BIOAVAILABILITY ENHANCEMENT

A Novel Spray-Drying Technology to Improve the Bioavailability of Biopharmaceutical Classification System Class II Molecules

By: David Shi, PhD; Andrew Loxley, PhD; Robert W. Lee, PhD; and David Fairhurst, PhD

INTRODUCTION

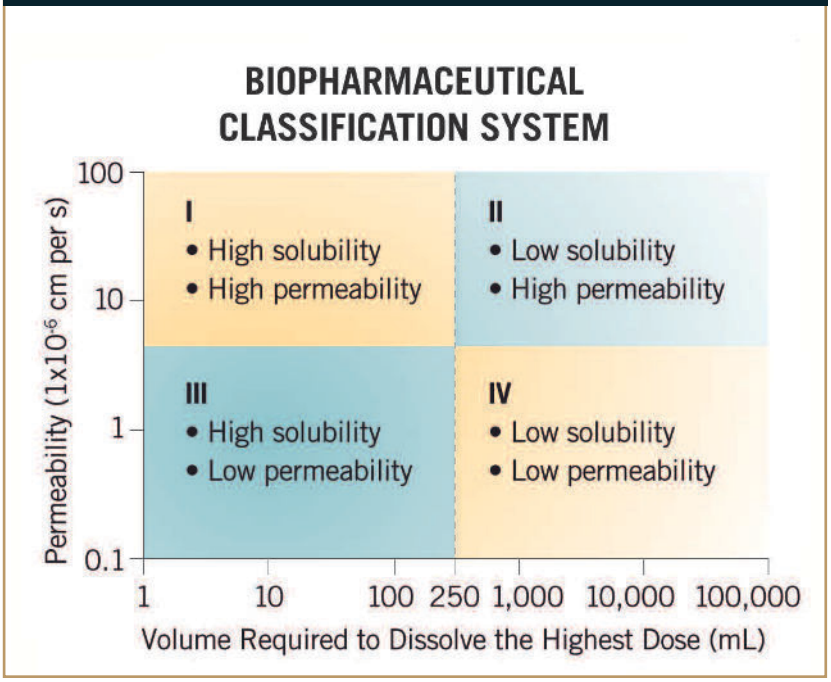
In life-cycle management of pharmaceutical products, novel drug delivery technologies that offer positive differentiation over first-generation products provide an important means for staying competitive in today's business environment. This article will briefly discuss a proven and scalable solid dispersion approach based on spray-drying that is suitable for Biopharmaceutical Classification System (BCS) (Figure 1) Class II active pharmaceutical ingredients (APIs) and new chemical entities (NCEs).[1-4]

Many existing APIs and NCEs are poorly water soluble and subsequently have low oral bioavailability if formulated in unmodified form. Traditional approaches to overcoming this include (1) improvement of water miscibility by employing self-emulsification, lipid-based techniques, solubilization into micellar cores, or alternatively complexation with cyclodextrins; (2) reduction of particle size to nano-scale via mechanical milling or high-shear processing accompanied by particle stabilization; and (3) impacting crystal lattice energy using polymorphs or co-crystals, or through the creation of solid dispersions of drug in inert carriers or matrices.[5-11]

Increasingly, solid dispersions are being looked at as a viable solution to this pervasive issue. Although only a few solid dispersions are currently marketed, the approach has some inherent advantages over other approaches. Presence of an active compound as a molecular or nano-particle dispersion combines the benefits of decreasing crystal lattice energy and maximizing surface area, thus facilitating better contact with dissolution media. Fortuitously, many of the carriers that can be employed for the production of solid dispersions are generally recognized as safe (GRAS) and are already extensively used as excipients in marketed products, easing the regulatory burden.

Particle Sciences has developed DOSE™ a formulaic approach to dosage form development that rapidly narrows in

FIGURE 1



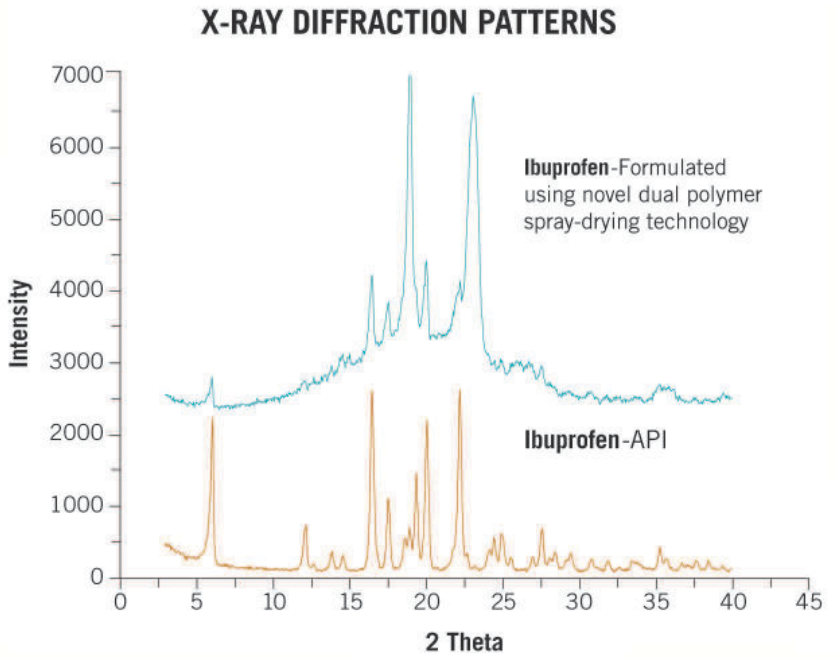
on the drug delivery technology of choice. When solid dispersions are called for, Particle Sciences has a number of approaches, one of these is a unique solid dispersion technology based on spray-drying using a dual-polymer system that significantly improves the dissolution and bioavailability of poorly soluble APIs. The technology has been proven in human trials and has been scaled to commercial levels. Under Particle Sciences DOSE system, APIs are first extensively characterized as to their physicochemical characteristics, including a proprietary solubility screen. Then after excipient compatibility studies, formulation prototypes are screened for their impact on solubility and permeability. This methodical iterative approach allows one to rapidly narrow in on the formulation approaches most likely to yield the desired results.

THE DRUG DELIVERY PROBLEM

An increasing number of compounds coming out of discovery are poorly soluble. By some estimates, 40% to 70% of new lead compounds in development fall into this category.[12,13] Additionally, many new compounds also exhibit poor permeability. In 1993, the BCS was proposed as a way to facilitate the marketing of generic drugs. The system classifies a given compound by its aqueous solubility and gut permeability.

Beyond its regulatory use, the BCS provides a very useful framework in which to evaluate APIs and chart a logical course to achieve the desired pharmacokinetics (PK), including greater bioavailability. For BCS II and IV molecules, in which solubility is the main or largely contributing limiting property, there are a number of approaches, including increasing surface area through particle size reduction, surface morphology modification, and solid solutions.

FIGURE 2



A NOVEL DUAL-POLYMER SPRAY-DRYING SOLUTION

Generating human data as quickly as possible is the goal of every drug developer, and there are several philosophies as to how best to achieve first in human (FIH) dosing. It has been estimated that three to six formulation changes occur from FIH to commercialization.[14] At Particle Sciences, we believe that FIH experience should be in a formulation that will provide useful developmental data. For a BCS I molecule, the prototypical formulation could be a simple powder-filled capsule. For a poorly water-soluble molecule, BCS II or IV, such a simple system is unlikely to provide any commercially helpful data, speed development, or bring to light clinically relevant findings. Therefore, an FIH formulation designed to deliver the drug in a commercially viable way is, in our view, important. For drugs with limited aqueous solubility, one such approach discussed in this paper involves a patented dual-polymer system utilizing GRAS excipients and traditional processing techniques.

In this approach, the API is solubilized in a water-miscible organic solvent, usually ethanol. A mixture of an amphiphilic and a hydrophilic polymer are prepared as a mixed

FIGURE 3

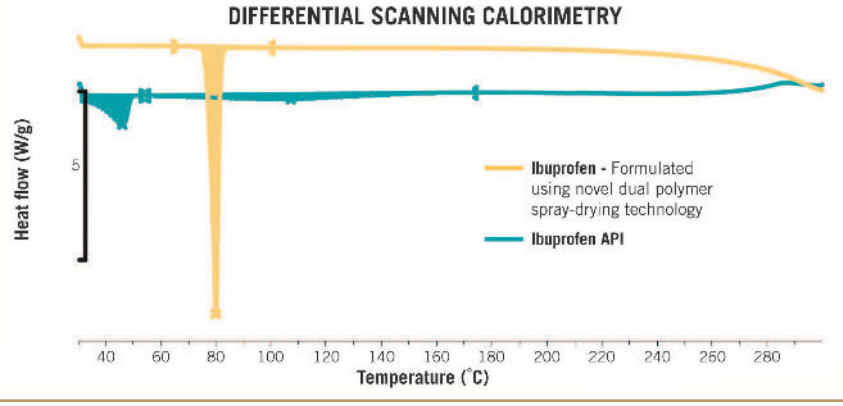
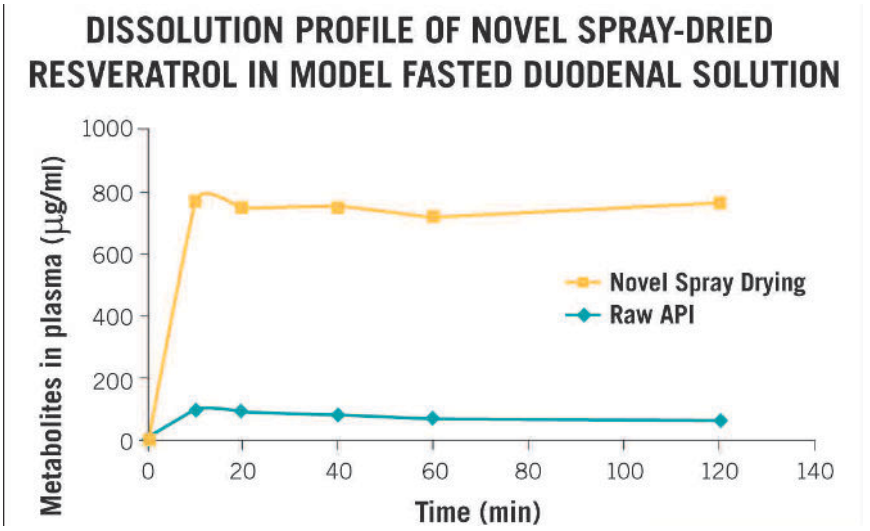
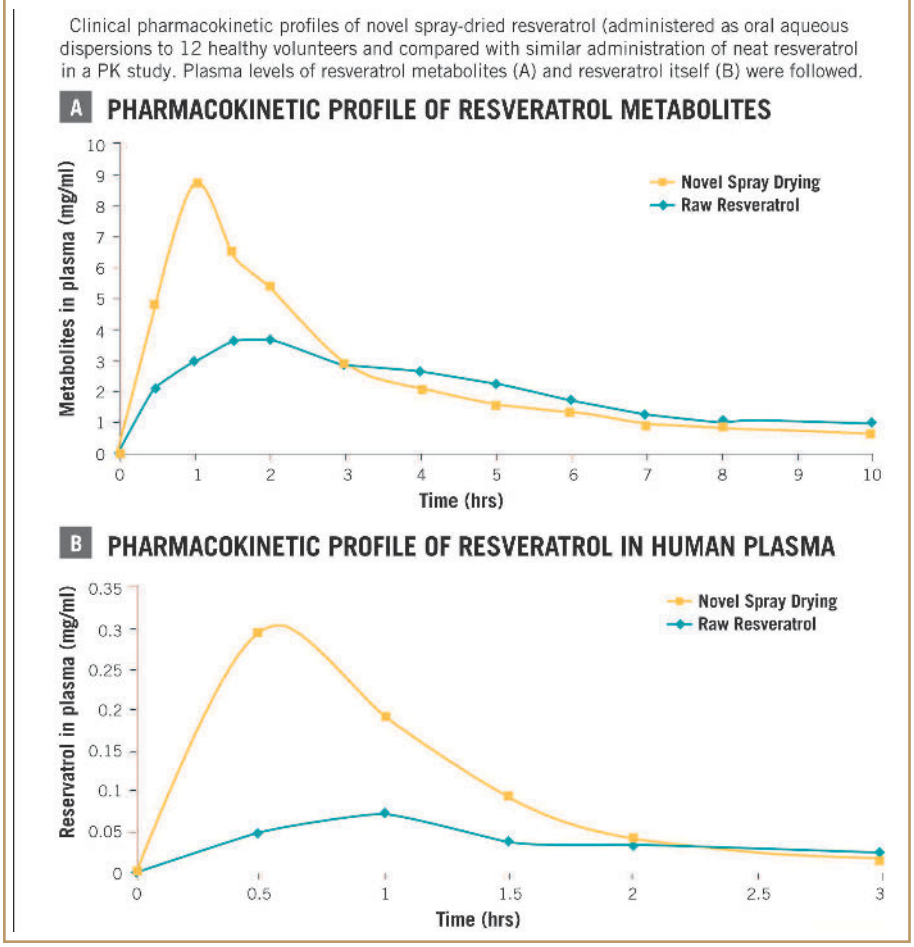


FIGURE 4



aqueous solution. The organic API solution and the aqueous polymer mixed solution are then mixed under carefully controlled temperature and agitation rate to form a transparent or hazy solution, which is subsequently spray-dried. The exact compositions of the feed stocks are determined in an extensive, yet efficient, preformulation phase utilizing Design of Experiment (DoE) methodology, when appropriate. Key drivers include the API's solubility in various organic solvents, the API's molecular weight, the solubilities of the polymeric excipients, and the compatibility of the API and polymeric excipients in the spray-drying solution.

FIGURE 5



In the context of this technology, amphiphilic polymers are defined as soluble both in organic solvents and in water. Examples of amphiphilic polymers suitable for use include but are not limited to polyethylene oxides (PEO, also commonly referred to as polyethylene glycol or PEG), PEO derivatives, PEO copolymers, such as PEO/polypropylene glycol (PPG) copolymers, PEG-modified starches, poloxamers, poloxamines, polyvinylpyrrolidones, hydroxypropyl cellulose, hypromellose, and esters thereof, vinyl acetate/vinylpyrrolidone random copolymers, polyacrylic acid, and polyacrylates.

Hydrophilic polymers are defined as those soluble in water or in a single-phase mixture of organic solvent and water, but not soluble in organic solvent alone. Examples of hydrophilic polymers include but are not limited to starch, sodium carboxymethylcellulose, hydroxyethylcellulose, polyvinyl alcohol, sodium alginate, chitosan, and carrageenan. Notably, these formulations utilize only FDA-approved polymers.

The use of hydrophilic polymers that ionize at different pH allows for the design of formulations targeted either to the stomach or the intestine. For example, chitosan, which is ionized at low pH, promotes drug release in the stomach, while sodium carboxymethyl cellulose and sodium alginate, ionized at neutral conditions, facilitate release in the small intestine.

The resulting powder is free flowing and will contain 25% or more API. Characteristics of the drug product include the following:

- Solubilized drug homogeneously interwoven into a polymer matrix.
- Drug in crystalline form within the polymer matrix.

- Depressed API melting temperature and enthalpy of fusion (Figure 1).
- Spontaneous formation of colloidal dispersions upon contact with aqueous media.
- Enhanced dissolution rate/solubility of the drug in aqueous media as well as prolonged supersaturation in relevant biological fluids, and GI site-targeted release of the drug.

CHARACTERIZATION

Powder X-ray diffraction (PXRD) is first used to characterize the API powder and the spray-dried formulation. As can be seen in Figure 2, the model drug (Ibuprofen) shows characteristic PXRD diffraction peaks, and a drug product containing 25% of the API, prepared by the novel dual-polymer spray-drying approach also shows some of the these same peaks, indicating that the API is present in crystalline form. In contrast to some systems that are dependent on amorphous API forms, this technology results in very stable particle constructs because the crystalline form of the drug is the most thermodynamically favored state.

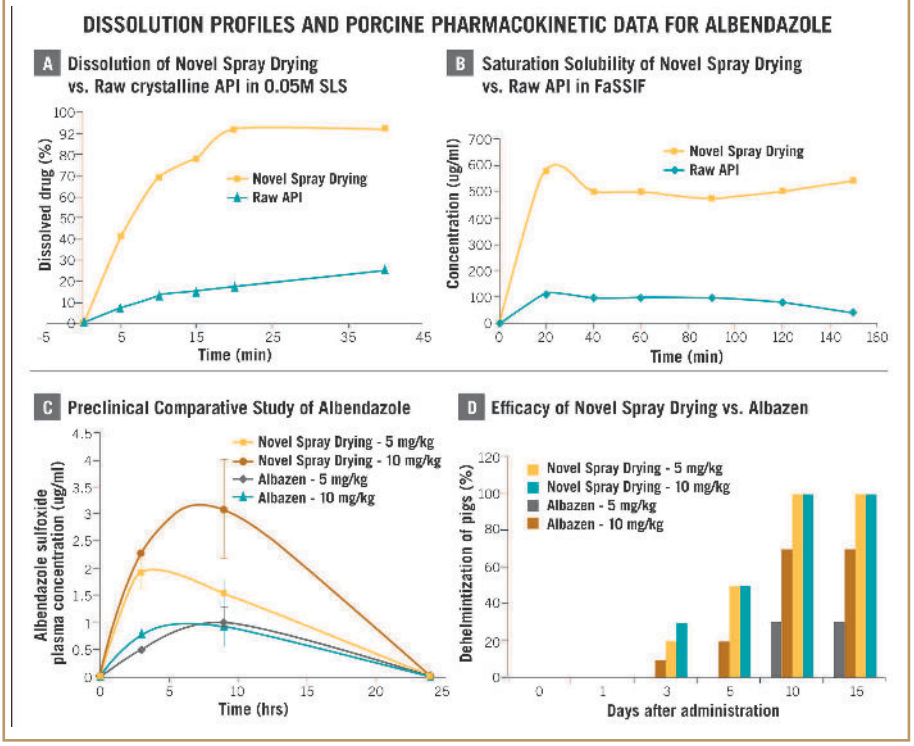
In Figure 3, the impact of the technology on melting temperature and enthalpy of fusion is clearly demonstrated. It is believed that these thermal property alterations are at least in part responsible for the significant increase in solubility provided by this technology.

Several commercial compounds have been thoroughly evaluated using this novel technology. Figure 4 shows the dissolution profiles and clinical two-way pharmacokinetic data for Resveratrol. Clearly, the rate of dissolution is faster using the novel dual-polymer spray-drying approach, and reaches a higher final concentration than neat API.

Figure 5 shows clinical data showing higher C_{max} and AUC for the novel spray-dried resveratrol formulation in comparison with neat API, indicating significant increases in bioavailability when using this novel spray-drying approach.

Figure 6 shows the dissolution profiles and porcine pharmacokinetic data for albendazole (A: dissolution profiles in 0.05 M SLS of raw API and API product formulated using the novel dual-polymer spray-drying approach; B: dissolution profiles in fasted simulated intestinal fluid of raw API and drug product formulated using the novel dual-polymer spray-drying approach; C: porcine PK data for commercial product versus product made by the novel dual-polymer spray-drying approach; and D: efficacy in porcine model of commercial product versus product made by using the novel dual- polymer spray-drying approach (data generated by Solubest, Ltd, Israel). The API solubility is enhanced, PK data are improved compared to a commercial product, and efficacy in the animal model is improved.

FIGURE 6



CONCLUSION

Whether reformulating an existing compound or working with an NCE, the ability to understand and manipulate those factors within our control that dictate PK behavior is key. For compounds with low solubility, we have presented one approach to oral dosage form development. Using GRAS ingredients and a readily scaled and patented process, employing this novel spray-drying technology results in stable crystalline constructs that increase API bioavailability by increasing the solubility of the API. To date, the technology has been demonstrated in more than a dozen compounds and is currently being scaled for Phase III for at least one. ◆

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BIOGRAPHIES

Dr. David Shi, as a Polymer Scientist with a PhD in Polymer Chemistry, has more than 15 years experience in development of new materials and drug delivery systems for bio/medical applications. He joined Particle Sciences, a contract research organization in Bethlehem, PA, as Formulation Scientist in 2009. He specializes in pharmaceutical formulation development and drug delivery technologies. In the past 10 years, his research has been focused on improving drug delivery in oral, topical, inhalation, and injectable dosage forms. His expertise includes nanoencapsulation, microencapsulation, liposomes, spray-drying, and organic and polymer synthesis. Dr. Shi is co-inventor of 10 issued patents related to novel drug delivery systems, some of which have been licensed, and has authored several peer-reviewed journal articles.

Dr. Andrew Loxley is Director of New Technologies at Particles Sciences Inc., a contract research organization in Bethlehem, PA, specializing in pharmaceutical formulation development. He leads a variety of projects, based on novel and proprietary nanotechnologies and combination devices, in fields from HIV vaccine and microbicide development, to gene-silencing SiRNA delivery. Prior to joining Particles Sciences, he led development efforts in next-generation lithium ion batteries at A123 Systems Inc, electrophoretic displays at EINK Corp., and emulsion polymers at Synthomer Ltd. British-born, he earned his BSc in Chemistry from the Univeristy of Sussex and his PhD in Physical Chemistry focusing on microencapsulation from the University of Bristol.

Dr. Robert W. Lee is Vice President of Pharmaceutical Development at Particle Sciences Inc. He is responsible for product development as well as providing support to clinical manufacturing operations and business development. His responsibilities include oversight of formulation development, drug delivery, analytical sciences, quality control, and quality assurance. Before joining Particle Sciences, Dr. Lee held senior management positions at Novavax, Inc., Lyotropic Therapeutics, Inc., and Imcor Pharmaceutical Co. He has also been in research positions at élan Drug Delivery, NanoSystems, and Sterling Winthrop. Dr. Lee holds bachelors in Biology and Chemistry from the University of Washington and a PhD in Physical Bioorganic Chemistry from the University of California-Santa Barbara. He has published articles in numerous peer-reviewed journals and three book chapters plus holds 11 issued patents and 14 provisional or PCT patent applications. Dr. Lee has more than 20 years of experience in pharmaceutical research and development of both therapeutic drugs and diagnostic imaging agents. He maintains strong academic ties, including an appointment as Adjunct Associate Professor of Pharmaceutical Chemistry at the University of Kansas in 1992, and serving as a reviewer for both the International Journal of Pharmaceutics and Journal of Pharmaceutical Sciences and Editorial Advisory Board member for Drug Development & Delivery.

Dr. David Fairhurst is Corporate Research Fellow at Particle Sciences Inc. He earned his PhD in Physical Chemistry in 1968 from Liverpool Polytechnic, UK, where he was also a Lecturer (in Physical Chemistry) for 4 years. He spent 2 years as a Visiting Associate Professor in the Center for Surface and Coatings Research at Lehigh University and subsequently held senior research positions with the UK Chemical Defense Establishment, Porton Down, and with Union Carbide Corporation, USA. The work encompassed exploratory and basic research, product formulations, and development and technical services. He has spent the past 40 years in using colloid and surface chemistry to solve problems in industrial and pharmaceutical applications and has published more than 100 technical papers, scientific articles, and book chapters in the open literature. Prior to joining PSI in 1993, he was, for 7 years, Director of Applications at Brookhaven Instruments Corporation and is an internationally recognized authority on dispersion and emulsion technology and in the assessment and characterization of particle size.