emerged—synchrotron pair distribution function (PDF) analysis. In this analytical approach, the amorphous X-ray pattern is transformed using a Fourier transform algorithm to produce a pattern that shows all atom-atom distances in the amorphous complex. This method requires a synchrotron X-ray source because of its intensity and short wavelength. Studies by PANalytical have shown that conventional X-ray sources produce artifacts when analyzed using the PDF method.

In our laboratory, we have collaborated with Dr. Chris Benmore of Argonne National Laboratory to utilize the PDF method to determine the structure of amorphous complexes and we have utilized this method to determine sameness of formulations prepared in different ways.

To illustrate some of the studies we have conducted, Fig. 2 shows the PDF and difference PDF of four amorphous drugs. The difference PDF is determined by subtracting the calculated PDF of the intramolecular contacts of the pure drug (*i.e.*, atom-atom distances within a drug molecule) calculated from the single crystal X-ray structure from the PDF of the amorphous drug. The difference PDF remaining shows atom-atom intermolecular distances in the material, or in other words, atom-atom distances between neighboring drug molecules. The arrows in Fig. 2 designate nearest neighbor and next nearest neighbor contacts in the material. Figure 3 illustrates how such contacts can arise from a hypothetical amorphous material containing spheres.

In an ideal amorphous complex, individual molecules of the API should be separated by other components. If API molecules are not next to each other, crystallization will be inhibited. To illustrate how PDF analysis can be used to predict the stability of various amorphous complexes, we applied the synchrotron pair distribution function method to an amorphous material containing the base lapatinib and the acidic polymer HPMCP (hydroxypropylmethyl cellulose phthalate). We utilized the neutral polymer HPMC (hydroxypropylmethyl cellulose) as a control. For this study, we prepared various mixtures of drug and polymer and utilized the difference PDF method by subtracting the intramolecular PDF from lapatinib from the PDF of the lapatinib-HPMCP complex. The PDF of the HPMC or HPMCP was also removed, thereby leaving only any detectable intermolecular lapatinib responses. Figure 4 shows the results of this study. In the left panel are the difference PDF patterns of HPMC-lapatinib complex at various lapatinib amounts. The 3:1 polymer to drug pattern contains only nearest neighbor and next nearest neighbor contacts and the 1:3 (1 part drug: 3 parts polymer) drug loading complex contains only nearest neighbor contacts. Therefore, in all the lapatinib:HPMC complexes, intermolecular lapatinib interactions are detected, indicating that there are neighboring lapatinib molecules. In the right panel are the difference PDF patterns of HPMCP-lapatinib complexes at the same polymer:lapatinib amounts. The 1:1 (1 part drug: 1 parts polymer) drug loading complex contains only nearest neighbor contacts. The 1:3 (1 part drug: 3 parts polymer) drug loading complex contains no nearest neighbor contacts. Therefore, the HPMCP polymer effectively isolated the lapatinib molecules from one another, thus eliminating all domains of pure drug from the complex. Our interpretation of this data is that the salt formation of the drug with the polymer eliminates all drug-drug interactions. Importantly, this complex (1 part drug: 3 parts polymer) is the only

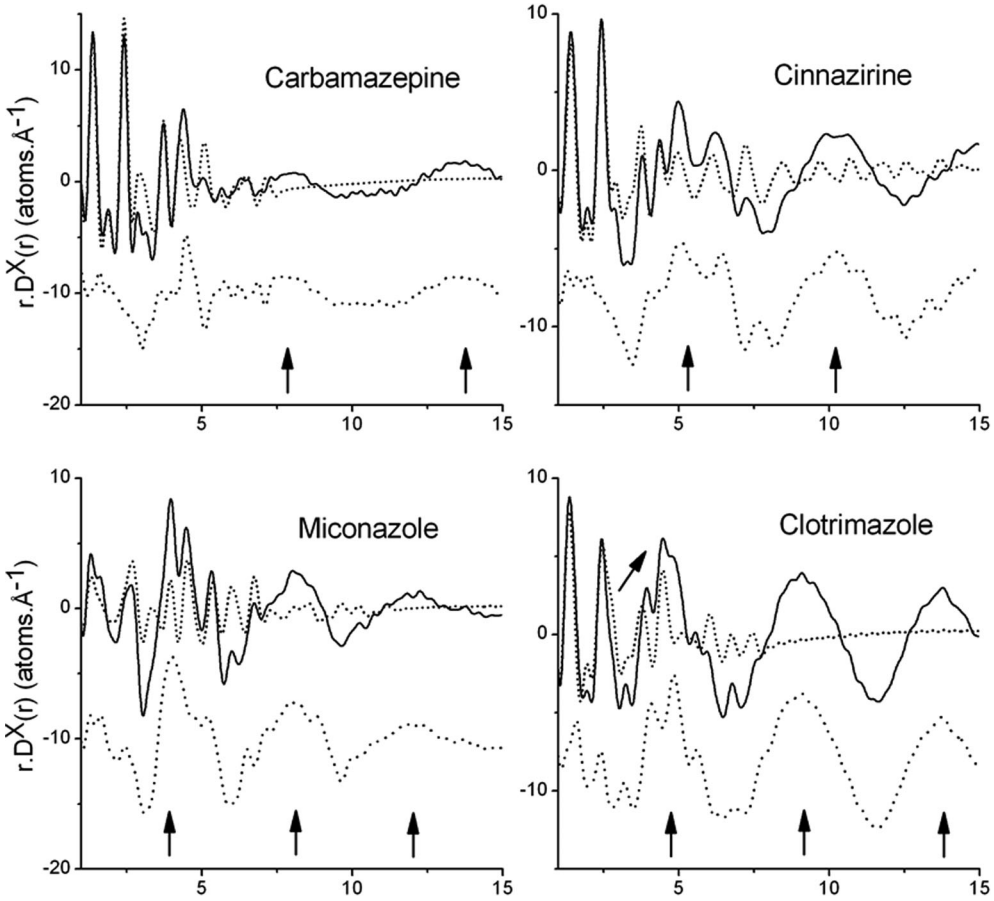

Fig. 2. PDF structure analysis of pure amorphous drugs showing domains containing nearest neighbor, next nearest neighbor, and next next nearest neighbor contacts

complex that shows good stability when exposed to 40°C/75% RH in an open container. Therefore, it is possible to use PDF analysis to determine if domains of drug are present in a complex, which would suggest the complex might be less stable over time. Amorphous complexes without domains are miscible and expected to be more stable towards crystallization than complexes containing domains.

The fact that salt formation only occurs in amorphous systems with low drug loading is also consistent with solid-state NMR studies which also showed that only the low drug loading systems contained predominately protonated amine (salt) groups.

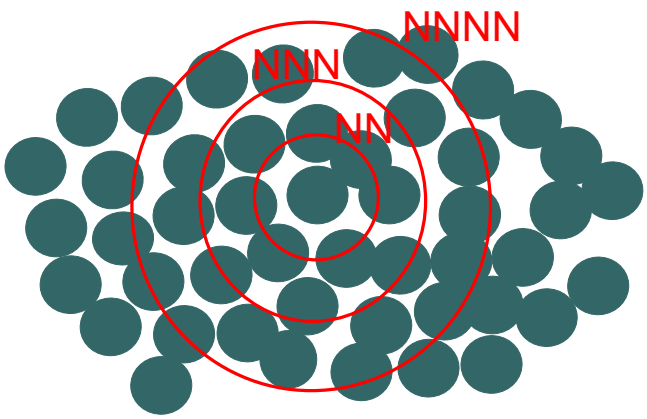

Fig. 3. Hypothetical amorphous material showing nearest neighbor, next nearest neighbor, and next next nearest neighbor contacts

These results suggest that PDF analysis of the structure of amorphous materials is among the most powerful available methods since it provides atom-atom distances. Using difference PDF allows even more sensitive analysis. SSNMR and IR methods have been used for structural analysis of amorphous materials and are powerful methods but do not provide atom-atom distances or angstrom resolution. Put another way, PDF X-ray methods have potentially more information just as X-ray methods have potentially more information than SSNMR or other spectroscopic methods for polymorphs and crystalline solids. One of the most exiting aspects of the PDF method is that it provides information on domains down to the angstrom level. Both SSNMR and IR spectra of noncrystalline materials show broad peaks. SSNMR relaxation time analysis provides information on domains but the resolution is about 10 times larger than PDF methods which allow analysis of domains down to the angstrom level.

LAB ON A DROP

Synchrotron methods provide the opportunity to carry out X-ray studies on a levitated drop of solution (14). Levitation is accomplished using acoustic waves. Studies of pure drug solutions levitated and analyzed both before and after evaporation by synchrotron X-rays allowed determination of crystallization and also PDF patterns. Further, it is

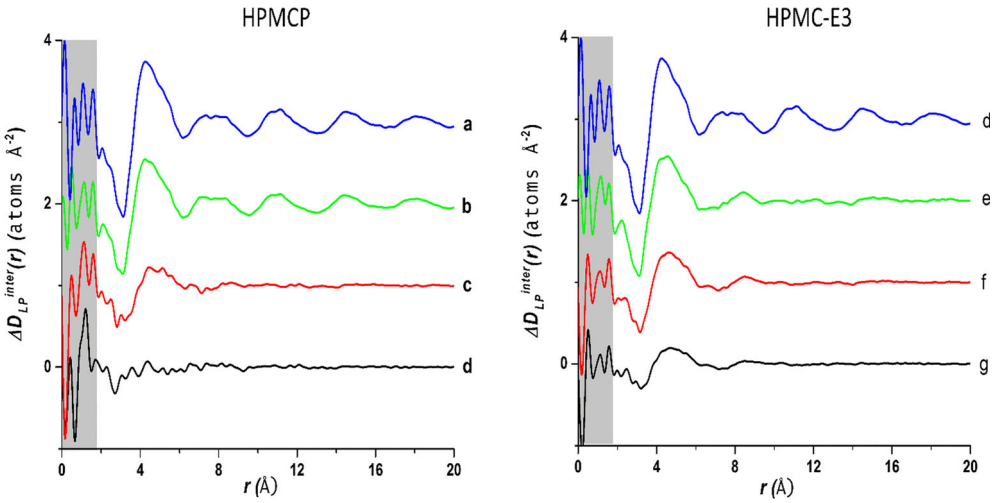

Fig. 4. PDF of HPMC-lapatinib and HPMCP-lapatinib showing that only the 1:3 lapatinib:HPMCP dispersion showing no domains

possible to screen for amorphous complexes by levitating drops of solution containing drug and polymer. Volatile solvents evaporate in about 15 min to form a solid particle that can be analyzed using PDF. A levitated drop screen uses only a small amount of material (on the order of 0.1 mg of drug per drop) and typically can be completed in about 30 min. Therefore, multiple analyses (or amorphous screens) can be conducted in a day or two of beam time. Other analytical studies can also be carried out on drops including infrared analysis. In cases where only small amounts of material are available or if time is of the essence, this strategy is the way to proceed.

SAMENESS STUDIES USING SYNCHROTRON X-RAYS

PDF methods also provide a way to determine sameness of amorphous systems prepared in different ways:

1. Determine the sameness of amorphous dispersions prepared by spray drying and hot melt extrusion.
2. Determine the sameness of API samples prepared under different milling, crystallization, or drying conditions

These studies are possible because the PDF provides information on the miscibility of the system and the presence of domains. For API samples prepared in different ways, the PDF pattern reflects the degree of disorder in the material.

We have also used PDF methods to provide information on the structures of liquid crystals, and Professor Simon Billinge, one of our collaborators, has used synchrotron-based methods to analyze nanoparticles (15). All of these methods provide important regulatory information including the sameness of different trial formulations and clinical trial lots.

FORMULATION DESIGN BASED ON INFORMATION SOURCES

Formulation design is possible utilizing information from on-line sources like Drug Bank and software packages such as GastroPlus (16).

Drug Bank provides detailed cheminformatics on a number of factors that must be determined to design a formulation. Of particular interest is the chemical structure from which it is possible to derive the number of rotatable bonds, the number of hydrogen bond donors and acceptors, the molecular weight, and experimental and predicted properties including logP, p*K*a, rule of 5, and solubility. With this information, it is possible to determine what type of formulation should be designed. For example, itraconazole has a water solubility of 9 μg/ml and a very high logP. It does not pass the Lipinski rule of 5. It has a relatively low p*K*a of 3.92 suggesting salt formation could be difficult. Thus, a pharmaceutical scientist would conclude that special measures are required to design a formulation of this antifungal compound.

GastroPlus is a software package that simulates drug absorption, pharmacokinetics, and pharmacodynamics in humans and animals, utilizing the drug's physical and chemical properties such as p*K*a, logP, solubility, permeability, and pharmacokinetic attributes, derived from *in vitro* measurement or *in silico* calculation.

ADDRESSING STABILITY IN FORMULATION DESIGN—PHYSICAL TRANSFORMATIONS BETWEEN SOLID FORMS

Figure 5 shows the dissolution profiles of the different crystal forms of furosemide in buffer solution at various pH values at 37°C (17), while Fig. 6 shows the concentration *versus* time plots for theophylline anhydrous and hydrated crystal forms (18). In Fig. 5, there is no conversion to the most stable crystal form during the experiment. In contrast, in Fig. 6, the less stable anhydrate converts to the hydrate during the experiment providing unequivocal proof that the hydrate is more stable (less soluble) than the anhydrate. In these examples, it is obvious which form of theophylline is the less soluble. Under these conditions, this form will never convert to the other, and can therefore be referred to as the thermodynamically more stable form.

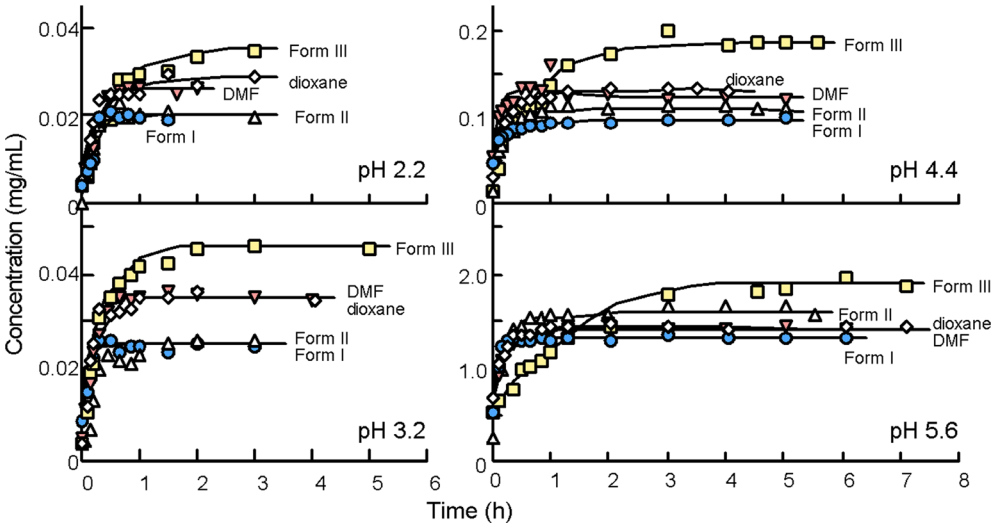

Fig. 5. Dissolution profiles of furosemide forms

PREDICT PROCESS INDUCED DISORDER EARLY

Processing and manufacturing of solid forms can lead to process induced disorder and/or amorphization, which can lead to unwanted solid-state transformations and reactions. X-ray and synchrotron X-ray studies looking at linewidth can provide important information on process-induced disorder. Chen and others studied crystals with two different mechanical properties and then induced various defects by altering conditions during milling and compacting. They then evaluated each sample with synchrotron PDF analysis and were able to determine which processing conditions produced fewer defects for each crystal type (19). Using this approach is an excellent example of LbD as it provides valuable information that can be used prior to determination of the manufacturing process.

QUALITY BY DESIGN

As shown in Fig. 6, product design is the first step in Quality by Design. In this step, the product is designed with patient needs in mind. For example, for an oral dosage form of a poorly soluble drug, a product that is able to dissolve in the intestinal tract must be designed. For lopinavir/ritonavir, an important protease inhibitor, for example, a solid dosage form that was stable and could be easily handled by patients with HIV, was designed. Initially, a gel-cap containing ritonavir was developed but this dosage form had to be stored at refrigerator temperatures due to instability of the drug. Later, a tablet which was stable at ambient temperatures was developed using amorphous lopinavir/ritonavir.

Product design involves selecting the right polymorph/solid form, the right dosage form, and the correct components, and involves designing the product with the desired stability. Product design also requires an understanding of the potential sources of variability, and how to control variability. Often, product design can be predicted and achieved using small-scale experiments especially if the focus is on understanding the solid-state chemistry including which excipients need to be inert and not interacting. For lopinavir/ritonavir, an amorphous dispersion with a high glass transition temperature achieved the desired stability and avoided the need to store the product in the refrigerator.

Next is process design. A process for making the designed product needs to be developed. This process must first work at minimum with an acceptable level of variability on a small scale to prepare clinical supplies. Every effort should be made to select excipients that do not influence the variability of the product. An understanding of how the process affects critical quality attributes must be developed. Also, process controls must be initiated. The overall goal is to reduce variability of the critical quality attributes in this step. If possible, a design space should begin to be developed. The design space is usually fully developed near commercialization but an early design space can be approached even at this stage. For example, if a melt extrusion process is being used to make an amorphous product, various parameters need to be controlled including temperatures, extrusion speed, temperature of cooling, and milling speed.

In some cases, processes and product are linked. Dockerty, Kogulas, and Horspool reviewed and defined Pharmaceutical Material Science (20). They suggested that this area is focused on streamlined selection of active

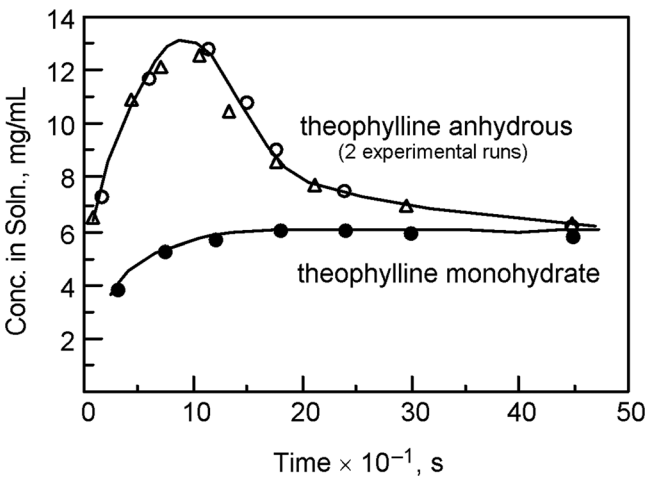

Fig. 6. Dissolution profiles of anhydrous theophylline and theophylline monohydrate

Fig. 7. Quality by Design (QbD) wheel modified to illustrate the integration of product development life cycle

pharmaceutical ingredient (API), solid forms, and reduced numbers of complex formulations, rapid drug product design, and intellectual property (IP) creation. They also indicated that the particle engineering toolbox contains, in addition to conventional crystallization methods, five processes that can produce unique solid materials: (1) supercritical fluid technologies, (2) mixing intensification process technologies, (3) segmented flow tubular reactors, (4) droplet to particle methods, and (5) solution atomization sonocrystallization technologies.

Next, the performance of the process is monitored (inner portion at 9 o'clock in Fig. 7). Initial monitoring may include both on-line/in-line instruments and off-line measurements. For example, a crystallization process can be monitored on-line/in-line using Raman (40) or infrared spectroscopy, UV/Vis spectrometry, and *in situ* particle size analysis (21). Presumably, the lopinavir/ritonavir extrusion process is monitored by following temperatures, extrusion speed, temperature of cooling, and milling speed. Additionally, it is likely that X-ray diffraction is used to make sure the product is amorphous. The T_g can be determined using DSC. Finally, the product performance is monitored by measuring dissolution rates and the blood levels in animals and humans (toxicokinetics and pharmacokinetics). Additionally, an IVIVC (*in-vitro in-vivo* correlation) dissolution test may be developed to provide a laboratory method to obtain a preliminary measurement of product performance. The product performance must show low variability and the process must be validated to the extent that it is reasonably safeguarded from sources of variability.

ACCELERATED DEVELOPMENT

The lab on a drop methods and synchrotron methods enable very rapid development. This fits in very well with an accelerated development program. The fIND (fast to IND) program outlines one such method (22). This program develops drugs (*e.g.*, rare disease drugs) from structure on paper to the start of clinical trials in 75 weeks. The diagram shown in Fig. 8 shows this plan. As shown in this figure, the first lot of the API (produced by 10 weeks) is used in the second step which is the determination of the solid formulation. This latter step typically requires about 20 weeks to complete and produces the amorphous complex described above. In some cases, the lab on a drop method can be used to accelerate the studies, especially if material is limited. Once the solid form is discovered, it is put directly into the preclinical toxicology studies. The drug product studies follow, leading to clinical supplies for the IND trial.

Although access to a beamline is perceived to be difficult, by analogy, the protein crystallography community has developed excellent ways to access the beamline. There are even some beamlines dedicated to protein data collection and owned by a group of companies. Currently, there are two beamlines at Argonne National Laboratories that allow PDF and Brookhaven National laboratory has just opened a new beamline with good access for PDF. There are also several beamlines in Europe that allow collection of good data for PDF. Unfortunately, X-ray data collected on conventional instruments sometimes contains artifacts and cannot be reliably used, currently.

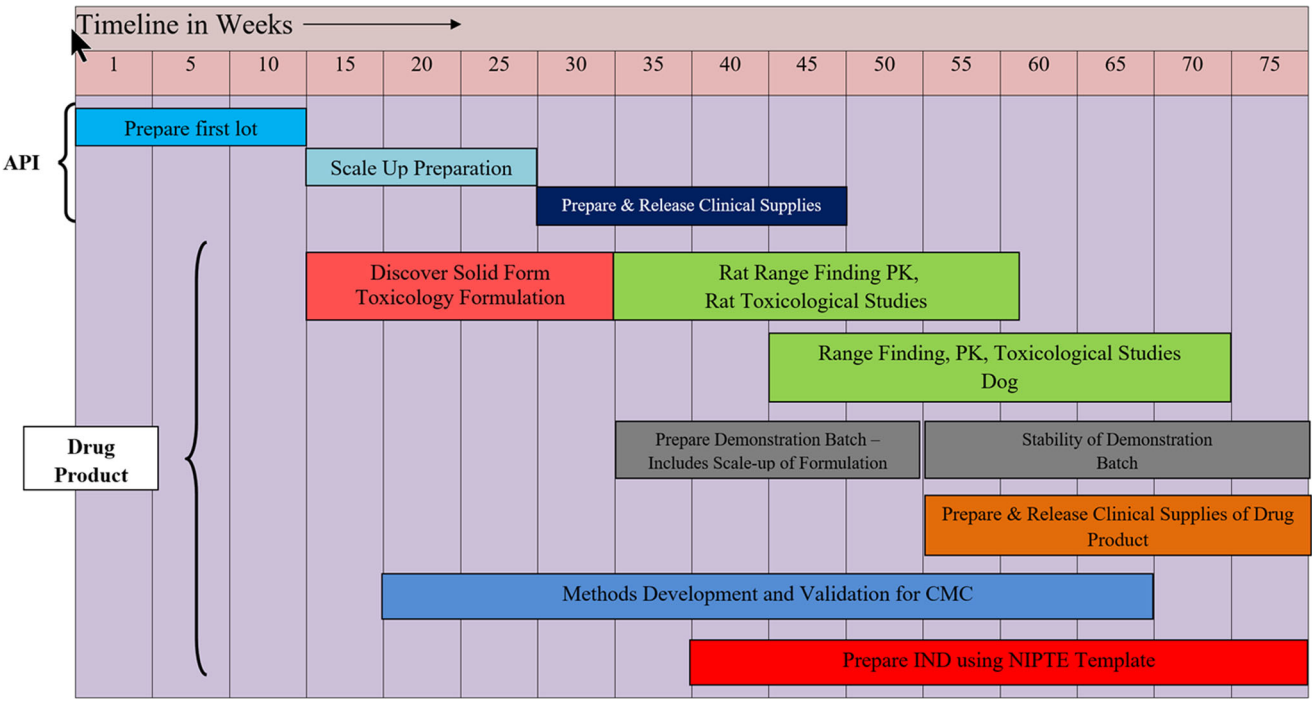

Fig. 8. fIND accelerated development strategy for filing an IND

CONCLUSION

In this review, we have tried to show how formulation design can be accomplished rapidly using both knowledge of the system and synchrotron methods. We have also tried to show how knowledge of the structure of the system can lead to quality by design. As time goes on, many advances in the areas highlighted by this review are expected.

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