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Innovative medicines by supercritical fluid particle design: Four decades of progress

Yongda Sun[1,2*]

[1]3S PharmaTech, (3SPT LLC), Newark, California, United States of America

[2]3S PharmaEng Co., Ltd, Shenzhen, Guangdong, China

Abstract

Innovative medicines are increasingly relying on advanced technologies spanning discovery, formulation, manufacturing, and regulation. Supercritical fluid particle design (SCF PD) is an emerging pharmaceutical platform that has evolved from laboratory research to industrial application over the past four decades. Transforming active pharmaceutical ingredients into innovative medicines requires coordinated optimization in aspects such as particle size, crystal form and morphology, solubility, absorption, bioactivity, functional structure, stability, and biocompatibility. In achieving this goal, SCF PD can not only produce pure drug particles but also manufacture composite particles with functional structures, such as hybrid nanoparticles, co-crystals, porous particles, and coated particles, which can be used in controlled-release, taste-masking, carrier-free inhalation, and other drug delivery system formulations. With the advancement of technology, equipment, and processes, innovative medicines developed through SCF PD have entered clinical trials and Good Manufacturing Practices production, such as StaniTab® sirolimus nanocrystal direct-compression tablets, Dasynoc® dasatinib hybrid nanodispersion tablets, Nano-enzalutamide 160 mg single-dose amorphous nanopowder tablets, and Zindol® ginger extract capsules. This narrative review focuses on the advances in innovative medicines for poorly soluble drugs, anticancer drugs, and inhalation drugs, emphasizing the simplification of complex manufacturing processes, dose reduction, improvement of medicine quality, enhancement of therapeutic efficacy, and increased patient adherence, providing important guidance for better utilization of SCF PD technology in the production of innovative medicines.

Keywords: Innovative medicines; Supercritical fluid particle design; 3S-improved supercritical anti-solvent; Nanoparticles; Poorly soluble drugs; Anticancer drugs; Inhalation drugs

***Corresponding author:**
Yongda Sun
(cnydsun@hotmail.com)

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1. Introduction

Supercritical fluid particle design (SCF PD) has been under development for over 40 years. Since the 1980s, it has been gradually moving from fundamental research to pharmaceutical industrialization. Roughly every 10 years, it goes through a stage: fundamental research, applied research, pharmaceutical development, formulation in clinical trials, and industrialization (Figure 1).

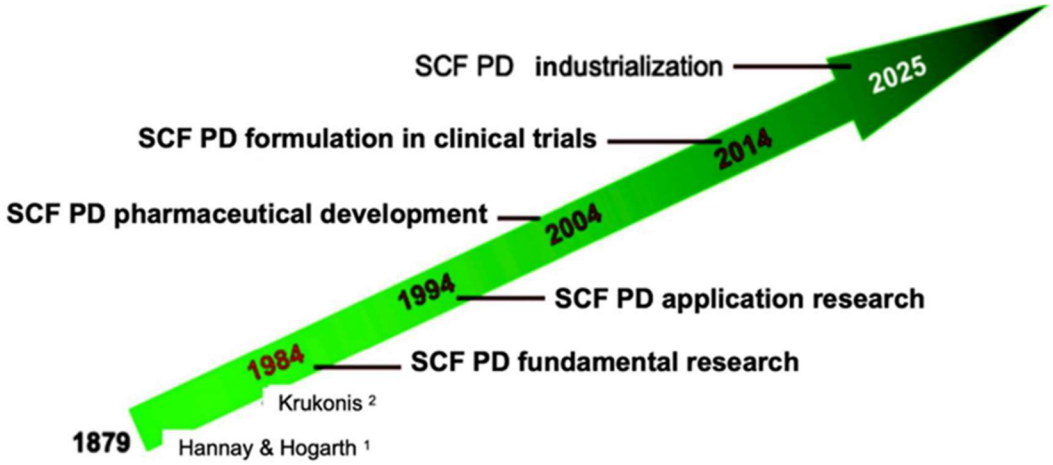


Figure 1. The evolving history of supercritical fluid particle design (SCF PD) technology at a glance. Image created by the author with WPS Office.

The phenomenon of supercritical fluid precipitation was discovered by British scientists Hannay and Hogarth[1] in 1879. Industrial development began over 40 years ago. Due to energy and environmental crises, supercritical fluid extraction (SFE), an energy-saving and environmentally friendly technology, was first used to remove caffeine from coffee beans and to extract natural products, such as hops and spices. It was not until 1984 that American scientist Krukonis[2] proposed the concept of supercritical fluid nucleation, and the fundamental research of SCF PD gradually expanded from the preparation of ultrafine powders of inorganic and polymer materials to the design of drug particles and drug delivery systems (DDS).

From 1994 to 2004, various SCF PD processes and equipment emerged one after another. The papers by Jung and Perrut[3] in 2001 and York *et al.*[4] in 2004 reflect these advances. The United Kingdom (UK) company Bradford Particle Design (BPD) developed the groundbreaking Solution Enhanced Dispersion by Supercritical Fluids (SEDS) system, and was acquired by the American company Inhale (Nektar) for USD 200 million in 2001[5], marking a new stage for SCF PD in the pharmaceutical field.

The SCF PD pharmaceuticals entered clinical research over the following decade. Some candidates passed Phase III clinical trials and were acquired by large companies. For example, Levadex®, a dihydroergotamine dry powder inhaler produced by MAP Pharmaceuticals for the treatment of migraines,[6] passed Food and Drug Administration (FDA) Phase III review and was acquired by Allergan in 2013 for USD 958 million.[7] Zoledronic acid, initially used to treat malignant hypercalcemia, was later redeveloped using the Enhance® process by Thar Pharmaceuticals and applied to the treatment of complex regional pain syndrome, entering Phase III clinical trials and eventually being acquired by Grünenthal in 2016.[8] In terms of academics, the special issue "Drug delivery applications of supercritical fluid technology" in *Advanced Drug Delivery Reviews*, published in 2008, summarized SCF PD pharmaceutical achievements during this period.

Over the past decade, SCF PD has entered the industrialization stage. Some pharmaceutical companies have already adopted this new technology for Good Manufacturing Practices (GMP) or current GMP (cGMP) production. The following are some highlights from the scientific literature, patents, and related industry reports:

(i) XSprayPharma AB (XSpray) applies the HyNap™ (hybrid nanoparticles) technology to increase the solubility and bioavailability of protein kinase inhibitors (PKIs). For example, the area under the curve $(AUC)_{0-24h}$ of nilotinib hybrid nanoparticles was 730% of that of the benchmark nilotinib formulation (Tasigna).[9]

(ii) In June 2019, the first production line for Dasynoc® (dasatinib) began operations. Dasynoc® has been granted orphan drug status by the FDA in the United States (US) for treatment of chronic myeloid leukemia and acute lymphoblastic leukemia, and is currently under FDA review for market approval under the 505(b)(2) New Drug Application (NDA) regulatory pathway.[10]

(iii) Pierre Fabre Medicament, a French company, established the supercritical fluid research and development center, using the Formulcoat®, Formuldisp®, and Formulplex® processes[11] for pilot-scale and cGMP production of various solid dosage forms. The capacity for taste-masking formulations reaches 50 kg/h.

(iv) France's StaniPharm and EthyPharm collaborated to produce rapamycin nanocrystalline composite powder using the StaniTab® process[12] for direct compression into tablets. This greatly simplified the process and enabled rapid large-scale production in compliance with GMP standards.

(v) Aphios Corporation in the US adopted the SuperFluids™ process[13] to focus on developing nanomedicines for antitumor, anti-infection, and anti-dementia applications. Zindol®, a ginger-based preparation for treating nausea and vomiting caused by chemotherapy, pregnancy, surgery, or exercise, entered Phase III clinical trials and is in trial production and sales.[14]

(vi) KingYork Group in Tianjin, China, the largest corticosteroid enterprise in Asia, adopted the 3S-improved supercritical anti-solvent (3S-iSAS) process to produce budesonide (BUD) crystalline microspheres. In the carrier-free inhalation in vitro assessment, the lung deposition rate reached 32.9%, surpassing Pulmicort®'s 28.4%.[15]

(vii) Honz Pharmaceutical Co., Ltd., a children's medicine company in China, developed itraconazole (ITZ) microparticles using SCF PD, producing three polymorphic particles and an amorphous particle to enhance the ITZ solubility from 4.4 μg/mL to 108.5 μg/mL; these particles can be further applied to different formulations to meet the requirements of consistency evaluation.[16]

In short, after over 40 years of development, SCF PD has grown from a small seedling into a towering tree, establishing a green pharmaceutical platform and bearing abundant fruit. This article provides a narrative review of the innovative medicines developed through SCF PD, from the perspective of a researcher who participated in the entire development process of SCF PD. It briefly describes equipment and process improvements, with particular emphasis on innovative medicines for poorly soluble drugs, anticancer drugs, and inhalation drugs.

2. Supercritical fluid particle design

Supercritical fluid particle design is an emerging breakthrough technology that uses supercritical carbon dioxide ($ScCO_2$) as a green solvent to produce fine particles. It has been widely applied in chemical engineering, materials engineering,[17] and biomacromolecular nanomedicine and biomedical engineering,[18] such as high-efficiency catalysts, high-energy explosives, high-performance battery materials, and advanced biopharmaceuticals. For innovative medicines, SCF PD can produce small, smart, and stable particles of the solid dosage form with suitable physical and characteristic properties.[19,20] Here, "small" refers to particle sizes from nano to micron scale; "smart" refers to engineered functional structures (e.g., coatings and porosity) suitable for various DDS; and "stable" refers to maintaining unchanged quality over a long period at room temperature. SCF PD provides different routes for designing fine particles to enhance formulation performance and enable successful control and tuning of particle properties in a single-step process.

In the SCF PD process, the drug solution is mixed with $ScCO_2$ and then atomized through a nozzle, leading to the rapid formation of drug particles. This approach enables precise control over key physicochemical properties, such as particle size, crystal form, crystal habit, surface energy, and surface charge. Moreover, co-processing drug solution and excipient solution allows the formation of composite particles with unique functional structures, such as co-crystals, salts, coated particles, porous particles, and uniformly dispersed particles. These features facilitate the development of various DDS aimed at enhancing solubility, controlling drug release, masking taste, enabling long-acting injection, and supporting carrier-free inhalation.[21,22]

Additionally, SCF PD can reduce solvent use and waste streams compared to traditional processes, and it can also be configured for sterile manufacture.[23] However, its environmental and waste characteristics depend on process design and solvent recovery efficiency. SCF PD-based medicines have the following features: high yield, high activity, low residual solvents, good batch-to-batch consistency, and long-term stability at room temperature.

Many new processes emerged during the development of SCF PD. Based on the solubility of drugs in $ScCO_2$, these processes can be divided into two main categories. When a drug is soluble in $ScCO_2$, solvent-free particles can be prepared using supercritical solution rapid expansion[24] or supercritical solution saturation.[25] However, most drugs are insoluble in $ScCO_2$, and processes such as supercritical anti-solvent (SAS)[26] and gas anti-solvent[27] are commonly used. Subsequent intensifications in SAS-based processes include SEDS,[28] aerosol solvent extraction system,[29] supercritical anti-solvent enhanced mass transfer,[30] supercritical fluid emulsion extraction (SFEE),[31] compressed anti-solvent precipitation,[32] and the 3S-iSAS.[33] The main features of configuration in SAS-based processes are shown in Table 1.

3. The improvements in equipment and process

Improving equipment, especially the nozzle configuration and particle format in the vessel, is a key issue. Based on research on the advantages and disadvantages of various configurations in SAS-based processes mentioned above,

Table 1. The main features of configuration in SAS-based processes

Process	Main features of the configuration
SAS	$ScCO_2$ and the solution are fed separately by an inlet and a nozzle
GAS	$ScCO_2$ is slowly added to the solution until saturation
SEDS	$ScCO_2$ and the solution are fed through a coaxial nozzle
ASES	The solution is fed through a nozzle located at the top of the vessel
SAS-EM	An ultrasonic vibration device was added at the solution inlet
SFEE	$ScCO_2$ is sprayed into the microemulsion from the bottom of the vessel
PCA	Solution spraying time is shorter as an intermittent run
3S-iSAS	$ScCO_2$ and solution are fed through an impinging jet nozzle into the particle formation vessel with an optimal aspect ratio

Abbreviations: 3S-iSAS: 3S-improved supercritical anti-solvent; ASES: Aerosol solvent extraction system; GAS: Gas anti-solvent; PCA: Compressed anti-solvent precipitation; SAS: Supercritical anti-solvent; SAS-EM: Supercritical anti-solvent enhanced mass transfer; SEDS: Solution Enhanced Dispersion by Supercritical Fluids; SFEE: Supercritical fluid emulsion extraction.

as well as related computational fluid dynamics (CFD) simulations, the 3S-iSAS apparatus incorporates three improvements to prevent nozzle clogging, enhance the utilization of the turbulent kinetic energy of CO_2, and enable precise control of drug particle formation through cosolvent assistance (Figure 2):

(i) Using an impinging jet nozzle to prevent clogging and fully utilize the kinetic energy of $ScCO_2$.
(ii) Employing a particle formation vessel with an optimized aspect ratio to improve temporal streamlines (particle trajectories) and turbulent eddies.
(iii) Adding an auxiliary cosolvent feed channel to aid particle formation.

The reconfigured 3S-iSAS apparatus (Figure 3), based on the three components described above, is a three-pump system. CO_2, drug solution, and cosolvent are separately fed by three high-pressure pumps through heaters and pulse dampeners into the impinging jet nozzle within the particle formation vessel, which is placed inside a controllable-temperature oven. The pressure inside the vessel is controlled by a back-pressure regulator at the bottom, and a cyclone separator is used to handle the discharged residual liquids. The flow rate of the discharged gaseous CO_2 is measured using a rotameter. The temperature and pressure inside the vessel are measured with sensors with accuracies of ±0.1 °C and ±0.1 MPa, respectively. By manipulating the process conditions of pressure, temperature, the concentration of the drug solution, and the flow rates of the drug solution, CO_2, and cosolvents, it is possible to fully customize the size, morphology, and surface characteristics of the formed drug particles.

Computational fluid dynamics simulations, using FLUENT and a realizable κ–ε model, have verified that the first two improvements mentioned above achieved the expected objectives.[34] The first focus of the CFD study was to gradually reduce the nozzle spacing until overlap to achieve effective diffusion. The effective diffusion coefficient, D_{eff} (the sum of the molecular and turbulent diffusion coefficients), is a crucial physical parameter for characterizing the rate of component transfer. A larger D_{eff} value (m^2/s) indicates faster component diffusion and smaller resulting drug particles. CFD simulation reveals the distribution contour of D_{eff} within the vessel. As the nozzle spacing decreases, the D_{eff} value increases. When the nozzles overlap, the D_{eff} value reaches the maximum (CFD E in Figure 4), indicating that the turbulent energy of $ScCO_2$ is fully utilized.

Computational fluid dynamics simulations also studied the effect of the aspect ratio of the particle formation vessel on the distribution of flow turbulent eddies and temporal streamlines under the optimal 90° impinging jet configuration. Since the jets of drug solution and $ScCO_2$ collide outside the nozzle, clogging is completely avoided. When the vessel had an optimal aspect ratio, CFD simulations of a 90-degree impinging jet configuration showed that the turbulent eddy region rose from the bottom to the top and was confined to the flow area near the nozzle. As a result, large-scale turbulent eddies disappeared, preventing particle trapping and avoiding abnormal particle growth caused by collisions, adhesion, deformation, and breakage. Meanwhile, a large number of small turbulent eddies were produced near the nozzle, facilitating the formation of bionic microspheres. In addition, the temporal streamlines depicting particle trajectories ran parallel to the vessel walls, allowing the formed drug particles to reach the vessel bottom in the shortest time (CFD 4 or CFD 5 in Figure 5), thus achieving a narrower and more uniform particle size distribution.

Furthermore, by using a high-speed particle image velocimetry camera, transient images of drug particles in the jet flow near the nozzle were captured (Figure 6A). By measuring and analyzing consecutive images at 2-ms intervals, velocity distribution maps were obtained (Figure 6B), confirming the presence of numerous tiny eddies in the jet. Under the rotational shear action of these eddies,

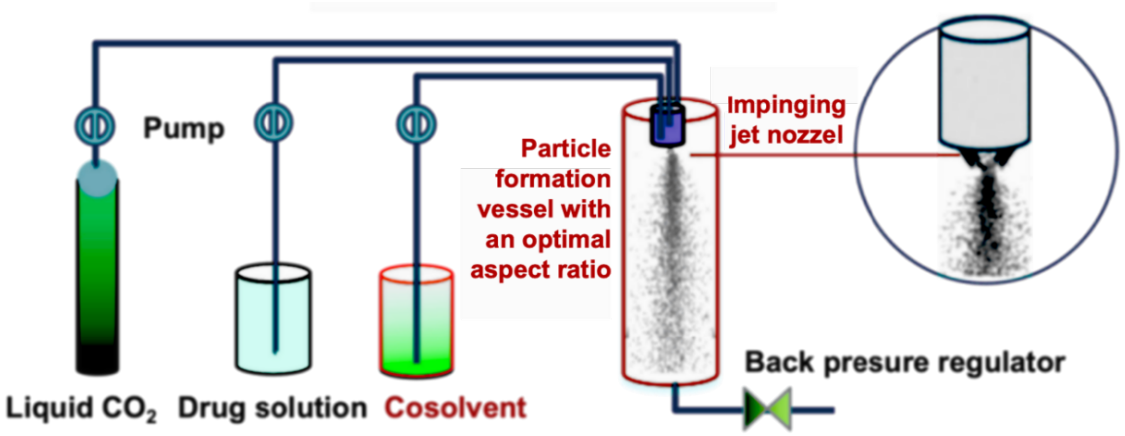


Figure 2. Schematic diagram illustrating the three-component improvements in the 3S-improved supercritical anti-solvent apparatus. Image created by the author with WPS Office

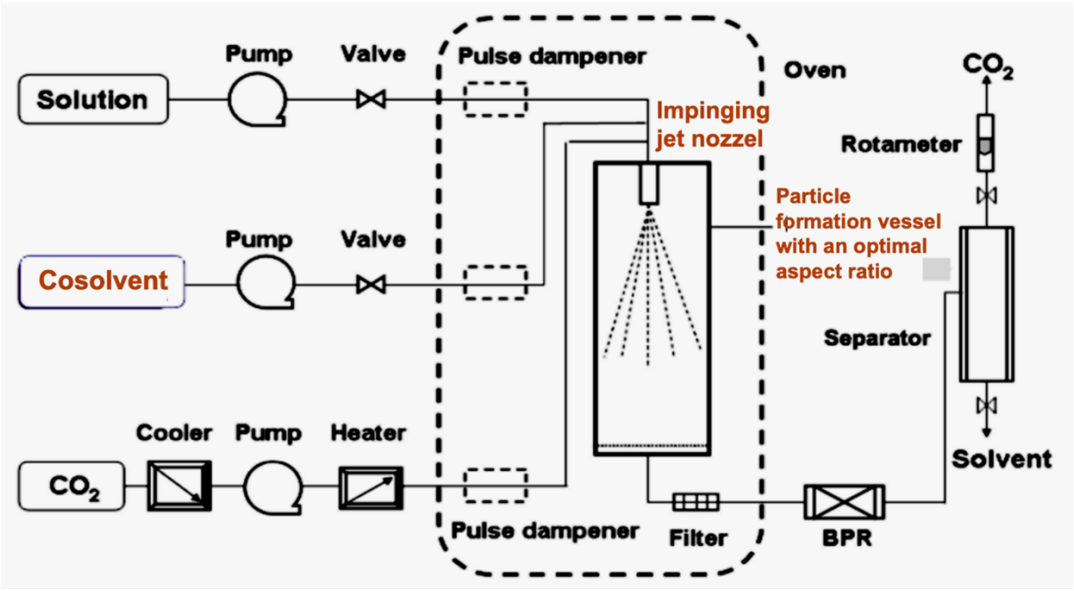


Figure 3. Flowchart of the reconfigured 3S-improved supercritical anti-solvent apparatus based on improvements to three components. Image created by the author with WPS Office.
Abbreviation: BPR: Back-pressure regulator.

indentations formed on the surface of the particles in a soft matter state, thereby forming bionic inhalation crystalline microspheres of budesonide-based series (BICM-BUDs) resembling red blood cells. The illustration in the upper left corner of Figure 6B demonstrates a BICM-BUDs formed in a small turbulent eddy.

In terms of process improvement for 3S-iSAS, four routes were established to design various DDS particles (Figure 7) and to realize the vision of small, smart, and stable particles for super drugs:

(i) 3S-Small™ process for generating nano- to micron-scale drug particles to enhance solubility, dissolution, and rapid release in inhalation, suspension, and transdermal delivery.
(ii) 3S-Specific™ process for rapid screening of polymorphs and for the preparation of selected crystal forms or seeds.
(iii) 3S-Smart™ process for altering physicochemical properties or creating functional structures to improve solubility, permeability, unpleasant taste, or release rate.
(iv) 3S-Biodrug™ process for enhancing the activity of biotherapeutic drugs (such as proteins, peptides, and vaccines), thereby improving delivery effectiveness via inhalation or injection.

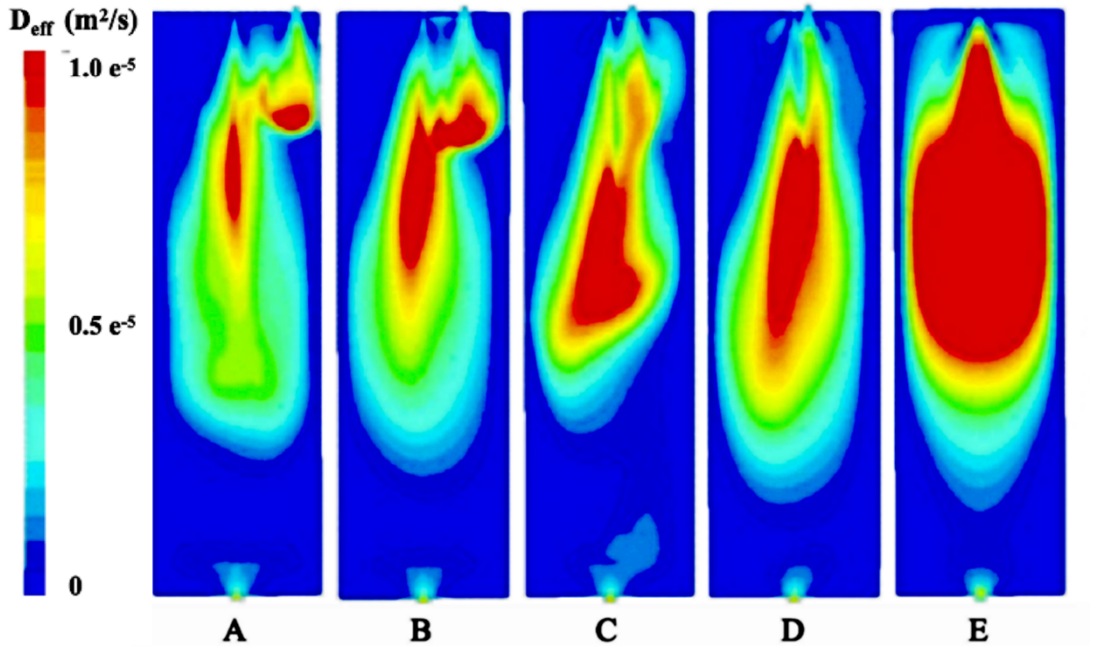


Figure 4. Computational fluid dynamics (CFD) simulation of the effective diffusion coefficient (D_{eff}) distribution profile inside the particle formation vessel of the 3S-improved supercritical anti-solvent apparatus. As the nozzle spacing decreases until overlapping, the D_{eff} value increases to a maximum in CFD E, indicating that the turbulent energy of $ScCO_2$ is fully utilized. Reprinted from Wang.[34]

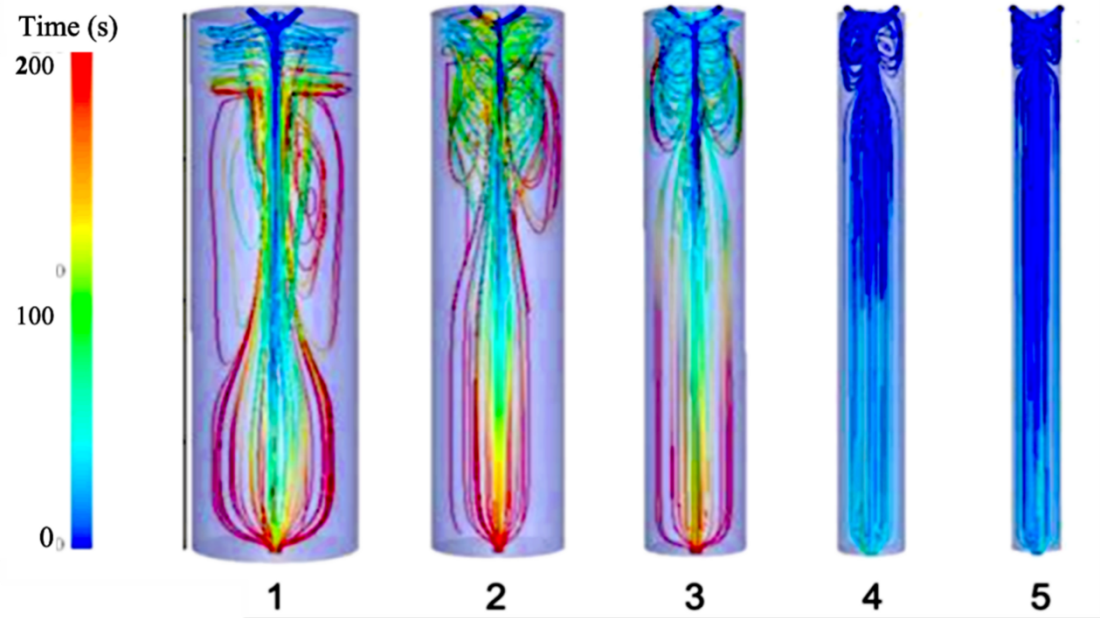


Figure 5. Computational fluid dynamics (CFD) simulations of a 90° impinging jet configuration show that changes in the aspect ratio of the particle formation vessel affect the time streaklines (particle trajectories) and the distribution of turbulent vortices. In CFD 4 and CFD 5, the large-scale turbulent eddies disappear, and a large number of small turbulent eddies are generated near the nozzle. The temporal streaklines describing the particle trajectories run parallel to the container walls. Reprinted from Wang.[34]

4. Innovative medicine

With improvements in equipment and processes, the pharmaceutical application of SCF PD has made significant progress. Some innovative candidates are worth noting, such as the hydrogel nanoformulation TTX101

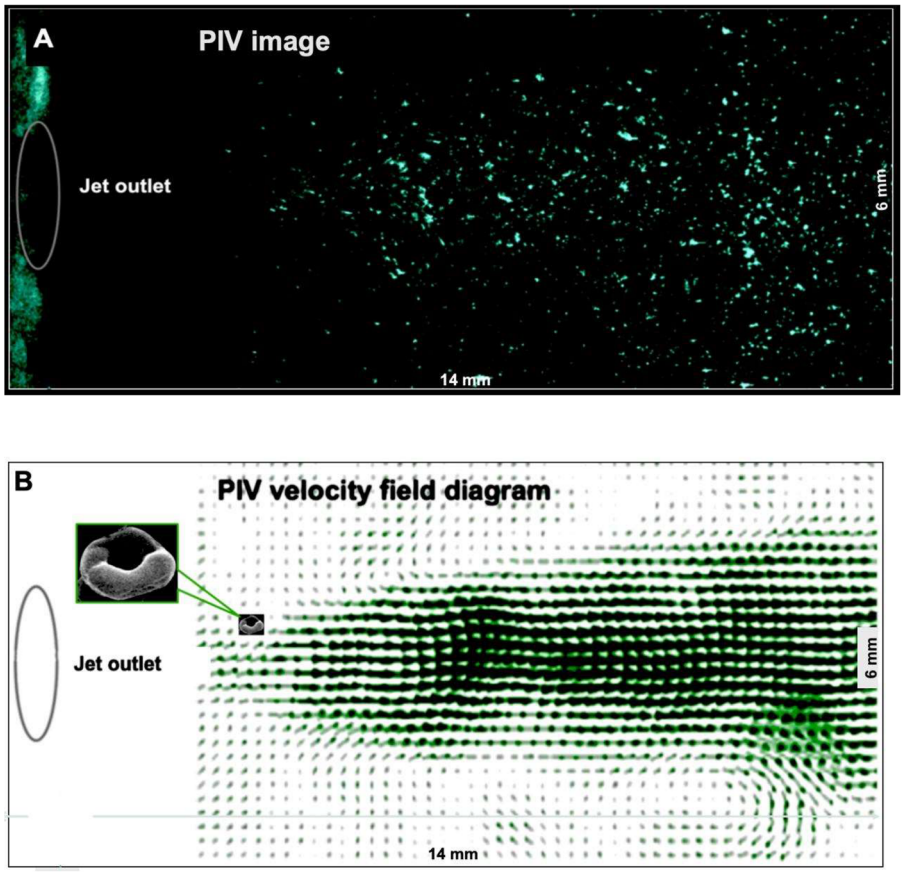


Figure 6. The instantaneous images of drug particles in the jet flow near the nozzle. (A) Captured by a high-speed particle image velocimetry (PIV) camera. (B) The velocity field obtained by measuring particle displacement from consecutive images taken at 2-ms intervals confirms the presence of numerous tiny eddies in the jet flow. The illustration in the upper left corner demonstrates a bionic inhalation crystalline microspheres of budesonide-based series (BICM-BUDs) formed in a small turbulent eddy. Image from the author.

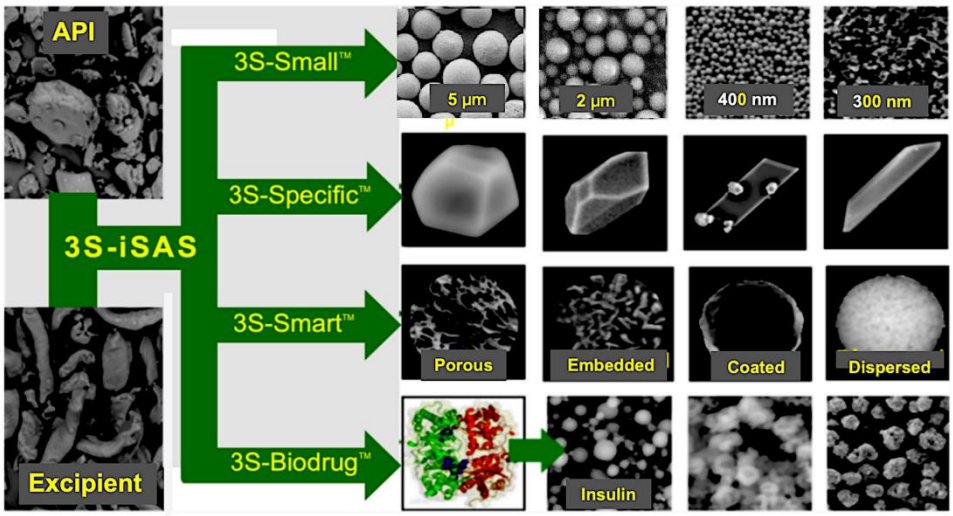


Figure 7. The 3S-improved supercritical anti-solvent (3S-iSAS) process for various drug delivery systems comprises four routes: 3S-Small™, 3S-Specific™, 3S-Smart™, and 3S-Biodrug™. Image created by the author with WPS Office.
Abbreviation: API: Active pharmaceutical ingredient.

for post-surgical treatment of malignant glioma, the inhalable insulin microspheres for treating diabetes, and BICM-BUDs for treating asthma and chronic obstructive pulmonary disease. Some innovative medicines have already been successfully developed, received orphan drug designation from the FDA, and entered GMP production, or been launched, such as the StaniTab® tablets of sirolimus with improved solubility through nano-composite powder formulation for preventing rejection in kidney transplant patients, Dasynoc® of dasatinib with reduced dosage through hybrid nanoparticle formulation for treating chronic myeloid leukemia and acute lymphoblastic leukemia, the nano-enzalutamide 160 mg single tablets for treating prostate cancerthe, and Zindol® of ginger-extract capsules for treating chemotherapy-induced nausea and vomiting.

4.1. Innovative medicines for poorly soluble drugs

In terms of enhancing drug dissolution, nanoparticles and microparticles offer significant advantages. Their large specific surface area not only increases dissolution but also accelerates drug release, allowing for higher drug concentrations at the absorption site in a shorter time. For poorly soluble drugs in the Biopharmaceutical Classification System (BCS) Classes II and IV, micronization is the most attractive approach.[35] Among marketed drugs, 30% are Class II, and 10% are Class IV; among drug candidates in the pipeline, 60–70% are Class II and 10–20% are Class IV.[36] The proportion of poorly soluble drugs is high. SCF PD has great potential for enhancing the solubility of such drugs, including amoxicillin, phenytoin sodium, ketoprofen, indomethacin, ampicillin, ipratropium bromide, paclitaxel, sirolimus, valsartan, lanatoside C, polycaprolactone, acetaminophen, griseofulvin, lidocaine, nifedipine, lovastatin, celecoxib, and rofecoxib.[37-39] Even for the same drug, particles with different sizes can be produced and delivered to specific target organs. For example, particles of 0.1–0.3 μm are used for intravenous administration, 1–5 μm for pulmonary administration, and 10–100 μm for oral administration.

There are several approaches for SCF PD to enhance the solubility of poorly soluble drugs. The first is to prepare nano- or microparticles. The theoretical basis is the Noyes–Whitney equation,[40,41] which indicates that the dissolution rate is proportional to the particle surface area. Additionally, the Ostwald–Freundlich equation indicates that solubility increases exponentially as particle size decreases below 1 μm. The second is to prepare particles in the preferred crystal form. The multiple crystal forms of a drug can affect its solubility, bioavailability, and other properties. Screening for the dominant crystal form or habit of a drug can increase solubility and improve bioavailability. The third is to prepare composite particles. By using functional excipients, smart structures such as uniform dispersion, embedding, coating, and porosity can be formed, increasing solubility or controlling drug release.

Nanocrystals and nanoscale amorphous drugs are effective strategies to improve the bioavailability of poorly water-soluble drugs.[42] For example, Rapamune® tablets (sirolimus, Wyeth),[43] used to prevent rejection in kidney transplant patients, are prepared from powdered formulations through wet milling or high-pressure homogenization, but these methods are relatively complex. To simplify this complex process, the StaniTab® method was used to produce GMP-compliant sirolimus nanocrystal composite powder, which was then directly compressed into tablets. The dissolution characteristics of the StaniTab® tablets were highly similar to those of commercial Rapamune® 2 mg tablets,[44] as shown in Figure 8.

Using the SCF PD to prepare coated composite particles has great potential to improve the solubility of poorly soluble drugs and mask their taste. Honz Pharmaceutical Co., Ltd. has achieved success in the solubilization, taste masking, and green manufacturing of children's medicines. For example, the main component of Sporanox™ capsules is ITZ, which is poorly soluble, and the manufacturing process of Sporanox™ capsules is very complex. By using the 3S-Smart™ process, the coated taste-masking particles were first produced and then formulated into granules.[45] The in vitro dissolution curve of these granules is comparable to that of Sporanox™ capsules. Another example is oral taste masking and solubilization of nimesulide granules using coated composite particles.[46,47] The 30 mg nimesulide granules exhibited superior in vitro dissolution characteristics compared to the existing 50 mg granules on the market (Figure 9).

4.2. Innovative medicines for anticancer drugs

Innovative anticancer medicine is another focus area of SCF PD. Anticancer drugs are often highly toxic, poorly soluble, and have low bioavailability. SCF PD technology makes full use of particle size and crystal form control, as well as composite microparticle preparation processes, not only enabling poorly soluble drugs to be formulated into nano- or micron-sized preparations, but also allowing them to be combined with biodegradable pharmaceutical polymers to create functionally unique composite microparticle preparations, opening up new avenues for anticancer biopharmaceuticals.

Anticancer medicines hold a prominent position in the market. On the one hand, the continuously increasing number of patients leads to a growing demand for various

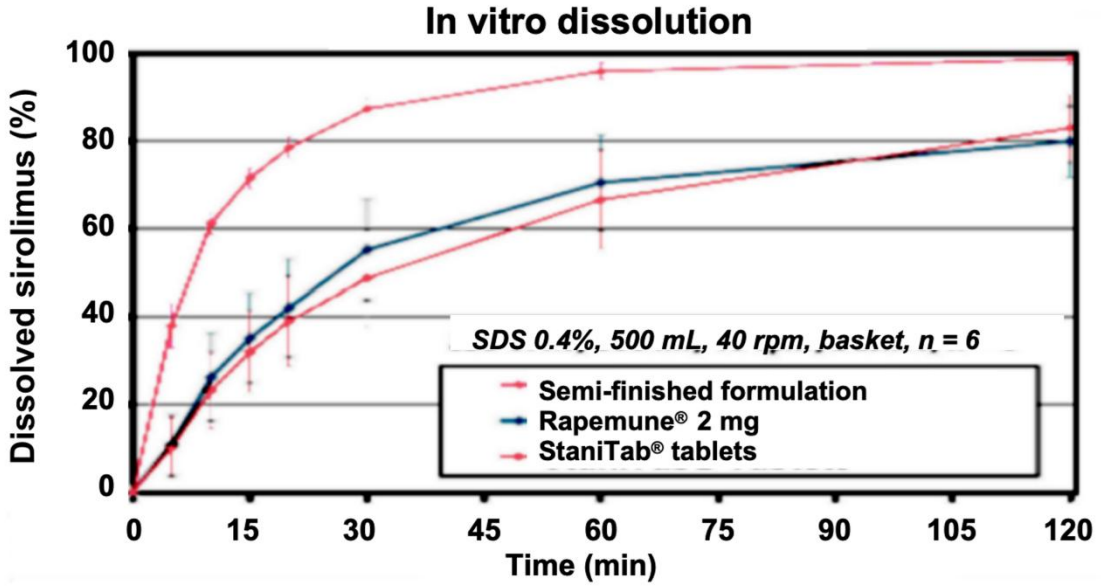


Figure 8. The dissolution profile of 2 mg StaniTab® tablets compressed from sirolimus nanocrystal composite powder is highly similar to that of commercial Rapamune® tablets. The in vitro dissolution tests were conducted using a United States Pharmacopeia Type I apparatus with a 0.4% sodium dodecyl sulfate dissolution medium at 37°C and a basket rotation speed of 40 rpm. The samples were analyzed using high-performance liquid chromatography with ultraviolet detection after filtration. Modified from Deschamps *et al.*[44]

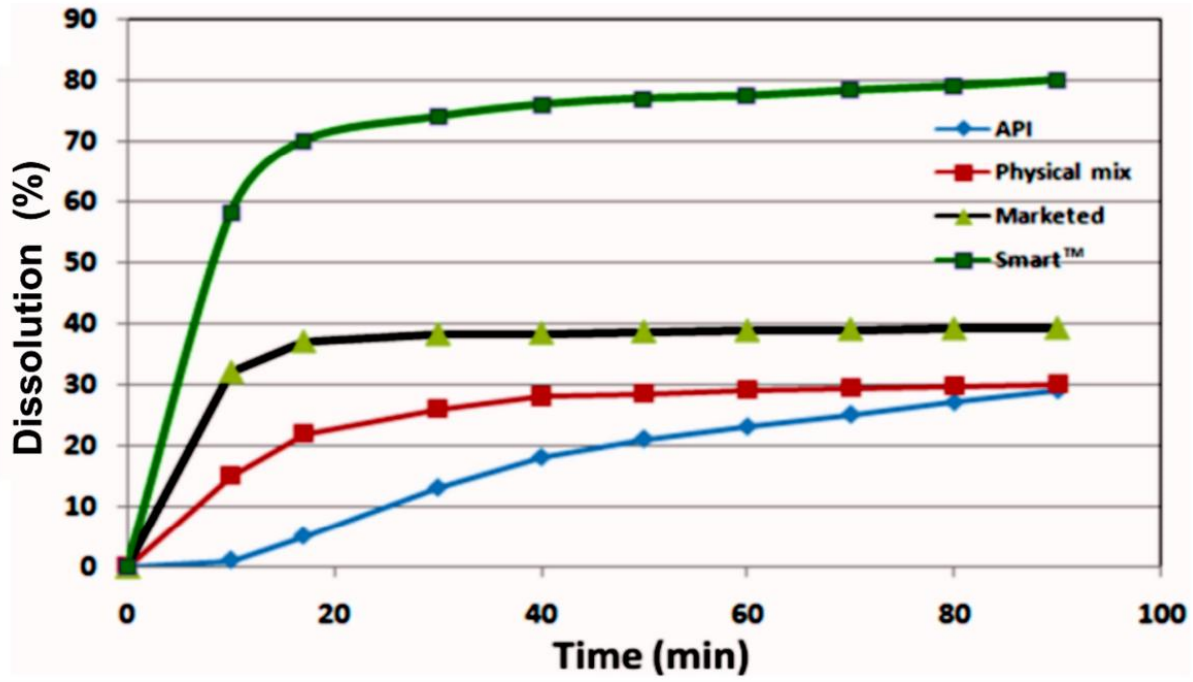


Figure 9. The 30 mg nimesulide granules produced using coated composite particles exhibit superior in vitro dissolution characteristics compared to the existing 50 mg nimesulide granules on the market. The in vitro dissolution tests were conducted using a dissolution tester (SYSTEM 860BDL-12, Logan Instruments Corp., United States), with a dissolution medium of phosphate buffer solution (pH 6.8) at 37 °C and stirred at 75 rpm. The samples were analyzed using a UV spectrophotometer (UV-2450, Shimadzu, Japan) at 393 nm after filtering. Modified from Liu *et al.*[47]

types and dosages of anticancer medicines; on the other hand, improving therapeutic efficacy remains an urgent issue to be addressed. For example, PKIs are a major class of targeted anticancer medicines that revolutionized cancer treatment when they entered the market over 20 years ago. There are over 80 PKIs available in the US market. Despite their clinical advantages, resistance, side effects, low dissolution, and low absorption pose significant challenges.

Most PKIs fall into Class II or IV compounds in the BCS, with very low water solubility, resulting in inadequate oral bioavailability. Their high lipophilicity (AlogP > 5)[48] exacerbates uneven gastrointestinal absorption and first-pass metabolism, significantly reducing the plasma concentration of new drugs. Traditional tablets struggle to achieve consistent release and usually rely on technologies such as nanoparticles, co-crystals, and amorphous solid dispersions to address this issue. Even so, according to the properties of FDA-approved small molecule PKIs,[49] some of their solubility remains very low, lipophilicity remains high, doses are relatively high, solvent residues exceed limits, and stability is poor. For example, lapatinib has a solubility of 22.3 μg/mL, AlogP of 6.14, and dosage of 1,250 mg/day; dasatinib has a solubility of 12.3 μg/mL, AlogP of 3.31, and dosage of 100 mg/day; nilotinib has a solubility of 2.01 μg/mL, AlogP of 6.36, and dosage of 600 mg/day; axitinib has a solubility of 0.55 μg/mL, AlogP of 4.64, and dosage of 300 mg/day; and cabozantinib has a solubility of 1.99 μg/mL, AlogP of 5.54, and dosage of 40 mg/day.

The SCF PD formulations have achieved significant success in addressing these issues: improved solubility, reduced dosage requirements, compliance with solvent-residue limits, extended shelf life at room temperature of 2–3 years, and greatly simplified manufacturing processes.

XSpray has developed four PKI candidates using the HyNap™ process:[50] Dasynoc®-XS004 (dasatinib), XS003 (nilotinib), XS008 (axitinib), and XS025 (cabozantinib). These are novel oral, immediate-release, nano-amorphous solid dispersion formulations that dissolve readily and exhibit pH-independent, uniform absorption. Specifically, in vitro biopharmaceutical studies of XS004 have shown that, compared to its crystalline reference, its solubility increases continuously over the pH range of 1.2–8.0. *In vivo*, XS004 is bioequivalent at a 30% lower dose and demonstrates increased absorption and bioavailability, while intra- and inter-individual variability is reduced by 2.1–4.8 times compared to the reference.[51] XS004 is designed to reduce dependence on stomach acid pH, thereby optimizing absorption and bioavailability, and minimizing drug interactions. This may improve the long-term efficacy and tolerability of dasatinib in chronic myeloid leukemia.[52] XS004 tablets are completely amorphous during long-term storage, as confirmed by an extremely sensitive instrument, indicating that XS004 remains amorphous and free of crystallinity for more than three years at room temperature.[53]

In the development of antitumor, anti-infection, and anti-Alzheimer's drugs, Aphios Corporation developed a commercial platform from laboratory to GMP production to produce anticancer medicines from medicinal plants and marine organisms using the SuperFluids™ process. The product pipeline includes Zindol®, a capsule formulation of an enhanced ginger product for the treatment of chemotherapy-induced nausea and vomiting, which has completed Phase III clinical trials and is now on the market.[54] Besides, the anti-Alzheimer's medicine APH-0703 is in Phase II clinical trials.

Gliomas are a type of brain cancer that is difficult to treat and has a high risk of recurrence after surgery. Nanoform in Finland and TargTex in Portugal have collaborated to develop an innovative medicine, TTX101, for postoperative treatment. The hydrogel nanoformulation TTX101, produced using the CESS® (Controlled Expansion Supercritical Solutions) process, enabled a 200-fold increase in drug load compared to bulk and a 5-fold increase compared to nanomilling. *In vivo* data and imaging in rats showed no tumors at doses below the maximum loading dose.[55] The FDA granted orphan-drug designation to TTX101 for the treatment of malignant gliomas.[56,57] Nanoform signed a GMP manufacturing program with TargTex following the successful formulation development.[58]

Another innovation is the nanocrystalline enzalutamide tablet. It is an alternative to the amorphous solid dispersion used in Xtandi®,[59] the first FDA-approved androgen receptor inhibitor, approved in 2012, and approved by the EMA in 2013 for the treatment of prostate cancer. The nano-enzalutamide tablet formulation is a 160 mg single tablet developed in collaboration between Nanoform and ONConcept and is preferred for prostate cancer patients with tablet burden and swallowing difficulties. A completed single-dose, randomized, bioavailability study compared enzalutamide 160 mg film-coated tablets (Bluepharma) and Xtandi® 4 × 40 mg film-coated tablets (Astellas Pharma Europe B.V.), and the clinical trial showed encouraging results.[60]

Leuprorelin acetate is used to treat endometriosis, uterine fibroids, prostate cancer, and postmenopausal breast cancer. It is unstable in body fluids and is rapidly excreted. The bioavailability of oral, rectal, and nasal administration is extremely low. However, when formulated into long-acting sustained-release microspheres, it can be injected once a month or every six months, such as the

newer six-month 45 mg depot leuprorelin formulation.[61] However, the manufacturing process using the traditional emulsion method is highly complex,[62] accompanied by higher active ingredient loss and residual solvents. The 3S-Smart™ process can greatly simplify production and improve the quality of these microspheres (Figure 10), with drug loading rates of 15–25%. The particle size can be controlled at 5–25 μm, with lower residual solvent and 98.8% activity. The likelihood of clogging during clinical injection is extremely low.

Tamoxifen citrate, a gold-standard targeted medicine for the treatment and prevention of breast cancer,[63] has two crystal forms: Form A, with a single peak in the infrared spectrum at 1700–1740 cm^{-1}, and Form B (active pharmaceutical ingredient [API]), with two peaks in this region. Only Form A can be used for clinical treatment. Traditional techniques for producing Form A involve multiple processes and may even require the addition of seeds. However, the 3S-Specific™ process enables a complete transformation from Form B (API) to Form A in a single process. Figure 11 shows the scanning electron microscopy (SEM) and Fourier transform infrared spectroscopy (FTIR) images of Form A. This new process offers an extremely simplified method for the complete polymorphic transformation of anticancer drugs.

4.3. Innovative medicines for inhalation drugs

Innovative inhalants are a significant area of SCF PD application. It is well known that the efficacy of inhalants depends on several interdependent factors:[64] formulation, microgram-level packaging, metered-dose inhalers with dose counters, correct usage, and compliance with regulatory frameworks. Therefore, small drug particles are the foundation of the entire inhalant industry chain. The current development trends in inhalants can be summarized as transitioning from carrier-dependent to carrier-free, from single drugs to drug combinations, from microparticles to nanoparticles, from small molecules to large biological molecules, and from treating local diseases to systemic diseases.[65] However, all forms of development face a fundamental challenge: the aggregation of drug particles. Currently, no inhalant has been able to eliminate this root problem, and various technologies can only address the symptoms rather than the cause. Although formulations and devices are becoming increasingly complex, achieving the expected proportion of the drug that actually reaches the lungs remains difficult. Therefore, inhalants urgently need new technology that addresses the root cause, producing inhalable drug particles with minimal aggregation. SCF PD has great potential in this area and can play a breakthrough role.

Ferro Corporation in the US is a global leader in providing fine chemical products. In 2004, it established a dedicated SCF PD engineering laboratory, focusing on purification and formulation using the SFEE® process to

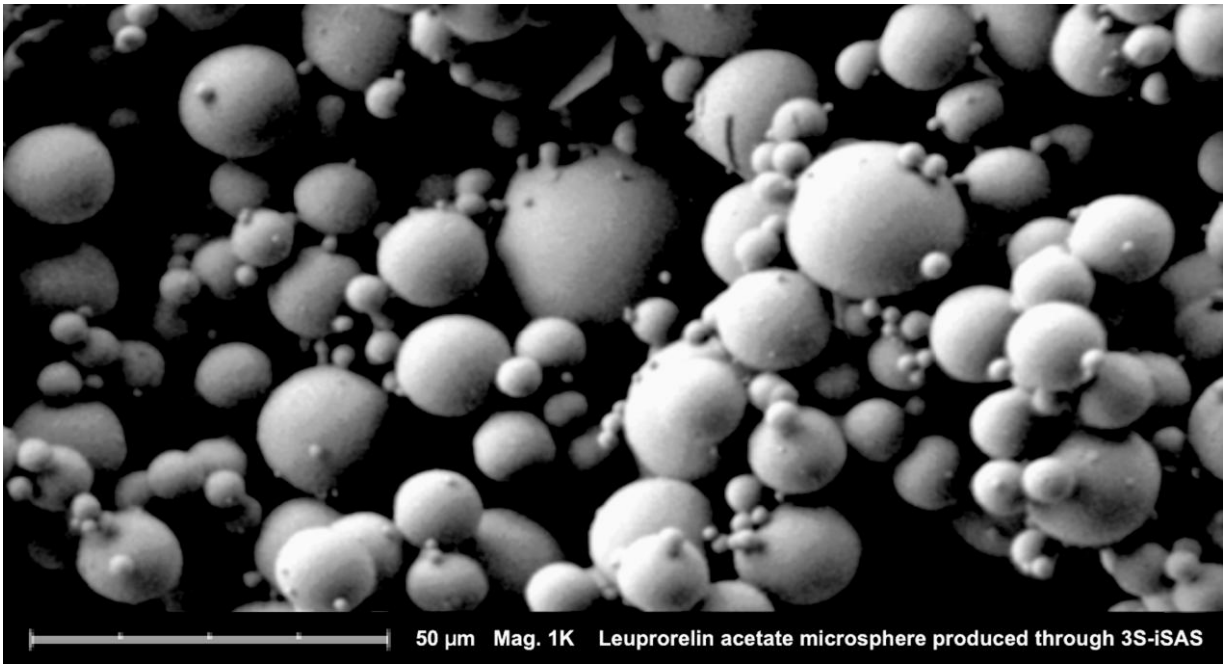


Figure 10. Scanning electron microscopy image of leuprolide acetate long-acting, sustained-release microspheres, produced through the 3S-Smart™ process, which greatly simplifies the production process and improves its quality. Scale bar: 50 μm; magnification: 1,000×. Image from the author.

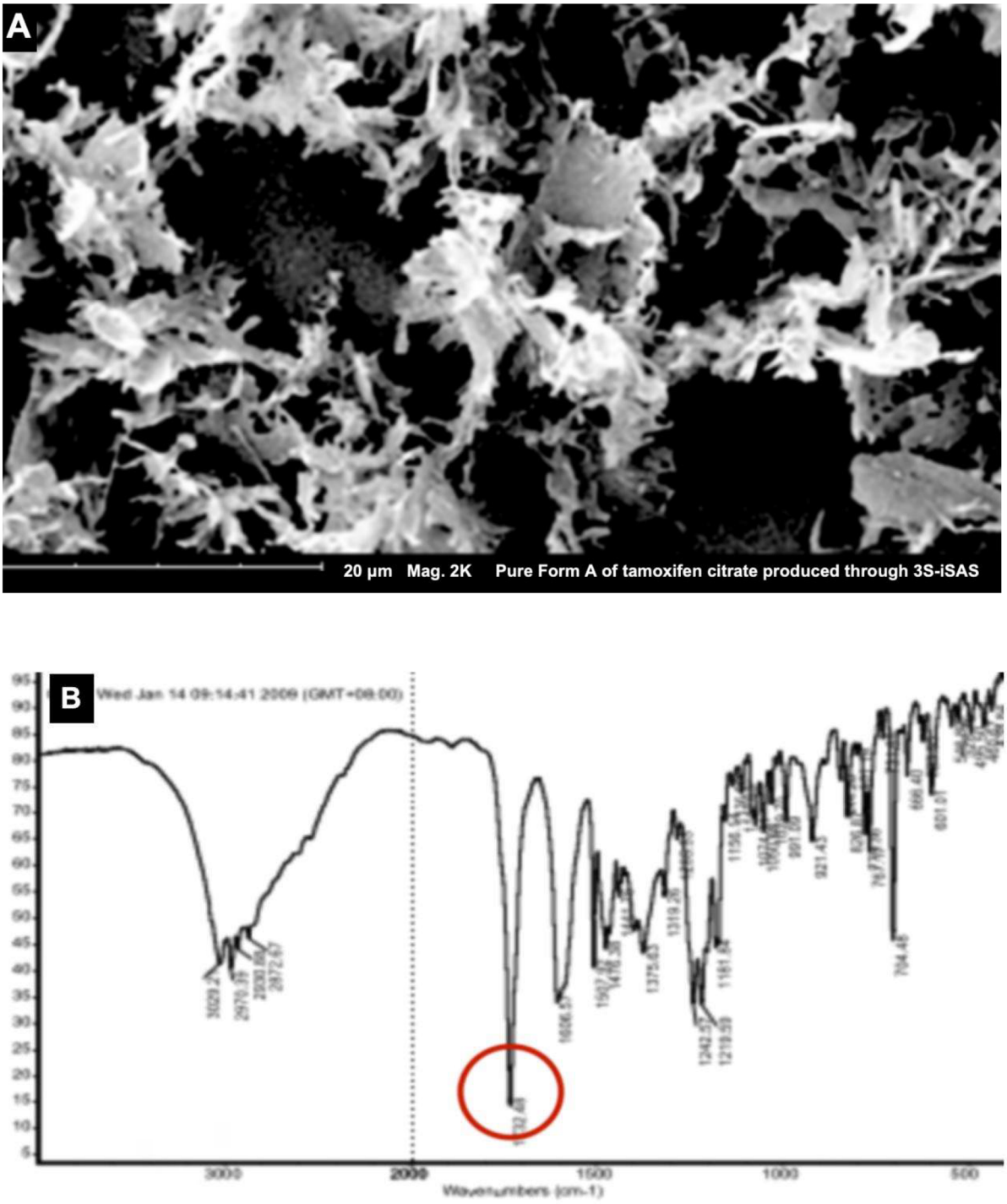


Figure 11. Characteristics of tamoxifen citrate Form A. (A) Scanning electron microscopy image. (B) Fourier transform infrared spectroscopy image. Form A is obtained by completely converting Form B (API) through a single-step 3S-Specific™ process. In the infrared spectrum range of 1700–1740 cm^{-1}, Form A exhibits a single peak. Image from the author.
Abbreviation: API: Active pharmaceutical ingredient.

produce excipient-free nanocrystals of poorly soluble drugs, increasing solubility by 5–10 times.[66] SFEE® has also been developed as a continuous process for producing solid-lipid nanoparticles (SLNs) in respiratory drug suspensions, with particle sizes ranging from 10 to 100 nm, encapsulation rates of 80–90%, and solvent residues below 20 ppm. The median particle size of indomethacin SLN is 20 nm, and that of ketoprofen SLN is 60 nm. The indomethacin nanoparticle suspension is transparent and stable and can be filtered through a 0.22 μm ultrafiltration membrane at a drug loading of less than 20%. This drug solution is used in spray formulations, with a fine particle fraction ($FPF_{<3.5\ \mu m}$) reaching 65% for ketoprofen and 79% for indomethacin.[67]

Recombinant human insulin is the most effective drug for treating diabetes, and there has long been a desire to switch from injections to inhalation administration. The dry powder inhalers Exubera® (launched by Pfizer and Nektar in 2006) and Afrezza® (launched by MannKind in 2014) caused a sensation at one point but were withdrawn from the market in 2007 and 2016, respectively, due to poor sales[68], indicating that their formulations and spray-drying processes still need improvement. As a later entrant, SCF PD shows tremendous potential. The Chinese National Academy of Nanotechnology and Engineering developed inhalation recombinant human insulin (IRHI) using the SCF PD process. The particle size distribution of IRHI was extremely narrow: D_{10} = 0.729 μm, D_{50} = 1.525 μm, D_{90} = 3.232 μm, over 99% within 5 μm (Figure 12). For a comparison of the properties of IRHI and API, please refer to Table 2. The potency of IRHI was measured by high-performance liquid chromatography as 96.8% of the API. The contents of high-molecular-weight protein and deamidated (A21) protein were both below pharmacopoeial limits. Residual solvents were greatly reduced, and the stability at room temperature exceeded two years, with no aggregation or degradation observed.[69]

Budesonide is a popular drug for treating asthma and chronic obstructive pulmonary disease. AstraZeneca has successfully launched a series of BUD-based inhalers, including Pulmicort®, Turbuhaler® (BUD), Symbicort®, Turbuhaler® (BUD/formoterol), and Breztri®, Aerospheres® (BUD/glycopyrronium bromide/formoterol). They all use milled BUD particles (Milled) as the main ingredient, without using lactose particles as a carrier. Both Pulmicort® and Symbicort® are produced using the soft aggregate sphere process[70], while Breztri® is produced using the co-suspension sphere process.[71] These processes cleverly utilize the tendency of particles to aggregate or adhere, but do not fundamentally solve the problem of particle aggregation. Moreover, these processes are quite complex, setting a relatively high barrier for generic inhalers.

3S PharmaTech identified that the root cause of drug particle aggregation is high surface energy. The 3S-iSAS process can fundamentally solve this problem and has successfully produced BICM-BUDs with a low surface energy profile[72], including the single-component BUD, BICM-B; the dual-component BUD/formoterol, BICM-BF; and the triple-component BUD/glycopyrronium bromide/formoterol, BICM-BGF. They are all very similar to red blood cells, but their surfaces appear plush-like (Figure 13). The unique "nano-in-micron" structure was observed for the first time in BICM-BGF using high-resolution SEM. The surface is covered with dense nanowhiskers, while the underlying layer exhibits a self-similar, ring-like, interwoven texture (Figure 14). They rarely aggregate and exhibit excellent dispersibility with uniform particles. The particle size distribution of the pilot-scale BICM-B is narrowly normal, with D_{10} = 0.82 μm, D_{50} = 2.61 μm, and D_{90} = 4.83 μm (Figure 15). They performed exceptionally well in the carrier-free in vitro inhalation assessment, at 60 L/min, 25 °C, and relative humidity of 40–60%, with 1.6 mg of sample aerosolized into a next-generation impactor (NGI; MSP, US; n = 3). For example, the $FPF_{<5\ \mu m}$ of BICM-B reached 32.9%, significantly higher than Pulmicort® (28.4%).[73] Milled was only 7.33% due to severe aggregation (Figure 16).

Intuitively, the excellent aerodynamic properties of BICM-B stem from its outstanding characteristics, such as particle size, shape, and dispersibility. In particular, its unique "nano-in-micron" texture makes it lightweight, tougher, hydrophobic, and self-lubricating. Essentially, they are directly related to a higher-dimensional quantity: the surface energy of particles.[74]

As can be seen in Figure 17, the total surface energy profile, the cohesion work W^{1-2}_{coh}, and the adhesion work with water W^{W}_{adh} were measured using the second-generation inverse gas chromatography–surface energy analyzer (iGC-SEA, Surface Measurements System Ltd., UK) for BICM-B and Milled. BICM-B showed a low and flat total surface energy profile, meaning that the energy of all particles is almost at the same level and independent of size, making them less likely to aggregate. In contrast, Milled showed a high and steep profile, indicating that its energy distribution differs from BICM-B and naturally tends to shift toward a more stable, lower-energy state through aggregation. Similarly, the cohesion work W^{1-2}_{coh} reflects the aggregation characteristics of the particles, while the adhesion with water work W^{W}_{adh} reflects the hydrophobicity of the particles. Both curves showed the same trend as the total surface energy profiles. Obviously, changes in morphology and physical properties between

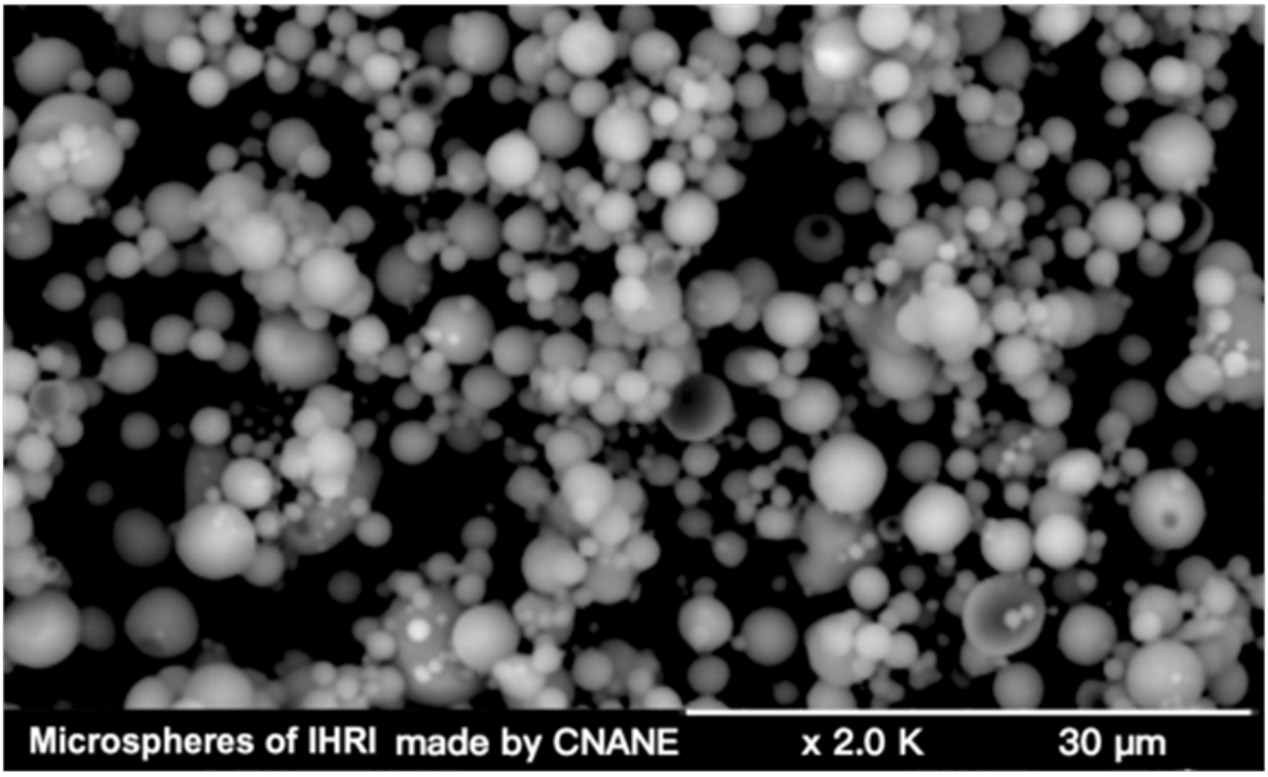


Figure 12. Scanning electron microscopy image of inhalation recombinant human insulin (IRHI) produced by the Chinese National Academy of Nanotechnology and Engineering (CNANE). The particle size distribution is extremely narrow: D_{10} = 0.729 µm, D_{50} = 1.525 µm, D_{90} = 3.232 µm, over 99% within 5 µm. Scale bar: 30 µm; magnification: 2,000×. Image from the author.

Table 2. Comparison of the properties of IHRI with API

Properties	IRHI	API of RHI
Crystal form	Amorphous	Amorphous
Insulin potency (U/mg)	26.9	28.5
Insulin desamido (A21) (%)	0.07	0.16
Insulin HMWP (%)	0.13	0.10
Moisture content (%)	5.5	4.6
Zinc (% w/w)	0.62	0.62
Residual solvent (ppm)	1,130	54,505

Abbreviations: API: Active pharmaceutical ingredient; HMWP: High-molecular-weight protein; IHRI: Inhalation recombinant human insulin; RHI: Recombinant human insulin.

BICM-B and Milled lead to corresponding changes in total surface energy, W^{1-2}_{coh}, or W^{W}_{adh}. Therefore, they can serve as a higher-dimensional overall measure relative to physical properties. In general, a low and flat surface

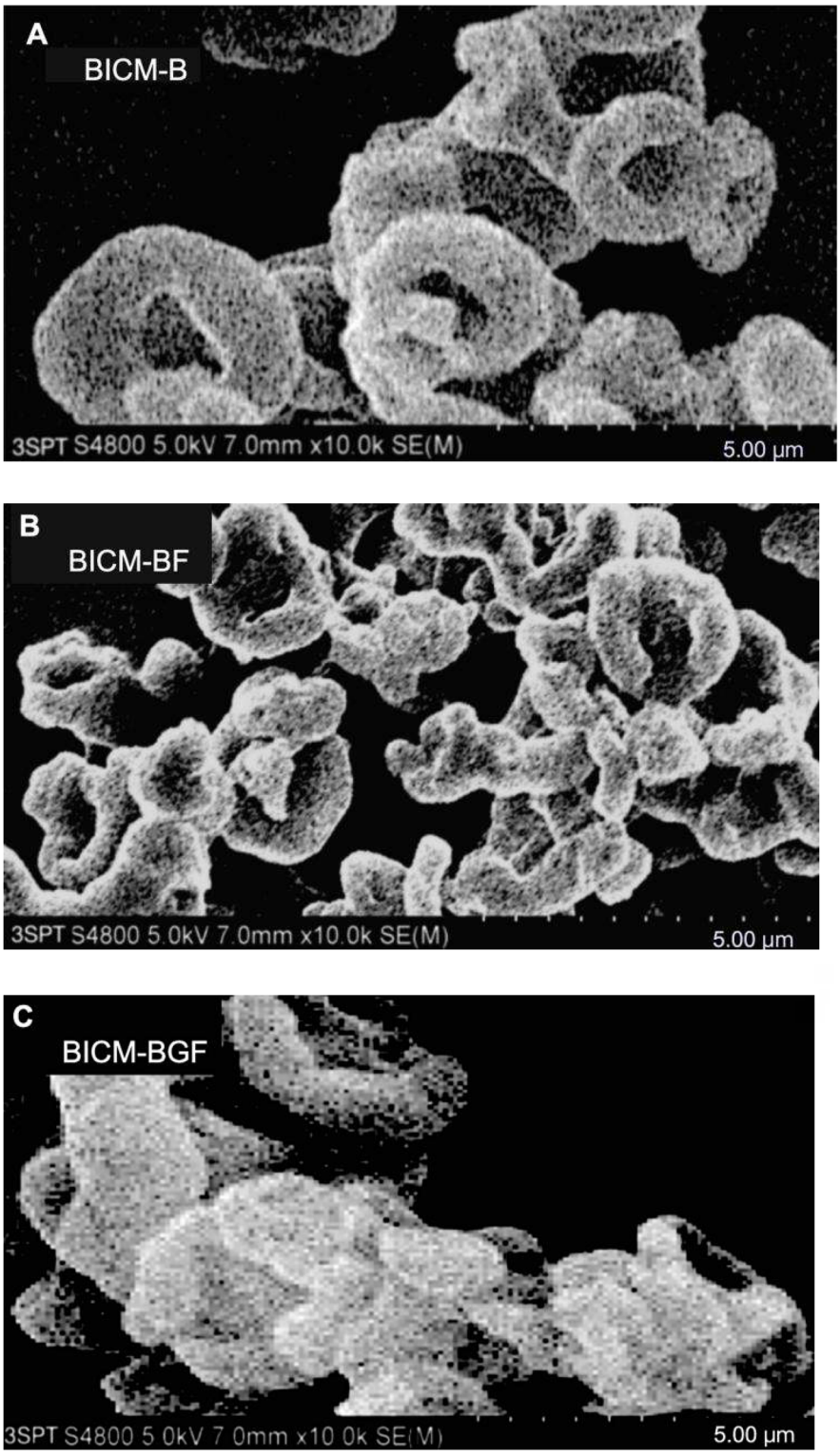


Figure 13. The high-resolution scanning electron microscopy images of bionic inhalation crystalline microspheres (BICM) of budesonide (BUD)-based series: (A) BUD (BICM-B), (B) BUD/formoterol (BICM-BF), and (C) BUD/glycopyrronium bromide/formoterol (BICM-BGF), prepared through the 3S-improved supercritical anti-solvent process. Their appearance is highly similar to that of red blood cells, but their surfaces appear plush-like. Scale bars: 5 µm; magnifications: 10,000×. Images from the author.

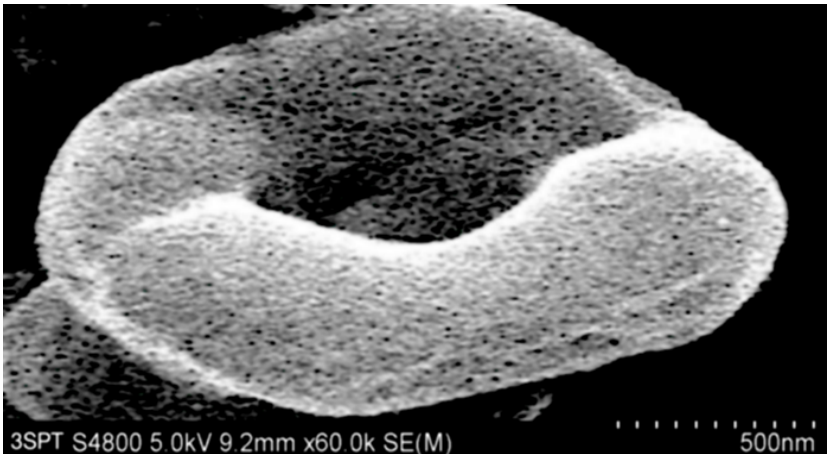


Figure 14. The high-resolution scanning electron microscopy image of bionic inhalation crystalline microspheres of budesonide/glycopyrronium bromide/formoterol (BICM-BGF) produced through the 3S-improved supercritical anti-solvent process. The unique "nano-in-micron" structure was observed for the first time in BICM-BGF. The surface is covered with dense nanowhiskers, while the underlying layer exhibits a self-similar, ring-like, interwoven texture. Scale bar: 500 nm; magnification: 60,000×. Image from the author.

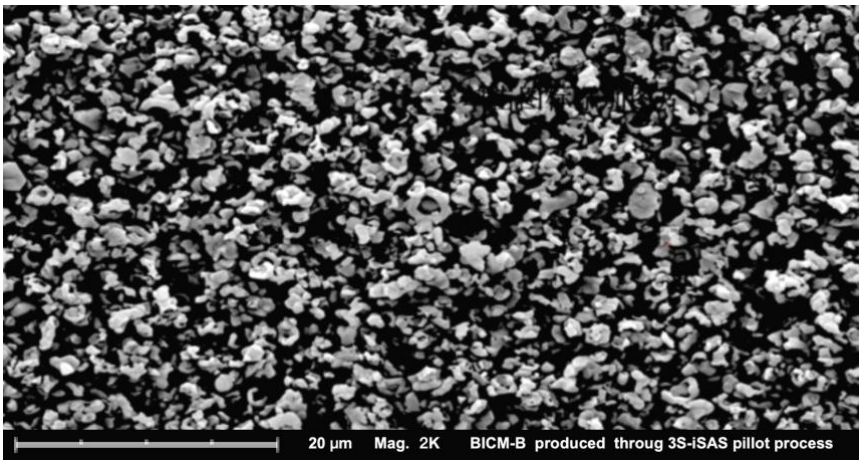


Figure 15. Scanning electron microscopy image of the pilot-scale bionic inhalation crystalline microspheres of budesonide (BICM-B) shows excellent dispersion with uniform particles and no agglomeration. The particle size distribution is narrowly normal, with D_{10} = 0.82 µm, D_{50} = 2.61 µm, and D_{90} = 4.83 µm. Scale bar: 20 µm; magnification: 2K. Image from the author.

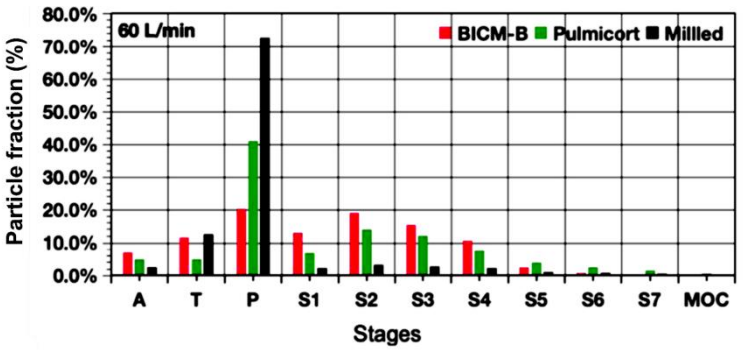


Figure 16. An in vitro inhalation assessment of bionic inhalation crystalline microspheres of budesonide (BICM-B) and of milled budesonide particles (Milled), as well as Pulmicort®, was conducted under carrier-free conditions at 60 L/min, 25 °C, and relative humidity of 40–60%, with 1.6 mg of sample aerosolized into the next-generation impactor (n = 3). The fine particle fraction ($FPF_{<5\ \mu m}$) of BICM-B was 32.9%, higher than Pulmicort®'s 28.4%, whereas due to severe agglomeration, the $FPF_{<5\ \mu m}$ of Milled was only 7.33%. Reprinted from Sun.[72]
Abbreviation: MOC:Micro-orifice collector.

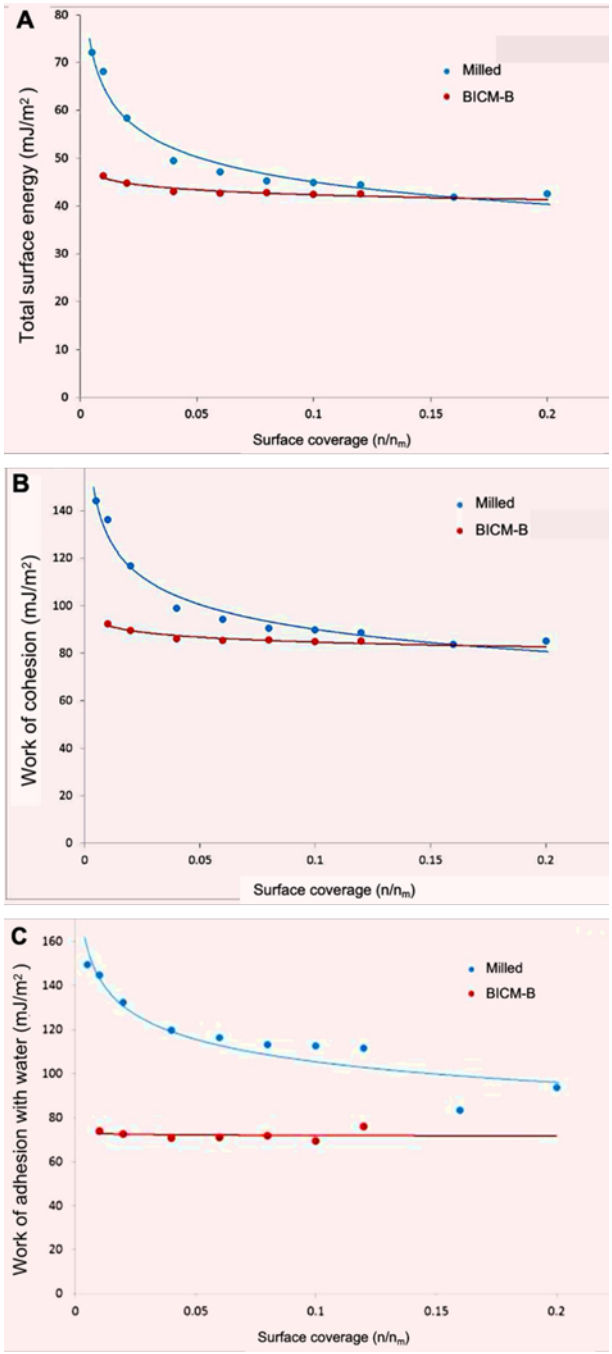


Figure 17. The total surface energy profiles, the cohesion work W^{1-2}_{coh}, and the adhesion work with water W^{W}_{adh} were measured using an inverse gas chromatography–surface energy analyzer for bionic inhalation crystalline microspheres of budesonide (BICM-B) and of milled budesonide particles (Milled). All three parameters show the same trend: BICM-B exhibits low and flat distribution curves, while Milled shows high and steep distribution curves. In general, a low and flat surface energy profile corresponds to higher crystallinity, stronger hydrophobicity, lower viscosity, less aggregation, and longer stability, and vice versa. Reprinted from Sun.[72]

energy profile corresponds to higher crystallinity, stronger hydrophobicity, lower viscosity, less aggregation, and longer stability, and vice versa.

5. Conclusion

Supercritical fluid particle design-based innovative medicines have broken through the limitations of traditional technologies. They have made unprecedented progress in low-solubility drugs, anticancer drugs, and inhalation drugs. Some products have completed Phase III clinical trials and been approved by the FDA, while others have entered the production and sales stages, highlighting the enormous potential of innovative DDS formulations. Obtaining FDA approval through the 505(b)(2) NDA regulatory pathway requires supporting data for new technologies such as SCF PD. Taking low-solubility drugs, anticancer drugs, and inhalation drugs as examples, some of them have been on the market for decades. Despite their significant efficacy, they have obvious shortcomings. Due to bottlenecks in the original technologies, these shortcomings cannot be remedied through subsequent improvements. SCF PD, with its outstanding ability to prepare small, smart, and stable drug particles, takes on the challenging task of innovatively improving original drugs. It has made breakthroughs in enhancing the solubility of low-solubility drugs, improving the efficacy of anticancer drugs, and upgrading inhalation formulations, solving previously difficult problems, thereby opening new avenues for bringing innovative medicines to market through the 505(b)(2) NDA channel.

Looking to the future, the commercialization of SCF PD still has significant work to be done. An important marker of commercialization is the scale of market sales and the extent of patient use. Although commercialization will bring a huge market to SCF PD, it also brings new challenges: innovative medicines must meet regulatory requirements, and production must comply with GMP standards. This involves multiple aspects, such as selecting APIs suitable for the SCF PD process to develop innovative drugs, improving SCF PD pharmaceutical equipment, ensuring that production operations comply with GMP regulations, and accelerating the approval of innovative medicines.

Artificial intelligence (AI) will play an important role in addressing these challenges. Nanoform has developed an AI-based drug candidate screening tool, STARMAP®, which is the AI version of the CESS® process and includes about 20,000 analytical drugs and drug candidate molecules from the public domain. It can identify which molecules are suitable for nanoformulations through computer-simulated experiments and understand their applications

across different therapeutic areas, target categories, and disease types.[75] Nanoform granted AstraZeneca a global license for STARMAP®. As Nanoform Chief Business Officer Christian Jones stated: "By combining Nanoform's AI-based STARMAP® approach with our internal nanotechnology expertise, we can help accelerate AstraZeneca's drug development goals and support more patient- and planet-centered drug development programs."[76] If other SCF PD pharmaceutical processes, whether developed independently or in collaboration, have corresponding AI versions, selecting drugs suitable for SCF PD processes will be effortless.

The upgrade of SCF PD pharmaceutical equipment should also be supported by AI technology, moving toward digital intelligence and system integration. First, supercritical fluid reactions can be combined with SCF PD to directly produce salt-based drug particle formulations. Second, SFE can be integrated with SCF PD, allowing lipophilic active pharmaceutical ingredients extracted in real time from natural raw materials via SFE to be directly converted into drug particle formulations through SCF PD, forming an integrated SFE–PD pharmaceutical platform. This approach can simplify multi-step processes, reduce production costs, and achieve energy-efficient, highly effective, and green sterile continuous manufacturing (Figure 18). Third, in the biopharmaceutical industry, the SCF PD process can be used to produce standard-compliant granular formulations from low-concentration biodrug solutions. This integrated production not only simplifies the process but also significantly enhances the production capacity and quality of formulations, achieving energy savings, environmental protection, and green manufacturing.

The commercialization of SCF PD will lead to a large number of innovative medicines being submitted to regulatory authorities for approval. This will drive the introduction of relevant policies and regulations, utilize AI to process a large volume of application data, speed up the approval process, enable pharmaceutical companies to obtain production licenses more quickly, and allow patients to access more and better SCF PD innovative medicines.

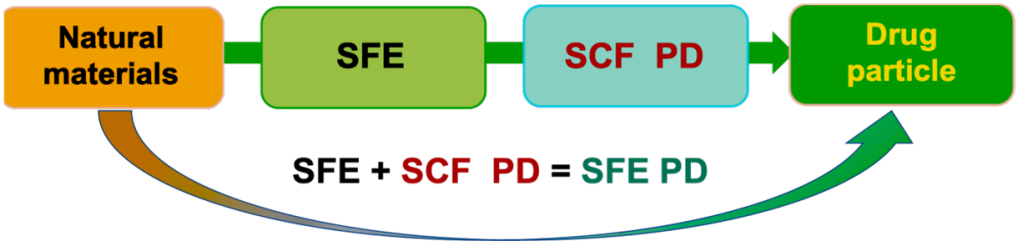


Figure 18. The schematic diagram of the integrated supercritical fluid extraction–particle design (SFE–PD) technology platform, which uses SFE to extract lipid-soluble drug components from natural raw materials, performs real-time online supercritical fluid particle design, and produces drug particles for innovative medicines. Image created by the author with WPS Office.

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Conflict of interest

Yongda Sun is an employee of 3S PharmaTech and 3S PharmaEng Co.; however, he was not involved in any activities that could constitute a conflict of interest in relation to this study.

Author contributions

This is a single-authored article.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

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