Comparative Assessment of Spray Drying and Hot Melt Extrusion as Manufacturing Processes for Amorphous Solid Dispersions

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Hibreniguss Terefe, PhD
V.P. Research & Development
Isaac Ghebre-Sellassie

- ExxPharma Therapeutics LLC

Amorphous solid dispersions of poorly soluble drug substances were prepared using a variety of technologies, the most popular of which are spray drying and hot melt extrusion. As a result, a majority of the oral dosage forms of poorly soluble drug substances in the market consist of amorphous solid dispersions manufactured by spray drying or melt extrusion. In this and subsequent articles, an attempt will be made to compare and contrast the two technologies, including their pros and cons, in five parts, i.e., (1) Historical Perspective, (2) Manufacturing Processing Conditions, (3) Scale up and Equipment Considerations, (4) Quality, Cost and Regulatory Implications, and (5) Downstream Process Interfacing.

Part I: Historical Perspective

Amorphous Solid Dispersions

Oral dosage forms are the most preferred drug delivery systems for many reasons including ease of administration, high patient compliance, handling convenience, relative product stability, dosage form flexibility and cost considerations. While development of dosage forms of many drug substances is straightforward, development of poorly soluble drug substances is challenging, particularly as related to bioavailability. Oral bioavailability of poorly soluble drug substances depends on several factors, such as solubility, permeability, first-pass metabolism, pre-systemic metabolism and susceptibility to efflux mechanisms. The most prominent causes of poor bioavailability are poor solubility and low permeability. The advent of high throughput screening tools in drug discovery has led to the emergence of increasingly lipophilic and high molecular weight compounds. Approximately 90% of new molecular entities coming out of companies' pipelines are poorly soluble, poorly permeable or both. Similarly, about 40% of marketed products, which initially were developed and approved based on unoptimized formulations or alternative dosage forms, have low solubility, low permeability or both.[1-3] As a result, formulation development of poorly soluble drug substances has been a persistent problem that continues to negatively impact the clinical viability of many promising molecules, thereby potentially preventing or delaying important life-saving medicines from reaching the patients.

To address the bioavailability issues, many pharmaceutical companies have developed or acquired various solubility enhancement technologies that employ different formulation approaches, such as particle size reduction (e.g., micronization and nano-milling), salts, co-crystals, self-emulsifying excipients and solid dispersions to enhance the solubility of poorly soluble drug substances.[4] Solid dispersions have many advantages over other solubility enhancement methods, particularly with respect to manufacturing efficiency. These advantages, in turn, have enabled solid dispersions to become the most preferred formulation components of oral dosage forms of poorly soluble drug substances whether the drugs are highly crystalline or lipophilic.

A solid dispersion can be defined as a dispersion of one or more active ingredients in an inert polymeric matrix in the solid state which is prepared by a melt or fusion method, a solvent method or a combination of the fusion and solvent methods.[5] In 1961 Sekiguchi and Obi prepared two types of solid dispersions containing crystalline polymeric carriers: eutectic mixtures, where the drug was crystalline, and monotectic mixtures, where the drug was amorphous.6 In the 1970's, crystalline polymeric matrices were replaced by amorphous polymeric carriers to generate three types of solid dispersions based on the physical state of the drug substance in the matrix; (a) glassy suspension if the dispersed drug exists in an amorphous state, (b) crystalline suspension if the drug exists as fine crystalline particles and (c) glassy solution if the drug exists as a molecular dispersion in the matrix. During the past three decades or so, glassy suspensions and glassy solutions, collectively known as amorphous solid dispersions, have become the most widely used solubility enhancement tools during the development and manufacturing of poorly soluble drug substances.

A review of the literature indicates that around 3451 articles and 1076 patent applications that deal with the development and manufacturing of solid dispersions were published between 1980 and 2015. The number of published articles and patent applications increased annually with more than 70% of them published between 2005 and 2015.[7] The numbers illustrate that amorphous solid dispersions are increasingly becoming critical components of dosage forms of poorly soluble and poorly bioavailable drug substances.

Amorphous solid dispersions (ASDs) manufacturing processes are: (a) solvent-based heat-free processes, which include spray drying, spray coating, coprecipitation, freeze drying, electrospinning, supercritical fluid-based technologies and micro-precipitation; and (b) solventfree, melt-based processes, which comprise size reduction, ultrasonic assisted compaction, melt granulation, melt extrusion, generally known as HME, and Kinetisol.[8] Out of the two groups, the most popular and commercially-proven manufacturing technologies are spray drying and hot melt extrusion, and will be discussed further.

Spray Drying

Spray drying, which has its origin in the United States, was first patented by Percy on April 9, 1872, under the title of "Improvement in Drying and Concentrating Liquid Substances by Atomizing".[9] Significant industrial use of spray drying was demonstrated in the 1920s when the technology was initially used to improve shelf-life and facilitate handling of powder detergents, and later as a drying process for the manufacture of powdered milk. During World War II, the need for reduced weight and volume of food and other materials during transport led to the surge of interest in spray drying technology. This was followed by further expansion of the application of the technology to a wide range of industrial manufacturing operations, including powdered soaps and detergents, instant coffee, corn starch, fertilizers, powdered polymer resins, mineral ores, and clays. In the 1940s, Bullock et.al. explored the application of spray drying as a drying process for pharmaceuticals during the preparation of infusions for reconstitution, extracts, inorganic medicinal salts and antibiotics. Since then, spray-drying has been used in diverse pharmaceutical applications, such as the preparation of free-flowing tablet excipients, biotherapeutic particles for pulmonary inhalations and amorphous solid dispersions as well as to dry or encapsulate crystalline active pharmaceutical ingredients.[10-12]

Application of spray drying technology in the preparation of amorphous solid dispersions of poorly water-soluble compounds can be traced back to 1965, when Tachibana, et.al. prepared an amorphous solid dispersion of β-carotene in polyvinylpyrrolidone (PVP) by first dissolving β-carotene and PVP in methanol and then spray drying the solution to generate the

dispersion.[13] In 1975, Kawashima, et.al., applied spray drying to improve the solubility and dissolution rate of salicylic acid, a poorly water-soluble drug substance.[14] In 1978, Sato, et.al., used spray drying to prepare stable amorphous macrolide antibiotic solids. The macrolide antibiotic and a cellulose polymer, selected from the group consisting of ethyl cellulose, hydroxypropyl cellulose and hydroxypropylmethyl cellulose were dissolved in a volatile organic solvent, selected from the group consisting of dichloromethane, 1,1,1-trichloroethane and chloroform, and the resulting solution was spray dried.[15] In 1986, Panoz, et.al. described the preparation of amorphous solid dispersion by a spray drying process.[16] Since then, many products which comprise spray dried amorphous solid dispersions have been developed and approved (Table 1).

Table 1. FDA Approved SD/HME ASD-based products

Product	Drug Substance	Company	Process	Approval Year
Prograf	Tacrolimos	Astellas	Spray drying	1994
Rezulin	Troglitazone	Pfizer	HME	1997
Afeditab	Nifedipine	Elan	Spray drying	2010
Kaletra	Lopinavir/Ritonavir	AbbVie	HME	2005
Intelence	Etarvine	Janssen	Spray drying	2008
Zortress	Everolimus	Janssen	Spray drying	2010
Norvir	Ritonavir	AbbVie	HME	2010
Onmel	Itraconazole	Sebela	HME	2010
Afinitor	Everolimus	Novartis	Spray drying	2010
Incivek	Telaprevir	Vertex	Spray drying	2011
Noxafil	Posaconazole	Merck	HME	2013
Belsomra	Suvorexant	Merck	HME	2014
Viekira XR	Dasabuvir sodium, Ombitasvir, aritaprevir, Ritonavir	AbbVie	HME	2016
Venclexta	Venetoclax	AbbVie	HME	2016
Kalydeco	Ivacaftor	Vertex	Spray drying	2019

Hot Melt Extrusion

Hot melt extrusion is a manufacturing process that utilizes continuous, small mass mixers called extruders. There are two types of extruders: single-screw extruders and twin-screw extruders. The earliest singlescrew extruder was designed by Sturges in 1871 while the earliest twinscrew extruders were designed by Wiegardin and Pfleiderer in 1879 and 1882, respectively.[17-19] Industrial use of single-screw extruders was first demonstrated in the early 1930s when the extruders were used to extrude thermoplastic materials. Commercial twin-screw extruders were introduced in the 1940s. Currently, more than half of all plastic products, including plastic bags, sheets, and pipes, are manufactured using twin screw extrusion processes. Even though the technology has had a wide application in the manufacture of food, natural rubber and plastics for almost a century, it only started to get attention in the pharma industry and academia as a drug product manufacturing tool in the 1980s.[20,21]

Since the early 1980's, application of melt extrusion in the development and manufacture of pharmaceutical products has increased steadily.[22-26] During this period, the technology has proven to be a convenient and cost-effective manufacturing process for the preparation of granules, pellets, modified release tablets, transdermal and transmucosal drug delivery systems, amorphous solid dispersions, and abuse deterrent formulations. The technology has also been used commercially to manufacture combination drug products, such as contraceptive rings, subcutaneous implantable rods, ophthalmic implants, etc.

The application of a twin-screw extrusion process to prepare solid dispersions of poorly soluble drug substances was first introduced in the pharma industry in 1992 by Ghebre-Sellassie et.al. The formulation and process were subsequently used to develop Rezulin™ tablets (troglitazone), the first drug product, that consisted of melt-extruded amorphous solid dispersions, to be approved by the FDA for marketing authorization in 1997.[23,24]

It took another eight years before the second product, Kaletra® tablets (Lopinavir/Ritonavir), that comprised melt extrusion-based amorphous solid dispersion, was approved by the FDA. Since then, as is apparent from Table 1, hot melt extrusion appears to be gaining momentum as the preferred manufacturing process for amorphous solid dispersions. Based on the advantages hot melt extrusion offers, the trend is expected to continue unabated for the foreseeable future.

Having addressed the historical origins of spray drying and hot melt extrusion as manufacturing processes for amorphous solid dispersions and their current status in the pharma industry, an attempt will be made in Part II to assess and discuss the operational characteristics of the two technologies, robustness and limitations of the manufacturing processes and the effect of the various processing conditions.

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Hibreniguss Terefe, PhD
V.P. Research & Development
Isaac Ghebre-Sellassie

- ExxPharma Therapeutics LLC

Part II: Manufacturing Process Considerations

Part I provided an overview of the historical perspective of the genesis and application of spray d
robust and efficient manufacturing processes[1]. In this section, an attempt will be made to compar
and melt extrusion amorphous solid dispersion manufacturing processes by focusing on three key components –feed material preparation, processing conditions and product characteristics.

Feed Material Preparation

Spray drying: Poorly soluble drug substances and functional excipients (solutes) are dissolved in various solvents, including methanol, ethanol, isopropanol, dichloromethane (DCM), acetone, methyl ethyl ketone, dioxane, tetrahydrofuran (THF), chloroform, ethyl acetate, and acetonitrile to prepare solute solutions/suspensions. Amongst these, DCM is widely used to dissolve solutes despite its toxicity potential due to its low boiling point (39.8 °C), high volatility and the excellent solubilizing power for various drugs and polymers. Other commonly used solvents are methanol, acetone or combinations thereof. Solvent mixtures are sometimes used to increase the solubilities of API and polymeric carriers.[2,3,4]

Solvent properties such as boiling point and vapor pressure are affected by the addition of a solute, i.e., solute type and concentration in the feed. Solutes also determine the viscosity, evaporation rate and pH of the feed, and the boiling point of the solvent is elevated by the addition of solute. As an illustration, it has been demonstrated that the addition of PVP in solvent systems consisting of various volumetric combinations of methanol, DCM and acetone showed concentration-dependent deviation in the evaporation rate of feed solution compared with that of the pure solvent mix.

The marked deviation in the evaporation rate of feed solution from the pure solvent was explained by the interaction of solvents with PVP in the solution since the vapor pressure of the polymeric solutions showed distinct concentration dependence[5].

Hot melt extrusion: Feed materials in hot melt extrusion processes include the API and functional excipients that are broadly classified as polymeric carriers, release modifying agents, fillers, thermal lubricants, stabilizing agents, plasticizers, antioxidants, and miscellaneous additives. The main component of the feed material is the polymeric carrier.[6,7] The components of the feed material are fed into the extruder individually, as a blend or as a granulation. Powder flow, particle size distribution and bulk density of the solid components are critical properties that impact accurate feeding of the powder into the extruder when fed either individually or as a powder blend. If the flow of the feed material is poor, the components are blended and granulated to generate free-flowing granules that facilitate accurate feeding of the feed material.

Equally important is also the viscosity of the liquid feed and should be carefully assessed[8].

Functional excipients incorporated in the feed material must meet the same levels of purity and safety as those used in traditional dosage forms, must facilitate melting inside the extruder, congeal and solidify as the material exits the extruder, must be thermostable and maintain acceptable physical and chemical stability during processing and upon long-term storage.

Processing Conditions

Spray drying: During spray drying, a stream of liquid feed is atomized continuously to generate very fine droplets through a process known as atomization as they are introduced into a chamber where they are contacted with a hot drying medium (air, nitrogen) and dried through solvent evaporation to form particles, which subsequently are separated from the drying medium using a cyclone or a bag filter. Hence, the spray drying process can be described as consisting of four events: atomization of the feed liquid, contact of droplets with the hot drying medium, drying of the droplets into particles and particle separation.[9,10,11,12,13]

The atomization step is at the heart of a spray drying process. Atomization pressure coupled with nozzle size determines the shape, structure, velocity and size distribution of the droplets and hence the particle size and morphology of the final product. The large surface-to-volume ratio of the droplets permits drying to occur at a faster rate.

Following atomization, the droplets come into intimate contact with the surrounding hot drying medium. To achieve rapid and uniform evaporation of the solvent from the surface of the droplets, it is critical that the flow of the drying medium throughout the drying chamber remains consistent. The droplets come in contact with the drying medium either in co-current or counter-current direction. In the concurrent direction, the liquid feed and drying medium pass through the drying chamber in the same direction while in counter-current direction, the liquid feed and the drying medium enter the drying chamber at the opposite ends. The former configuration is preferred for heat-labile materials while the latter is used only for heat resistant materials.

Evaporation of solvents during spray drying consists of two stages: the constant rate period and the falling rate period. When the droplets are first exposed to the hot medium, rapid evaporation takes place. The droplets are initially heated from their starting temperature to an equilibrium evaporation temperature during which removal of the solvent takes place at a constant rate (the “constant rate period”) while keeping the surfaces of the droplets sufficiently cool. The surfaces of the droplets remain saturated with solvent and the temperature remains constant and is known as wet-bulb temperature. Wet-bulb temperature is the temperature at which the drying gas becomes saturated with vapor from the liquid droplets.

As the solvent removal process continues, the solute dissolved in the liquid reaches a saturation concentration and starts to form a thin shell at the surface of the droplets leading to what is known as “crust formation”. At this stage, drying transforms from low to high temperature drying and the solvent removal process transitions to a diffusion-controlled process, constituting what is known as the “falling rate period”. During the falling rate period, the partial pressure of solvent vapor exceeds ambient pressure and leads to bubble formation and a subsequent rise in temperature. It is at the crust formation and bubble formation stages that the morphology of the particles takes shape.

Particle separation involves two steps: first, the dry powder is collected at the base of the drying chamber and then it is removed from the base of the drying chamber using a screw conveyor or pneumatic system. The particles collector comprises a cyclone separator, a bag filter, and an electrostatic precipitator.

The spray drying process is a complex process that depends upon the interplay between the various process parameters and the composition of the liquid feed as described below:

Atomization depends on process parameters such as atomization pressure, feed flow rate, and nozzle type, and feed material variables such as viscosity and surface tension of the feed liquid. While keeping the type of nozzle and liquid feed rate constant, an increase in atomization pressure leads to a decrease in droplet size. At constant atomization pressure, an increase in feed flow rate results in an increase in the droplet size.

The viscosity of the liquid feed is directly related to the droplet size. If liquid feed viscosity increases, the atomization energy supplied to the nozzle must be high enough to overcome the viscous forces and achieve breakage of the liquid bulk into smaller droplets, the shape of which is determined by surface tension.

The rate of solvent evaporation is dictated by process parameters such as spray angle, aspirator flow rate, inlet temperature, outlet temperature, and particle residence time in the spray chamber as well as material properties such as glass transition temperature.

The spray angle is related to the nozzle's liquid tangential velocity which is measured at the nozzle orifice. The liquid tangential velocity is the speed at which the feed liquid spins inside the nozzle before it is divided into fine droplets and sprayed into the drying chamber. To reduce the droplet size the tangential velocity is increased by widening the spray angle. The choice of spray angle is related to the type of airflow (co-current or counter-current). The wider angle is used for the co-current airflow and the narrower angle for the counter-current.

The aspirator supplies the drying air into the spray chamber. By altering the aspirator flow rate the amount of the drying air entering the chamber can be regulated.

The inlet temperature is the temperature of the drying air entering the chamber. Inlet temperature is associated with dryer evaporative capacity and thermal efficiency. Higher inlet temperature helps achieve higher throughput. Lower inlet temperature reduces wetbulb temperature and prevents degradation of compounds during the initial stage of spray drying. Selection of the optimal inlet temperature requires a careful trade-off between drying efficiency and material degradation.

The outlet temperature is the temperature of the solid particle-laden air before entering the cyclone. It is a result of the heat and mass balance in the drying chamber and is a dependent variable that cannot be regulated. Striking an optimum temperature difference between the inlet and the outlet temperature is the most critical during spray drying process.

Glass transition temperature (Tg) is related to the material property which is associated with product stickiness which is a major challenge that could occur during the spray drying process. If not handled appropriately, it leads to product agglomeration and causes problems of caking and lumping.

The residence time of particles in the spray chamber is an important factor that impacts product quality such as bulk density, degree of crystallinity, residual solvent, product thermal degradation.

As indicated previously, to maximize API and polymeric carrier solubility, it may be required to use mixed solvents.

Azeotropes are preferred in the event a single solvent cannot be used. It is, however, not always possible to find azeotropes that act as a common solvent; differences in evaporation rates of binary solvents may lead to differential supersaturation and hence precipitation of the drug substance and the polymeric carrier potentially resulting in phase separation. This phenomenon becomes even more complicated when sometimes other feed material components, although rare due to the limitation of the process, are incorporated in addition to the drug substance and polymeric carrier. Thus, the process is extremely challenging when mixed solvents are used to dissolve feed material components, and would require extensive experimentation to identify the right combination of feed material variables and process parameters. While converting a crystalline material to an amorphous form, other complications may arise. Some drug substances may form solvates or retain residual solvents that lower the glass transition temperature leading to caking of the product.

Hot melt extrusion is a melt extrusion process associated with the application of twin-screw extrusion technology to enhance the solubility/dissolution rate of poorly soluble drug substances through the formation of amorphous solid dispersion. During hot melt extrusion, materials are mixed intimately under controlled conditions of elevated temperatures, shear and pressure to generate a variety of extrudates (intermediate products). Physicochemical transformation within the extruder is a function of specific mechanical energy, specific thermal energy, residence time and product temperature. The independent variables are extruder length, screw configuration, screw speed, barrel temperature, feed rate and die configuration. Dependent variables include specific mechanical energy, specific thermal energy, residence time distribution, product temperature, pressure profile along the barrel and pressure in the die. Specific mechanical energy is a function of screw configuration, screw speed, feed rate, barrel temperature and raw material properties. Specific thermal energy is a function of barrel temperature, percent fill of extruder screws, thermal gradient between material and barrel surface and raw material properties. Residence time distribution is a function of screw speed and fi ll-volume. Product temperature is a function of specific thermal energy, specific mechanical energy and raw material properties.[14,15]

Screw configuration may consist of different functional segments i.e. conveying, melting, mixing venting, downstream feeding, and pumping of the molten material through the die. Different types of screw elements could be arranged in a number of ways to provide flexibility and locate the different unit operations such as feeding, melting, conveying, venting, etc. along the barrel length. Screw design configuration is critical to process efficiency and high product quality. The screw design needs to be configured to help achieve optimum specific mechanical energy and residence time distribution. Increasing feed rate results in a higher percent fill of extruder screws, a decrease in residence time distribution and an increase in the melt plug length and melt seal location along the screw.

Increasing screw speed reduces the percent fill of the screws, the residence time and the melt plug at a melt seal. High screw speed results in higher specific mechanical energy, higher melt temperature and lower pressure in the die. High barrel temperature decreases material melt viscosity, increases specific thermal energy, decreases specific mechanical energy and head pressure in the die and increases melt temperature.

As head pressure increases (for example due to narrow die hole or low die temperature), the length of molten material back up prior to the die increases, specific energy and melt temperature increase and throughput rate decreases. As material backs up along the extruder, the material can be forced out through the vent port next to the last barrel section, or in extreme cases, the equipment shuts off.

Process optimization requires consideration of all independent variables in conjunction with the feed material properties. Balancing independent variables would help to overcome both product-related and process-related limiting factors, and facilitate scale-up activities which will be discussed in subsequent sections.

Table 1: Comparison Spray Drying vs. Hot Melt Extrusion

Key Manufacturing Process Components	Spray Drying		Hot Melt Extrusion	
	Pros	Cons	Pros	Cons
Feed Material Preparation	• Relatively low API amount require	• Utilizes organic solvent with potential toxicity or environmental hazard and expensive solvent recovery process • Generally difficult to find common solvent to drug, carrier and other additional feed material components due to solubility differences • More than one solvent may be needed to solubilize the drug carrier and other feed material components • Not suitable to APIs that have very low solubility in low boiling point solvents	• Organic solvent-free • Multiple and flexible material feed options • A highly flexible process that permits multi-component feed material processing	• Feed material feed consistency highly dependent on powder flow property • To achieve uniform consistent material feeding pre-extrusion blending or granulation step may be required • Generally higher amount of API requirement during early stage development unless the process is handled creatively
Processing Conditions	• Generally non-thermal process	• Differential vaporization and supersaturation may lead to heterogeneous (amorphous and crystalline) matrices • Low Tg due to residual solvent or formation of solvates may lead to agglomeration and caking of the product during processing • Relatively sensitive process variables	• Generates extrudates that could be shaped to different types of dosage forms (such as powders, pellets, tablets, implants) • Once optimized, highly controlled and robust process variables	• A thermal process that potentially leads to thermal degradation (easily avoidable) • Complex processes that require a good understanding of material and process attributes, their interaction and impact on product quality
Product Characteristics	• Porous particles that facilitate dissolution	• Residual solvent in ASD at the end of the process, and hence the need for secondary drying steps • Porous material susceptible to moisture absorption and stability issues • Additional downstream steps such as densification, compaction, and agglomeration required to enhance the flow	• No residual solvent • High-density particles • Milling provides the desired particle size distribution to facilitate downstream manufacturing and enhance dissolution	• Potential degradants unless feed material and processing parameters optimized

Product Characteristics

Spray Drying and HME generate intermediate material that is subsequently used to develop a dosage form. Although both processes generate amorphous solid dispersions, the characteristics of the materials are different.[16,17,18,19]

Particle Size: Spray drying generates porous materials of various sizes depending upon the processing conditions. HME, on the other hand, generates materials that are dense, and the range of particle sizes is determined by inline- or offline milling process.

Bulk Density: Due to the porous nature of the particles, materials prepared by spray drying have low bulk density. HME generates materials that have high bulk density due to the high density of the particles.

Residual Solvents: Spray drying utilizes organic solvents to manufacture the particles and contain residual solvents in unacceptable range after drying. HME is a solvent-free process.

Water Content: The input material during HME may contain a small amount of moisture derived from the excipient or pre-extrusion granulation step. Due to high processing temperature, this moisture is expelled during the HME process and the material generated is practically moisture-free.

Humidity Effect: In both cases, the amorphous solid dispersions are hygroscopic and have the tendency to absorb moisture that would lead to crystallization unless moisture protective measures are taken during manufacturing (for example by controlling environmental humidity) and upon storage (such as appropriate package selection).

In conclusion, Spray Drying and HME are proven and accepted technologies to manufacture Amorphous Solid Dispersions. However, in selecting which process to employ, it is very critical to have a good understanding of the pros and cons (see Table 1), level of complexity, scalability, and cost-effectiveness of the two manufacturing processes.

In subsequent articles, we will discuss scale-up and equipment considerations; quality, cost and regulatory implications; and downstream process interfacing.

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About the Authors

***Isaac Ghebre-Sellassie, Ph.D.**, is Founder and CEO/CSO of ExxPharma Therapeutics. He has over 35 years of extensive executive and management experience and contributed over 40 articles, authored 14 book chapters, was granted 23 patents and edited three books - Pharmaceutical Pelletization Technology (1989), Multiparticulate Drug Delivery (1991) and Pharmaceutical Extrusion Technology (co-edited) first edition (2003), second edition (2018). His research interests include the design and development of novel formulations and processes that optimize drug delivery, and innovative manufacturing technologies that improve quality and increase manufacturing efficiency.*

***Hibreniguss Terefe, Ph.D.**, is V. P. Research and Development of ExxPharma Therapeutics LLC. He has more than 20 years of academic and industrial pharmaceutical research and development experience, particularly in the area of drug delivery technology. He has extensive experience in twin screw extrusion technologies, including hot melt extrusion and liquid assisted extrusion as applied to solubility enhancement, modified release and abuse deterrent formulations.*