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REVIEW ARTICLE

Advanced Manufacturing Processes and 3D Printing Approaches for Enhancing Solubility and Bioavailability of Poorly Water-Soluble Drugs

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Abstract

Poor aqueous solubility is a critical challenge in drug development, often leading to low oral bioavailability and limited therapeutic efficacy. To address this issue, advanced manufacturing processes and 3D printing technologies have emerged as powerful strategies for improving drug solubility and dissolution behavior. Advanced techniques such as hot-melt extrusion, spray drying, nanocrystal technology, co-crystallization, lipid-based systems, and amorphous solid dispersions enable stable formulations with enhanced solubility and scalable production. In parallel, 3D printing offers unique advantages in fabricating personalized, complex, and controlled-release dosage forms, making it an attractive approach for precision medicine. This review highlights the principles, advantages, and applications of these technologies in enhancing the solubility and bioavailability of poorly water-soluble drugs. Comparative insights into their effectiveness, case studies of successful formulations, and emerging trends are discussed. While challenges remain in terms of stability, regulatory acceptance, and large-scale translation, the integration of advanced manufacturing with 3D printing and computational tools holds immense potential to revolutionize future pharmaceutical development and patient-centered therapies.

Keywords: 3D Printing, bioavailability, water-soluble drugs, aqueous solubility, permeability.

1 Introduction

Oral drug delivery largely depends on both solubility and permeability. Solubility refers to the capacity of a solute—whether solid, liquid, or gas–to dissolve in a solvent, forming a homogeneous system. It is influenced by factors such as the nature of the solvent, temperature, and pressure [1]. The extent of

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solubility is expressed as the saturation concentration, beyond which additional solute cannot dissolve. In pharmaceuticals, solubility is defined as the maximum amount of drug that can be dissolved in a given solvent under specific conditions of temperature and pressure [2].

The oral route remains the most common form of drug administration due to its patient convenience, cost-effectiveness, design flexibility, and fewer sterility requirements. However, challenges such as poor aqueous solubility, limited permeability, low dissolution rate, first-pass metabolism, and efflux mechanisms often hinder effective formulation. Since solubility directly affects the concentration of drug available in systemic circulation, it plays a crucial role in determining therapeutic efficacy. Drugs with poor solubility exhibit slower absorption and reduced bioavailability, often resulting in suboptimal clinical outcomes [3].

According to IUPAC, solubility is the analytical composition of a saturated solution, expressed in terms of concentration, molality, mole fraction, or similar units. Based on the Biopharmaceutics Classification System (BCS), drugs are categorized into four classes [3]:

- Class I: high solubility, high permeability
- Class II: low solubility, high permeability
- Class III: high solubility, low permeability
- Class IV: low solubility, low permeability

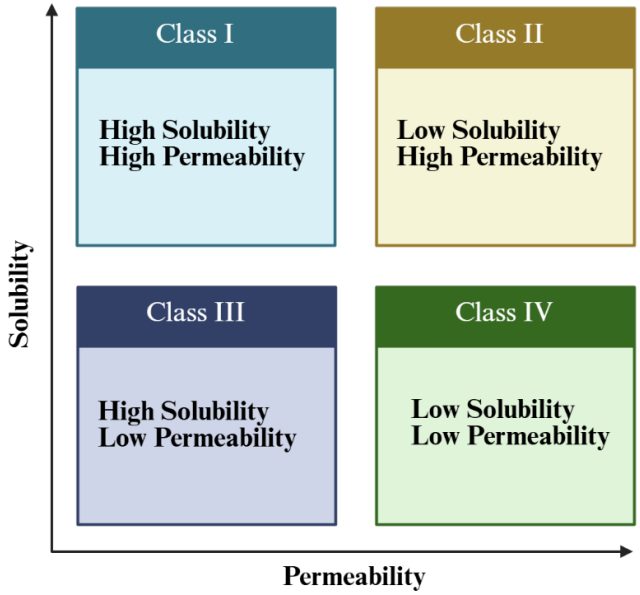

Figure 1. Biopharmaceutics classification system (BCS): categorization of drugs based on solubility and permeability.

Several factors influence the solubility and bioavailability of drugs, as illustrated in Figure 1:

1. **pH Levels**: pH reflects the concentration of hydrogen ions in a solution, with higher hydrogen ion content indicating lower pH. Strong acids or bases dissociate completely, while weak ones only partially dissociate. The pKa value is commonly used to assess acid strength; a lower pKa indicates stronger acidity and greater dissociation in water.
2. **Polarity of Drug and Solvent**: Ionization plays a critical role in drug solubility and absorption. In the gastrointestinal tract, drugs are usually absorbed in their non-ionized (lipid-soluble) form, while ionization in the bloodstream prevents their return to the GI tract and ensures systemic absorption. Generally, lipophilic (non-ionized) drugs are absorbed more effectively, whereas highly hydrophilic (ionized) drugs exhibit reduced absorption.
3. **Particle Size**: Drug solubility is inversely related to particle size; smaller particles dissolve more readily, while larger ones show reduced solubility under the same conditions of temperature, pressure, and polarity. Reduced particle size enhances dissolution and facilitates passive diffusion across membranes without the need for energy or transport proteins.
4. **Dissolution Process**: Most drugs undergo an endothermic dissolution, meaning solubility increases with temperature. Thus, the transition from storage conditions to body temperature favors improved solubility. Additionally, agitation (such as gastrointestinal motility) accelerates the dissolution rate, further enhancing drug absorption [4].

1.1 Does Solubility Affect Drug Absorption

Oral drug absorption depends on the disintegration of dosage forms into smaller molecules that can dissolve and pass through aqueous channels of the gastrointestinal tract (GIT) for systemic uptake. Several factors, including available surface area, food interactions, and blood flow, influence this process. For absorption, drugs generally require lipid solubility to cross biological membranes, unless they rely on active transport mechanisms or are small enough to diffuse through aqueous pores. Insufficient solubility can hinder transfer from the GIT to the bloodstream, resulting in poor bioavailability and reduced therapeutic effect [5]. Since solubility directly governs absorption, bioavailability, and ultimately

efficacy and safety, improving solubility is crucial for optimal performance. Multiple formulation strategies have been developed to enhance solubility and ensure consistent absorption. Among them, nanoscale drug delivery systems stand out due to their ability to control particle size, surface characteristics, and release properties, enabling not only improved bioavailability but also targeted delivery, controlled release, and dual diagnostic-therapeutic applications [6].

1.2 Poor Drug Solubility

Solubility remains a major challenge as many newly discovered molecules exhibit poor aqueous solubility. Low solubility limits absorption, preventing drugs from reaching effective systemic concentrations and resulting in poor bioavailability. In addition, poorly soluble drugs may encounter issues with metabolism, permeability, drug interactions, or require modified release strategies [7].

Rather than discarding these drug candidates and developing new ones, employing novel technologies or formulation strategies can reduce risk, lower costs, and accelerate drug development timelines. These challenges hinder the development of therapies, creating gaps in the treatment of life-threatening and rare diseases as well as other unmet medical needs [8]. With over 80% of new chemical entities (NCEs) classified as BCS Class II or IV, many compounds cannot progress due to limited understanding of their physicochemical properties and solubility constraints.

Driven by the prevalence of BCS Class II and IV drugs in development and the increasing demand for effective therapies, the bioavailability enhancement market is projected to grow steadily. Bioavailability, a key pharmacokinetic parameter, dictates the extent to which a drug reaches systemic circulation unchanged and is influenced by multiple factors, including solubility, pH, absorption area, permeability, metabolism, and administration route. Consequently, bioavailability plays a crucial role in determining whether an active pharmaceutical ingredient (API) succeeds or fails during early drug development [9].

Solubility can be quantitatively classified based on the amount of solvent required to dissolve a unit amount of solute, as detailed in Table 1. This classification system provides a standardized way to describe and compare the solubility characteristics of different compounds.

Table 1. Solubility classification based on solvent requirements.

Descriptive	Part of solvent required per part of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble	10,000 and over

1.3 Importance of Solubility

A major challenge in drug development for industries and researchers is enhancing the bioavailability of active pharmaceutical ingredients (APIs). Nearly 70% of new drug candidates face, or will face, issues with aqueous solubility. Since a drug must be in solution to be effectively absorbed, poor solubility can result in the failure of many high-potential molecules to reach the market [10].

Oral administration is the most widely used and convenient route for drug delivery due to its ease of use, high patient compliance, cost-effectiveness, minimal sterility requirements, and flexibility in dosage design. Consequently, many generic drug manufacturers focus on developing bioequivalent oral formulations. However, a key challenge in oral dosage form design is poor bioavailability, which depends on factors such as aqueous solubility, drug permeability, dissolution rate, first-pass and pre-systemic metabolism, and efflux mechanisms. Poor solubility and low permeability are the most common causes of low oral bioavailability. Solubility is critical not only for oral formulations but also for other dosage forms, as it determines the drug concentration in systemic circulation needed for the desired pharmacological effect [11].

Many drugs are weakly acidic or basic and exhibit poor aqueous solubility, with over 40% of new chemical entities (NCEs) being practically insoluble in water. Poorly soluble drugs often require higher doses to achieve therapeutic plasma concentrations, and their slow absorption can lead to variable bioavailability and gastrointestinal toxicity. For orally administered drugs, achieving adequate solubility at the absorption site is essential, making solubility a key rate-limiting factor in drug absorption.

Enhancing solubility and dissolution rate remains a major challenge in drug development, particularly for

BCS Class II drugs (low solubility, high permeability), where absorption is not limiting but drug release and solubility in gastrointestinal fluids are. Numerous formulation strategies exist to improve solubility, selected based on the physicochemical properties of the drug, excipient compatibility, and the intended dosage form. Poor solubility also increases development costs, extends timelines, and can impose higher dosing burdens on patients [12].

2 Importance of Enhancing Solubility and Bioavailability of Drugs

For a drug to achieve therapeutic effect, it must first dissolve in the aqueous environment of the body to reach its target site. When administered in solid form, poor water solubility and low dissolution rates can limit the amount of drug available for absorption, often resulting in subtherapeutic concentrations and treatment failure. Poor solubility is therefore a major challenge in oral drug development, affecting bioavailability and the success of new therapeutic candidates [13].

Advanced manufacturing processes and 3D printing offer innovative solutions for drug formulation, providing a green and efficient approach to particle engineering. Unlike traditional techniques such as crushing, milling, cryomilling, or grinding, these methods allow the production of microparticles or nanoparticles in a single step, under mild conditions, with narrow and controlled size distributions, enhancing solubility and bioavailability [14].

The purpose of this review is to provide an overview of advanced manufacturing processes and 3D printing technologies, focusing on antisolvent-mediated design and particle engineering of poorly water-soluble drugs. Key aspects, including micronization, formation of amorphous and crystalline solids, and solid dispersions with polymers and surfactants, are discussed in the context of antisolvent approaches. By integrating our expertise and experimental findings with a critical review of recent literature, we highlight the role of these technologies in enhancing solubility and bioavailability of challenging drug candidates.

3 Techniques for Solubility Enhancement

Solubility enhancement techniques can be broadly classified into conventional and non-conventional methods. Conventional methods include physical modifications, chemical modifications, and miscellaneous techniques.

Physical modifications involve particle size reduction (micronization, nanosuspensions), modification of crystal habit (polymorphs, amorphous forms, co-crystals), and drug dispersion in carriers (eutectic mixtures, solid dispersions, solid solutions, and cryogenic techniques).

Chemical modifications include pH adjustment, buffer systems, derivatization, complexation, and salt formation.

Miscellaneous methods comprise supercritical fluid processing, use of surfactants or solubilizers, cosolvency, hydrotropy, and novel excipients [15].

Some key solubility enhancement strategies are:

1. **Particle Size Reduction**: Increases surface area via milling or spray drying to improve dissolution, though it may risk degradation or poor performance with highly insoluble drugs.
2. **Micronization**: Employs jet or colloid mills to enhance dissolution rate without affecting equilibrium solubility, used for drugs like fenofibrate and griseofulvin.
3. **Cosolvency**: Utilizes solvent mixtures (e.g., ethanol, PEG 400) to reduce interfacial tension and increase solubility, commonly applied in parenteral formulations.
4. **Hydrotropy**: Uses hydrotropic agents (e.g., sodium acetate, sodium alginate) to improve solubility via weak interactions independent of pH.
5. **pH Adjustment**: Alters drug ionization to increase solubility and prevent precipitation, important for gastrointestinal absorption.
6. **Sonocrystallization**: Applies ultrasonic energy to control nucleation, reduce particle size, and generate porous or amorphous forms with higher solubility.
7. **Supercritical Antisolvent Technique**: Uses supercritical CO_2 to produce fine, soluble particles of heat-sensitive drugs, enhancing bioavailability.
8. **Solid Dispersions**: Disperses drugs in hydrophilic carriers (e.g., PVP, PEG) often with surfactants to significantly improve dissolution and absorption, as seen with ritonavir and celecoxib [16].

Traditional manufacturing methods such as turning, milling, drilling, and grinding rely on hard tools to shape materials. Modern manufacturing incorporates advanced technologies like automation, computation,

sensing, and networking to produce existing and novel products. In drug development, solubility—the ability of a substance to dissolve in a liquid to form a homogeneous molecular dispersion—is crucial. Most active pharmaceutical ingredients (APIs) are hydrophobic and poorly water-soluble, creating major challenges in formulation development. Limited aqueous solubility restricts the drug's bioavailability, absorption, and therapeutic efficacy, making solubility a critical parameter for successful drug design and achieving desired pharmacological responses.

4 The Role of Advanced Manufacturing Technologies in Production Process Performance

Advancements in manufacturing processes have attracted significant attention from both researchers and industry due to their potential to enhance productivity and efficiency. Various technological approaches have been developed to integrate different manufacturing processes with the common objectives of increasing material removal rates, improving surface integrity, reducing tool wear, shortening production times, and expanding application possibilities. Such integrated approaches are commonly referred to as hybrid manufacturing processes, which open new opportunities for producing components that are economically challenging or impossible with individual processes alone.

Traditionally, conventional manufacturing methods like CNC machining, forming, joining (e.g., welding), and dividing operations (e.g., sawing) have been widely used. Additive manufacturing has also been adopted across various industries. However, conventional processes have inherent limitations. CNC machining, for example, struggles with complex geometries due to tool accessibility and experiences high tool wear and thermal issues when working with hard materials. Rapid prototyping, though versatile, is limited by long production times and lower accuracy. Forming processes face constraints such as limited material formability and spring-back effects, while welding processes often have challenges in maintaining dimensional precision.

Hybrid manufacturing addresses these limitations by combining two or more processes with complementary principles, enhancing the advantages while mitigating individual drawbacks. Examples include integrating CNC machining with additive manufacturing to achieve high precision and machining speed, combining laser heating with forming to reduce spring-back, applying ultrasonic-assisted drilling to decrease tool wear and cutting forces, and using laser drilling with electrochemical machining (ECM) to minimize recast layers and heat-affected zones. Such hybrid approaches provide innovative solutions to improve efficiency, precision, and material performance in modern manufacturing [17].

4.1 Need and Significance of Advanced Manufacturing

Drivers of Advanced Manufacturing: Advanced manufacturing is primarily driven by three factors: material, process, and operational drivers. Material-driven processes emerge from the development of new, difficult-to-machine materials. Process-driven factors arise from specific product requirements, such as high precision, accuracy, and superior quality. Operational drivers focus on reducing time-to-market, increasing production rates, and lowering manufacturing costs [18].

Need for Advanced Manufacturing:

The adoption of advanced manufacturing is motivated by:

1. Limitations of conventional methods.
2. Rapid advancements in material properties.
3. High tolerance and stringent product requirements.

Advantages of Advanced Manufacturing:

- Cost-effective production.
- Automated data transfer and process control.
- Capability for miniaturization.
- High-precision and ultra-precision finishing.

5 Three-Dimensional Printing Technology as a Promising Tool in Bioavailability Enhancement of Poorly Water-Soluble Molecules

5.1 3D Printing in Additive Manufacturing

3D printing is an additive manufacturing technique that creates three-dimensional structures by depositing or binding materials layer by layer under computer control. Since Charles Hull developed the first stereolithography method in the early 1980s, numerous 3D printing techniques have emerged, becoming more accessible to both industry and the general public [19].

To ensure consistency, 3D printing techniques can be classified under three main principles: (i) inkjet

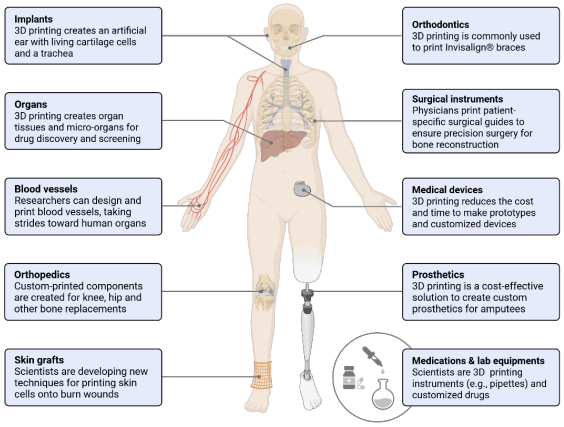

Figure 2. Applications of 3D Printing in Pharmaceuticals and Biomedicine: 3D printing technology enables the fabrication of personalized dosage forms, customized drug release profiles, polypills, and complex drug delivery systems.

systems, (ii) nozzle-based deposition systems, and (iii) photo-polymerization systems. In all cases, the desired 3D structure is first designed using Computer-Aided Design (CAD). The design is then converted into multiple slices in a suitable file format, which are processed by software that controls the printer to fabricate the object layer by layer [20]. The diverse applications of this technology in the pharmaceutical and biomedical fields, as illustrated in Figure 2, highlight its transformative potential.

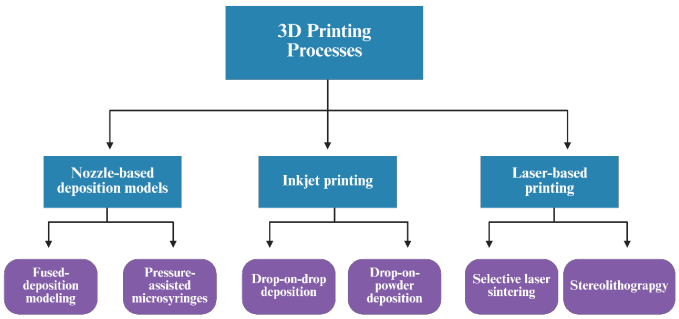

Figure 3. Schematic flow chart of the 3D printing process: from digital design to final product.

The process of creating a 3D printed object typically follows a standardized workflow. As depicted in Figure 3, it begins with digital design, proceeds through file conversion and slicing, and culminates in the layer-by-layer physical fabrication, ensuring precise control over the final product's structure and properties.

5.2 Enhancing Bioavailability Through Advanced Manufacturing Technology

Formulation Interventions and Advanced Manufacturing: Formulation strategies using advanced processing technologies are essential for ensuring therapeutic efficacy, especially for poorly soluble drugs. Without such interventions, these drugs may fail to reach adequate concentrations in the blood or target tissues, while highly soluble or rapidly cleared drugs may require frequent dosing, causing fluctuating tissue levels. In recent years, thermal processing techniques—such as melt mixing, spray congealing, sintering, and hot-melt extrusion—have advanced rapidly, alongside newer methods like dry powder coating, injection molding, and KinetiSol® dispersing, which have been adapted for pharmaceutical use [21].

Advanced manufacturing approaches aimed at improving solubility and bioavailability often employ nanotechnology (e.g., nanosuspensions, nanoemulsions), amorphous solid dispersions (ASDs), and lipid-based systems to enhance drug solubility and surface area. Other methods, including hot-melt extrusion (HME), spray-drying, supercritical fluid technology, and co-crystallization, help develop stable formulations that optimize drug absorption and therapeutic performance, as summarized in Figure 4.

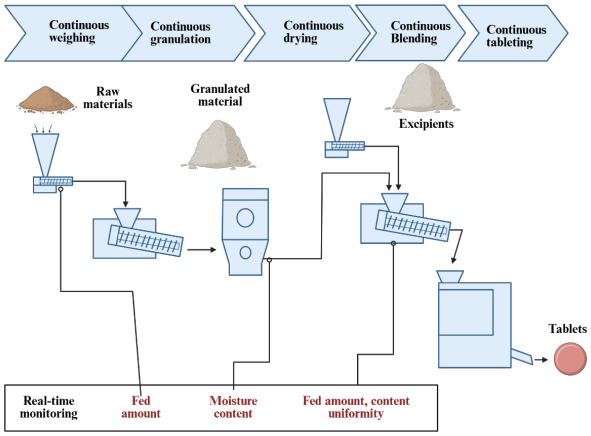

Figure 4. Overview of advanced manufacturing processes for enhancing drug solubility, bioavailability, and formulation performance.

5.3 Commonly Used Solubility Enhancement Techniques

5.3.1 Nanotechnology

Nano drug delivery systems have become a leading approach for enhancing drug solubility, dissolution, absorption, and overall therapeutic efficacy. By

reducing particle size to the nanoscale, these systems increase dissolution rates, minimize aggregation, and improve bioavailability—all without requiring salt formation or other chemical modifications [22].

A. Nano-suspension technique:

Nanosuspension Technique:

Nanosuspensions have been widely employed to enhance the solubility and bioavailability of poorly water-soluble drugs. For instance, fenofibrate formulated as a nanosuspension (Dissocube®) demonstrated a twofold improvement in bioavailability compared to a micronized fenofibrate suspension. Similarly, enhanced solubility and bioavailability of midazolam and glimepiride have been reported using nanosuspension formulations. A nanosuspension is a biphasic dosage form consisting of nano-sized drug particles stabilized by surfactants, suitable for oral, topical, parenteral, or pulmonary administration. Particle sizes typically range from 200 to 600 nm. Preparation methods include media milling, high-pressure homogenization (in aqueous or non-aqueous media), precipitation, and combined precipitation-high-pressure homogenization techniques (e.g., Nano-edge technology). Nanosuspensions improve solubility and absorption by reducing particle size to the submicron range, but maintaining particle stability over prolonged storage remains challenging due to issues like chemical instability, reactivity, and drug leakage [23] .

Media Milling: Nanosuspensions can be prepared using high-shear media mills. In this process, the milling chamber is loaded with milling media, water, the drug, and stabilizers, and rotated at high shear rates under controlled temperature conditions for several days (typically 2–7 days). The milling media may consist of glass, zirconium oxide, or cross-linked polystyrene beads. High-energy shear forces generated from the collisions between the milling media and the drug break down microparticles into nanosized particles, enhancing solubility and bioavailability [24].

B. High Pressure Homogenization.

High-Pressure Homogenization:

This method is widely used to prepare nanosuspensions of poorly water-soluble drugs. The drug and surfactant suspension is forced under high pressure through a nanosized aperture in the homogenizer. The process relies on cavitation forces in the aqueous phase, which are strong enough to break drug microparticles into nanoparticles. Challenges include the need for pre-milled small particles and multiple homogenization cycles. Drugs like spironolactone, budesonide, and omeprazole have shown improved dissolution rates and bioavailability through this technique [25].

C. Precipitation and Homogenization: Drug nanoparticles produced by precipitation tend to grow into larger microcrystals over time. These particles can exist in fully amorphous, partially amorphous, or fully crystalline forms, which may compromise long-term stability and bioavailability. To maintain the desired nanoscale size and improve stability, the precipitated suspensions are subsequently subjected to high-energy homogenization.

B. Nanoemulsion Technology: Advanced manufacturing methods such as 3D printing, nanocrystals, liposomes, and nanoemulsions have recently gained attention for improving drug solubility and bioavailability. Nanoemulsions are kinetically stable, isotropic colloidal systems composed of oil, water, and surfactants, with droplet sizes typically between 20–200 nm. Their small droplet size enhances dissolution, facilitates interaction with biological membranes, and improves absorption, thereby increasing oral bioavailability [25].

5.3.2 Lipid-Based Systems for Solubility Enhancement

A. Lipid-Based Drug Delivery Systems (LBDDS): Poorly water-soluble drugs often exhibit low dissolution and limited absorption, resulting in reduced bioavailability. LBDDS enhance solubility and gastrointestinal absorption by incorporating drugs into lipidic excipients, increasing surface area and solubilization. Key types include:

- **Lipid Solutions:** Drugs dissolved in natural or synthetic oils, such as medium-chain triglycerides; simple but suitable for low-dose drugs.
- **Emulsions and Microemulsions:** Oil-in-water dispersions stabilized with surfactants; microemulsions (<100 nm) provide high surface area and stability.
- **Self-Emulsifying Drug Delivery Systems (SEDDS/SMEDDS):** Mixtures of oils, surfactants, and co-solvents that spontaneously form fine emulsions or nanoemulsions in the GI tract, preventing precipitation and enhancing dissolution.
- **Solid Lipid Nanoparticles (SLNs) and**

Nanostructured Lipid Carriers (NLCs): Colloidal lipid carriers offering controlled release, protection from degradation, and improved permeability [26].

B. Solid Dispersions: The concept of solid dispersions was first introduced by Sekiguchi and Obi in the 1960s, who studied eutectic melts of sulfonamide drugs with water-soluble carriers to improve dissolution. Solid dispersions are formulations composed of at least two components, typically a hydrophobic drug dispersed in a hydrophilic matrix, aimed at enhancing drug solubility, absorption, and therapeutic efficacy. Common hydrophilic carriers include polyvinylpyrrolidone (PVP), polyethylene glycols (PEGs), and Plasdone S630, while surfactants such as Tween-80, docusate sodium, Myri-52, Pluronic-F68, and sodium lauryl sulfate (SLS) are often incorporated to further improve solubility. Drugs like celecoxib, halofantrine, and ritonavir have shown enhanced solubility when formulated as solid dispersions with suitable carriers, e.g., celecoxib with PVP and ritonavir with Gelucire [1].

C. Hot-Melt Extrusion (HME): HME is an advanced method similar to the fusion technique but incorporates intense mixing via an extruder, facilitating continuous and large-scale production. While high-shear forces and local temperature rises may pose challenges for heat-sensitive drugs, HME allows better control over drug–carrier miscibility and produces a form that is easier to handle and adaptable to subsequent processing without additional grinding [27]. A detailed schematic of this process is shown in Figure 5.

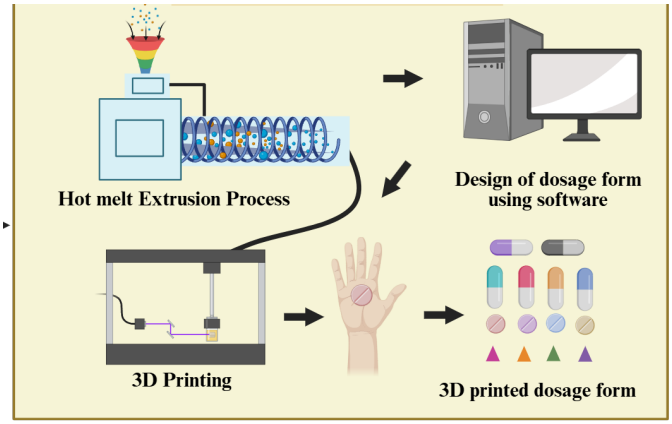

Figure 5. Hot melt extrusion (HME) process: an advanced manufacturing technique for improving drug solubility, bioavailability, and controlled release in pharmaceutical formulations.

D. Supercritical Fluid (SCF) Process: SCF technology has emerged as a promising method for nanosizing and solubility enhancement of poorly water-soluble drugs. Supercritical fluids—typically carbon dioxide at temperatures and pressures above their critical points—possess properties of both liquids and gases, allowing precise control over solvent power and mass transport. Drugs solubilized in SCFs can be recrystallized into submicron or nanoparticulate sizes, typically ranging from 5 to 2,000 nm. Techniques such as Precipitation with Compressed Antisolvent (PCA), Solution Enhanced Dispersion by SCF (SEDS), Supercritical Antisolvent (SAS), Rapid Expansion of Supercritical Solutions (RESS), Gas Anti-Solvent Recrystallization (GAS), and Aerosol Supercritical Extraction System (ASES) have been developed for tailored particle engineering. Pharmaceutical companies like Nektar Therapeutics and Lavipharm have utilized SCF technologies to enhance particle solubility and bioavailability [28].

E. Spray Drying: Spray drying is an efficient technique for producing ultra-fine drug particles with controlled size, morphology, and narrow size distribution, typically in the submicron-to-micron range. It is widely applied to improve the dissolution, absorption, and bioavailability of poorly soluble drugs. This technique can be used alone or combined with polymers and other excipients to produce drug-loaded carriers, providing scalable and reproducible processes for pharmaceutical development. Spray drying facilitates rapid solvent evaporation, allowing precise control over particle characteristics and supporting effective bench-to-bedside translation of innovative drug formulations [29]. The typical setup and process flow of spray drying for pharmaceutical applications are illustrated in Figure 6.

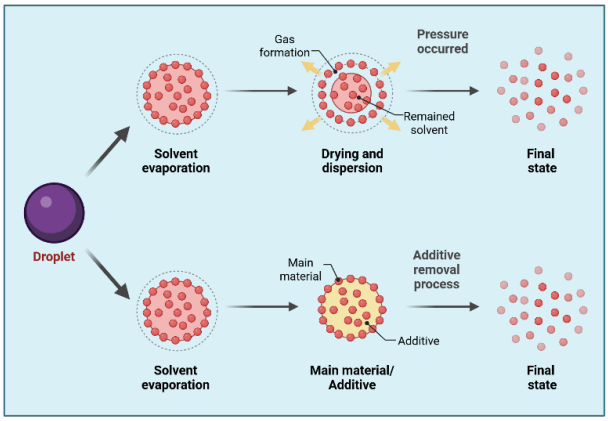

Figure 6. Spray drying technique: an advanced pharmaceutical manufacturing process for producing amorphous dispersions, enhancing solubility, and controlling drug release.

6 Three-Dimensional Printing Technology for Enhancing Bioavailability of Poorly Water-Soluble Drugs

3D printing, an additive manufacturing technique, offers significant potential for improving the bioavailability of poorly water-soluble drugs. This technology enables the fabrication of pharmaceutical products with intricate structures and geometries that are challenging or impossible to achieve through conventional manufacturing. Moreover, 3D printing allows the production of small, customizable batches tailored to specific doses, release profiles, and multi-drug incorporation, addressing patient-specific variations in physiology, genetics, and drug response [14]. Various 3D printing methods have been explored in research, aiming to enable on-demand manufacturing of individualized drug products. Key advantages include the development of personalized medicines, multi-compartment dosage forms, high-porosity tablets, implants, and immediate-release formulations, making 3D printing a versatile and promising approach in modern pharmaceutical development [30].

6.1 Techniques of 3D Printing

1. Nozzle-deposition models:

A. Fused Deposition Modeling (FDM): FDM is an additive manufacturing technique in which a thermoplastic filament—potentially loaded with drugs or additives—is melted and extruded through a heated nozzle. The extruded filament solidifies on a bed, which may also be heated, to form a 3D structure. The printer's extruder moves along the x- and z-axes, while the heated bed moves along the y-axis to create the desired geometry. FDM is commonly used for sustained-release formulations, though it can be adapted for immediate-release by adjusting key parameters. However, its dense solidified melt often slows drug dissolution, limiting its routine use for poorly soluble drugs [31].

Critical Factors in FDM:

1. **Infill Structure:** The infill represents the internal density of the printed object, ranging from 0% (hollow) to 100% (solid). Higher porosity (lower infill) increases the surface area exposed to aqueous media, enhancing dissolution but limiting drug loading. Studies show mixed results: in some cases, higher porosity improves release rates (e.g., haloperidol tablets), while in others, melt properties like polymer viscosity can reduce the impact of infill on dissolution.
2. **Geometry of the Printed Tablet:** Modifying the tablet's shape can significantly affect dissolution, with complex structures often improving drug release. However, very intricate or large designs may be difficult to swallow, prompting development of orodispersible forms that dissolve rapidly without the need to swallow intact tablets [32].

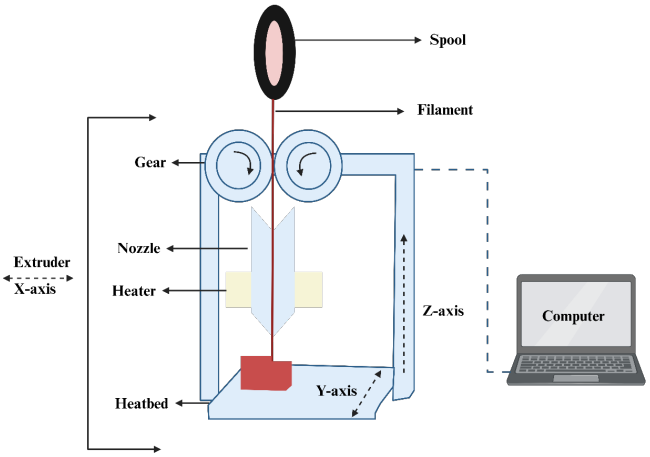

Figure 7. Fused deposition modeling (FDM): a 3D printing technique for fabricating customized drug dosage forms with controlled geometry and release profiles.

The FDM process, as illustrated in Figure 7, offers a flexible platform for creating dosage forms with tailored architectures. By precisely controlling parameters such as infill density and overall geometry, this technique allows for the fine-tuning of drug release kinetics to meet specific therapeutic needs.

B. Pressure-Assisted Micro-Syringe (PAM) Extrusion: PAM is another nozzle-based 3D printing method in which a semi-solid paste is extruded through a syringe controlled by software following a pre-designed shape. The paste is loaded into syringes with precisely defined orifice diameters, allowing accurate deposition of material to build complex drug delivery structures [33].

C. Formulation Considerations for PAM Technique: The PAM technique relies on softening materials under mild conditions, making it suitable for thermolabile drugs and the use of generally recognized as safe (GRAS) excipients. A critical challenge is achieving optimal material viscosity for smooth extrusion through the syringe orifice. The choice of wetting liquid is key to attaining the correct rheology. For example, hydroxypropylmethylcellulose (HPMC)

performs best with a water-ethanol mixture (90:10 V/V); too little ethanol creates an overly viscous mass, while too much results in rapid drying and a hard, non-extrudable mass. Polyvinylpyrrolidone (PVP) achieves optimal viscosity with pure water, whereas formulations with lipid excipients may not require wetting liquids at all [21].

Solubility Enhancement Strategies Using PAM: PAM is rarely used alone for producing amorphous solid dispersions (ASDs) to enhance solubility. Successful strategies often combine multiple approaches such as superdisintegrants, cyclodextrins, or increasing surface area. For instance:

- Carbamazepine was complexed with hydroxypropyl-β-cyclodextrin (HPBCD) and blended with HPMC; adding 2.5% w/w superdisintegrant Ac-Di-Sol® SD-711 produced orally dispersible tablets with rapid dissolution.
- Paracetamol mixed with PVP K25 and croscarmellose sodium achieved immediate release due to the microporous structure and disintegrant effect.
- Aspirin and hydrochlorothiazide dispersed with PVP K30 and sodium starch glycolate released over 75% of the drugs within 30 minutes.

Faster drug release can also be achieved by increasing soluble material concentration or adjusting spacing between printed lines. A major advantage of PAM over FDM is the mild processing temperature, which prevents degradation of thermolabile APIs [34] .

B. Inkjet-printing technology: Inkjet printing is a non-contact additive manufacturing technique that deposits droplets (1–100 picoliters) of a drug-containing "ink" onto a substrate in a precise, computer-controlled manner. A well-known example is Spritam® (levetiracetam), the first FDA-approved 3D-printed tablet, produced using Aprecia's ZipDose® drop-on-powder technology. This method layers powdered drug blends with a fluid binder to create highly porous tablets with rapid oral disintegration, high drug loading (up to 1000 mg), and effective taste masking, addressing challenges of patient compliance. The printability of inks depends on physical parameters such as viscosity, surface tension, and particle size, often characterized by the Ohnesorge (Oh) number and Z-value [35]. Clogging can occur due to oversized particles, particle aggregation, or particle-nozzle interactions, and can be mitigated by filters, non-volatile solvents, or surfactants/viscosifiers. For example, thiamine HCl ink was stabilized with polysorbate 20 and PVP to achieve optimal droplet formation. Control of nozzle voltage and geometry is also critical for consistent droplet ejection and to avoid satellite droplet formation [18].

C. Laser-Based Printing:

1. **Stereolithography (SLA):** SLA uses a focused laser to induce photopolymerization of a liquid resin layer-by-layer, producing precise free-form structures. Formulations typically involve acrylate-based monomers and photo-initiators, which undergo either cationic or radical polymerization when exposed to light. This method is particularly suited for creating intricate structures with controlled drug release profiles.
2. **Selective Laser Sintering (SLS):** SLS binds powder particles together using laser energy to locally sinter materials just below their melting point. In pharmaceuticals, it has been applied to create solid dispersions, such as paracetamol with polymers like Kollicoat® IR or Eudragit® L100-55. SLS-produced tablets showed drug release profiles influenced by polymer type, surface area, porosity, and drug content. For instance, paracetamol with PEO achieved complete release within 10 minutes due to increased surface area. This technique allows high precision in complex geometries without the need for support structures and offers strong potential for personalized and immediate-release drug formulations [36] .

Figure 8 provides a visual overview of these major 3D printing techniques, highlighting their distinct operational principles and applications in pharmaceutical manufacturing. The diverse capabilities of inkjet printing, laser-based methods (including SLS), extrusion-based systems like FDM, and stereolithography offer a versatile toolkit for developing customized dosage forms with precise control over structure and drug release behavior.

7 Is There Really a Difference Between Additive Manufacturing and 3D Printing?

3D printing employs an additive process to produce a final product, but it is not always synonymous with additive manufacturing. In contrast, everything produced through additive manufacturing can be considered a form of 3D printing. The distinction largely depends on scale and context: 3D printing typically refers to smaller-scale, at-home, or hobbyist operations, whereas additive manufacturing is

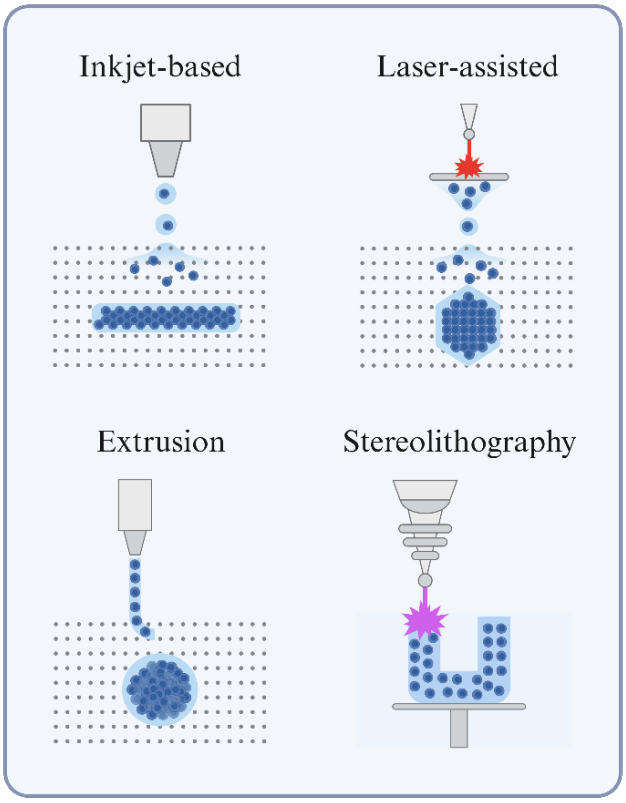

Figure 8. Common 3D printing techniques in pharmaceuticals: (A) Inkjet Printing – Precise droplet deposition, (B) Laser-Based Printing – Selective sintering or curing, (C) Extrusion-Based Printing – Layer-by-layer material deposition (FDM/HME), (D) Stereolithography (SLA) – Photopolymerization of liquid resins for complex structures.

associated with larger-scale, industrial production. Therefore, context is crucial when choosing which term to use. When describing a comprehensive workflow in a manufacturing or industrial setting, "additive manufacturing" is appropriate. For creating individual models or personal projects, "3D printing" is the more suitable term.

Established advanced manufacturing techniques—such as hot melt extrusion, spray drying, and nanocrystal technology—are proven methods for enhancing drug solubility and bioavailability. They achieve this by producing amorphous dispersions, reducing particle size, or improving surface properties. These approaches are scalable and widely adopted in industry; however, they often require high-energy processes that may degrade heat-sensitive drugs and offer limited flexibility for personalized dosing. In comparison, 3D printing provides distinct advantages for customizing dosage forms to individual patient needs, allowing for precise control over dose, release profiles, and even combination "polypill" designs. Despite its flexibility and accuracy, 3D printing currently faces limitations in scalability and regulatory approval relative to conventional advanced manufacturing methods [37]. These methods can be broadly categorized into distinct functional areas as summarized in Table 2.

As detailed in Table 2, the integration of advanced materials and sophisticated processing techniques plays a crucial role in modern pharmaceutical

Table 2. Advanced functional materials & processing in pharmaceutical preparation.

Area	Material / Processing Feature	How It Helps in Pharma Prep
Nanomaterials / Nanocomposites	Use of nanoparticles, polymeric matrices, or nanostructured carriers to encapsulate drugs; surface functionalization to control release or targeting	Improves solubility, stability, controlled release; targeted delivery to reduce side effects. [1]
Porous organic materials / porous supports	High surface area, controlled pore size, functional groups for adsorption or sensing	Useful for sample preparation (e.g. extraction), for controlled release, for stabilizing drugs etc. [2]
Processing Techniques / Advanced Processing	Mechanochemistry, controlled crystallization, surface engineering, advanced manufacturing (e.g. 3D printing, micro-compounding)	Helps in forming dosage forms with precise control of particle size, morphology, polymorphic form, etc., which in turn influence dissolution, bioavailability, stability. [3]
Characterization & Pre-formulation Tools	Measuring powder flow, compressibility, porosity, density; using expert systems (e.g. SeDeM-ODT) to predict how materials will behave in tablets etc.	Helps reduce trial-and-error in formulation design; predict manufacturability and end product quality.
Data & Modeling	Structure–property relationships, modeling processing effects, using statistical / multivariate analysis, mechanistic models etc.	Enables better prediction of how changes in material or process parameters will affect key attributes (e.g. release rate, mechanical strength, stability) of pharmaceutical products. [3]

development. This systematic approach, spanning from nanomaterials to predictive modeling, provides a comprehensive framework for addressing complex formulation challenges and improving therapeutic outcomes.

8 Case Study

Several poorly water-soluble drugs have demonstrated improved performance through advanced manufacturing and 3D printing approaches. Itraconazole formulated via spray drying with hydroxypropyl methylcellulose (HPMC) showed enhanced solubility and improved oral bioavailability compared to crystalline drug. Ritonavir, initially withdrawn due to poor solubility, was successfully reformulated using solid dispersion via hot melt extrusion, leading to the marketed product Norvir. Fenofibrate nanocrystals prepared using wet milling technology significantly improved dissolution rate and bioavailability, resulting in commercial products like Tricor. In the realm of 3D printing, Spritam® (levetiracetam) became the first FDA-approved 3D-printed tablet, demonstrating rapid disintegration and patient-friendly administration. Other studies have shown the potential of 3D-printed polypills combining multiple drugs (e.g., for cardiovascular therapy), highlighting the versatility of this approach in creating personalized and effective formulations.

9 Future Perspectives

Emerging technologies such as 3D printing, continuous manufacturing, microfluidics, and artificial intelligence-driven formulation design are opening new avenues for enhancing solubility and bioavailability of poorly soluble drugs. Personalized medicine using 3D printing, along with smart nanocarriers like lipid-based nanoparticles, polymeric micelles, and stimuli-responsive systems, holds strong promise for tailored therapies. Integration of computational modeling, machine learning, and in silico predictions may further optimize formulation strategies and reduce development costs.

However, challenges remain, including scalability, regulatory acceptance, reproducibility, and long-term stability of novel formulations. High manufacturing costs and specialized equipment also limit widespread adoption. Future research must focus on patient-centric, sustainable, and regulatory-compliant solutions, balancing innovation with practicality. With continued interdisciplinary collaboration, these technologies can revolutionize drug development and therapeutic outcomes.

10 Conclusion

Poor aqueous solubility remains one of the major barriers to successful drug development, often limiting bioavailability and therapeutic efficacy. Advanced manufacturing approaches such as hot-melt extrusion, spray drying, nanocrystal technology, co-crystallization, lipid-based systems, and amorphous solid dispersions, along with emerging 3D printing technologies, have shown great potential in overcoming these limitations. While advanced manufacturing ensures scalability and reproducibility, 3D printing enables personalized, on-demand dosage forms with enhanced solubility and bioavailability.

Despite promising progress, challenges related to stability, regulatory approval, and large-scale implementation must still be addressed. Continuous innovation, integration of computational tools, and interdisciplinary research will be key drivers in translating these technologies from laboratory to clinic, ultimately improving patient outcomes and expanding therapeutic possibilities.

Advanced Functional Materials & Processing

The materials (especially engineered/nanostructured), their composition, morphology, surfaces, etc. plus how they are processed (synthesized, formed, modified, assembled) to achieve specific functionalities - e.g. controlled release, biocompatibility, target specificity, stability, etc.

Pharmaceutical preparation refers to formulation (solid, liquid etc.), dosage form design, excipients, processing (granulation, compression, coating, etc.), ensuring stability, bioavailability, safety, etc.

Examples from Recent Research

1. Advanced porous organic materials for sample preparation in pharmaceutical analysis — materials designed to adsorb/enrich pharmaceutical analytes for better analytical accuracy in complex matrices.
2. Materials innovation & nanotechnology in drug delivery — producing biodegradable, responsive (pH, temperature etc.), targeted delivery systems.
3. Nanocomposites for enhanced therapeutic outcomes - combining different material types (polymeric, metallic, molecular targeting) to

tailor release profiles, reduce toxicity, improve effectiveness.

4. Characterisation of pharmaceutical powders via expert systems (SeDeM-ODT) - predicts suitability for direct compression tablets, evaluates disintegration etc.

5. Advanced materials and manufacturing processes — scale up, modeling how different manufacturing / processing routes influence the final material structure and thereby functionality. Advanced functional materials (AFMs), including nanoparticles of AFMs, play an important role in catalysis, optoelectronic and quantum materials, biomaterials, and energy harvesting, storage, and conversion materials. [38]

Correlations

Material properties ↔ Product performance: Things like particle size, porosity, surface area, crystallinity, polymorphism, particle shape directly affect dissolution rate, bioavailability, mechanical strength, stability.

Processing influences structure: The way you process (e.g. milling, compaction force, solvent/antisolvent in crystallization, temperature, humidity, etc.) shapes material microstructure, residual stresses, porosity, defects etc, which in turn influence performance.

Functionalization adds capabilities: Adding targeting ligands, responsive moieties, coatings, or embedding in matrices enables advanced behaviors (triggered release, targeting, stealth, etc.)

Trade-offs are common: For example, increasing porosity may improve release rate but reduce mechanical strength; or making materials very hydrophobic may impact solubility.

Challenges

- Achieving reproducibility at scale: Lab-scale functional materials often are not straightforward to scale up with same properties. Thermal, mixing, batch-to-batch variability can change outcomes.

- Stability: Nano or responsive materials may degrade, change over time or in certain environments (e.g. moisture, pH, enzymatic). Ensuring stability in the final dosage form is critical.

- Regulatory acceptance: New materials or excipients require safety, toxicity testing, and regulatory approval, which is a long process.

- Complexity vs cost: More complex materials or processing can incur higher cost, require specialized equipment and control (which may limit adoption.

Use This Correlation in Pharmaceutical; Products

- Use advanced material design to solve specific formulary problems - e.g. improving dissolution of poorly soluble API, or targeting delivery to a particular site.

- Leverage characterization and predictive modeling early in formulation development (pre-formulation) to reduce trial time.

- Carefully relate processing parameters to material structure (e.g. particle size, porosity etc.), then study how those structural features affect final dosage behavior (release, stability, mechanical strength etc.)

- Consider scale-up and manufacturability during early design - choose processing methods and materials that can feasibly be moved to larger scale while maintaining properties.

- Embrace multifunctional materials - materials that not only carry drug, but also provide other useful functions (e.g. imaging contrast, environmental response, post-delivery behavior etc.) if relevant.

The principles, advantages, and applications of these technologies in enhancing the solubility and bioavailability of poorly water-soluble drugs. Comparative insights into their effectiveness, case studies of successful formulations, and emerging trends were discussed. While challenges remain in terms of stability, regulatory acceptance, and large-scale translation, the integration of advanced manufacturing with 3D printing and computational tools holds immense potential to revolutionize future pharmaceutical development and patient-centered therapies.

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Conflicts of Interest

The authors declare no conflicts of interest.

Ethical Approval and Consent to Participate

Not applicable.

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