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TELMISARTAN – NANOCRYSTAL INNOVATIVE APPROACH TO ENHANCE ORAL BIOAVAILABILITY

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Abstract: Angiotensin II receptor blockers (ARBs), such as telmisartan, are frequently given to treat cardiovascular diseases including hypertension. Telmisartan, which is categorized as Class II in the Biopharmaceutics Classification System (BCS), has limited oral bioavailability and poor aqueous solubility despite its therapeutic potential. It is difficult to achieve consistent treatment efficacy because of these pharmacokinetic restrictions. Drug delivery systems based on nanocrystals have emerged as a viable solution to solubility-related problems as a result of recent developments in nanotechnology. Because of their large surface area and sub-micron particle size, nanocrystals greatly speed up the rate of dissolution and gastrointestinal absorption. The use of nanocrystal technology to increase Telmisartan's oral bioavailability is examined critically in this article. It covers a range of preparation processes, including as milling, precipitation, and high-pressure homogenization, as well as stabilization and characterization techniques. Furthermore, the review highlights recent in vitro and in vivo findings supporting the improved pharmacokinetic performance of Telmisartan nanocrystals. Incorporating nanocrystal formulation enhances drug absorption and presents opportunities for dose reduction and improved patient adherence. All things considered, this novel strategy marks a substantial breakthrough in the oral administration of poorly soluble hypertension medications such as Telmisartan

Index Terms - Telmisartan, nanocrystals, oral bioavailability, poorly soluble drugs, nanotechnology.

1. INTRODUCTION

Telmisartan is a long-acting ARB used in the treatment of hypertension, cardiovascular risk reduction, and heart failure. However, it belongs to the Biopharmaceutics Classification System (BCS) Class II, indicating poor water solubility and high permeability. The oral bioavailability of Telmisartan is approximately 42%, which poses a significant challenge in achieving consistent plasma drug levels. Nanocrystal formulation has emerged as an innovative and effective approach to enhance the solubility and absorption of poorly water-soluble drugs like Telmisartan.

2. Classification of Nanoparticles

Nanoparticles can be classified based on various criteria, including their composition, structure, origin, and functionality.

Table :1 Classification of Nanocrystal

S. No.	Basis of Classification	Type	Example /Description
1.	Based on Composition	Polymers (Organic Nanoparticles)	Dendrimers, Micelles, Liposomes, (biodegradable, non-toxic, ideal for targeted drug delivery).
		Inorganic Nanoparticles • Metal-based • Metal oxidebased Carbon-based	Al, Au, Ag, Cu, Fe, Zn nanoparticles; exhibit high surface area, reactivity, and unique optical properties Al ₂ O ₃ , CeO ₂ , Fe ₂ O ₃ , Fe ₃ O ₄ , SiO ₂ , TiO ₂ , ZnO (enhance reactivity and stability) Fullerenes, Graphene Carbon Nanotubes (CNTs), Carbon Nanofibers, Carbon Black (unique electrical and mechanical properties)
		Drug Nanocrystals	Pure crystall drug particles stabilized by surfactants/polymers; enhance solubility and bioavailability
2.	Based on structure	Nanospheres	Matrix-type system with uniformly dispersed drug.
		Nanocapsules	Core–shell system with drug confined in a cavity surrounded by polymeric membrane.
3.	Based on Origin	Natural Nanoparticles	Derived from biological sources (e.g., exosomes, protein-based NPs).
		Synthetic Nanoparticles	Engineered via physical, chemical, or mechanical methods
4.	Based on State of Matter	Solid Nanoparticles	Nanocrystals, solid lipid nanoparticles.

		Liquid Nanoparticles	Nano emulsions
		Hybrid Nanoparticles	Lipid–polymer hybrid systems

3. Nanocrystals: An Overview

Nanocrystals are a cutting-edge drug delivery system composed entirely of pure drug particles reduced to the nanometer scale, typically between 10 and 1000 nanometers, and stabilized using surfactants or polymers. Unlike other nanoparticulate systems that employ carrier matrices or excipients such as lipids, polymers, or inorganic materials, nanocrystals are composed of 100% active pharmaceutical ingredient (API). This unique carrier-free composition enables maximal drug loading capacity, as every particle within the formulation contributes directly to the therapeutic effect.

The absence of an inert carrier matrix not only increases the proportion of the active compound in the formulation but also minimizes formulation complexity, reduces potential toxicity from excipients, and allows for smaller dosage forms with the same or improved therapeutic efficacy. Because the entire nanoparticle is made of the API, nanocrystals can deliver a significantly higher drug payload per unit mass compared to conventional systems like liposomes or polymeric nanoparticles. This makes them particularly advantageous for high-dose or poorly soluble drugs, where achieving therapeutic concentrations is otherwise challenging.

Nanocrystal formulations also allow flexibility in administration routes—including oral, parenteral, pulmonary, and ocular—while maintaining stability and bioavailability. The reduced particle size of nanocrystals provides a dramatically increased surface area-to-volume ratio, leading to enhanced saturation solubility and dissolution rate. Consequently, poorly soluble drugs, particularly those classified under Biopharmaceutics Classification System (BCS) Class II and IV, exhibit improved aqueous solubility and faster gastrointestinal absorption. This results in enhanced systemic bioavailability, faster onset of action, and the potential for reduced dosage frequency and side effects.

4. Problem with telmisartan and approach used by the research to overcome it

The angiotensin II receptor blocker telmisartan (TEL) is classified as Class II in the Biopharmaceutics Classification System (BCS) due to its high permeability and low water solubility. Due to its extremely low intrinsic solubility (~0.078 mg/mL in water), it has a varied oral bioavailability of about 42–58% and restricted dissolving. TEL is a difficult option for oral formulations due to its poor solubility, high lipophilicity ($\log P \approx 6-7$), and pH-dependent dissolution. In recent years, a number of formulation techniques have been created and improved to get around these restrictions.

Telmisartan suffers from poor water solubility and limited delivery to target tissues, which restricts its therapeutic efficacy. Singh et al. (2025) addressed this issue by co-loading Telmisartan and 9-hydroxymethyl noscapine into stearic acid-based solid lipid nanoparticles. The nanoparticles exhibited a core size of ~36.6 nm, hydrodynamic size of ~406.8 nm, and a zeta potential of -36.2 mV, ensuring stability and efficient drug encapsulation. This dual-drug nanoparticle system demonstrated enhanced cellular uptake in H1299 lung cancer cells, formation of a stable complex with bovine serum albumin (BSA), and promising anticancer activity, highlighting the potential of nanonization strategies to improve solubility, bioavailability, and targeted therapeutic effects of Telmisartan.

Telmisartan's therapeutic efficacy is limited by its low oral bioavailability and poor water solubility. Madani et al., (2024) used a supercritical antisolvent (SAS) technique to create amorphous nano- to micro-sized telmisartan particles with regulated diameters ranging from 200 to 2000 nm in order to resolve this problem. Telmisartan's kinetic solubility and rate of dissolution were greatly enhanced by its transformation into its amorphous state. The SAS technique is a promising scalable method for improving the solubility and therapeutic performance of telmisartan, as evidenced by pharmacokinetic studies in rats that also showed a significant improvement in plasma concentration and oral bioavailability.

A key limitation of telmisartan is its inherently poor aqueous solubility and insufficient oral bioavailability. To overcome this, Sharma et al. (2023) developed nanocrystals of the drug using a solvent–antisolvent precipitation approach assisted by ultrasonication, employing PVP K30 and Tween 80 as stabilizers. These

nanocrystals showed partial amorphization, a 4.2-fold increase in dissolution rate, and a 3.6-fold improvement in oral bioavailability, collectively indicating better solubility, stability, and therapeutic potential.

Challenges in dissolving telmisartan in physiological fluids often limit its overall absorption and therapeutic output. Gupta et al. (2021) addressed these drawbacks by producing telmisartan nanocrystals through high-pressure homogenization, stabilized with Poloxamer 407. Their nanosuspension (210 nm) released more than 90% of the drug within 20 minutes and significantly enhanced pharmacokinetic parameters such as C_{max} and AUC, confirming improved solubility, absorption, and systemic availability.

In an effort to broaden both solubility and potential therapeutic applications of telmisartan, Öztürk et al. (2020) formulated poly(lactic acid) (PLA) nanoparticles using the emulsion– solvent evaporation method. The resulting particles (~272 nm) provided sustained release (~40% over 24 hours) and displayed stronger antiproliferative effects on MCF-7 breast cancer cells, demonstrating that polymeric nanocarriers can enhance solubility while enabling new therapeutic uses.

The limited dissolution and low bioavailability of telmisartan motivated Thakur et al. (2020) to design nanocrystals via a bottom-up precipitation technique coupled with lyophilization, using HPMC E5 and sodium lauryl sulfate as stabilizers. Their optimized formulation (~160 nm) produced a 2.8-fold solubility improvement, rapid drug release (95% within 25 minutes), and remained stable for six months, highlighting advances in solubility, dissolution performance, and storage stability.

Seeking to enhance telmisartan's overall therapeutic efficiency, Bajaj et al. (2012) prepared nanocrystals through an evaporative antisolvent precipitation method, stabilized with PVP K30, TPGS, and Poloxamer 188. The resulting sub-300-nm particles showed markedly improved saturation solubility, fast dissolution (85% in water and 95% in 0.1 N HCl within 30 minutes), and substantially increased bioavailability, underscoring the value of nanosizing for better absorption and drug performance.

5. METHODS OF PREPARATION OF NANOCRYSTALS

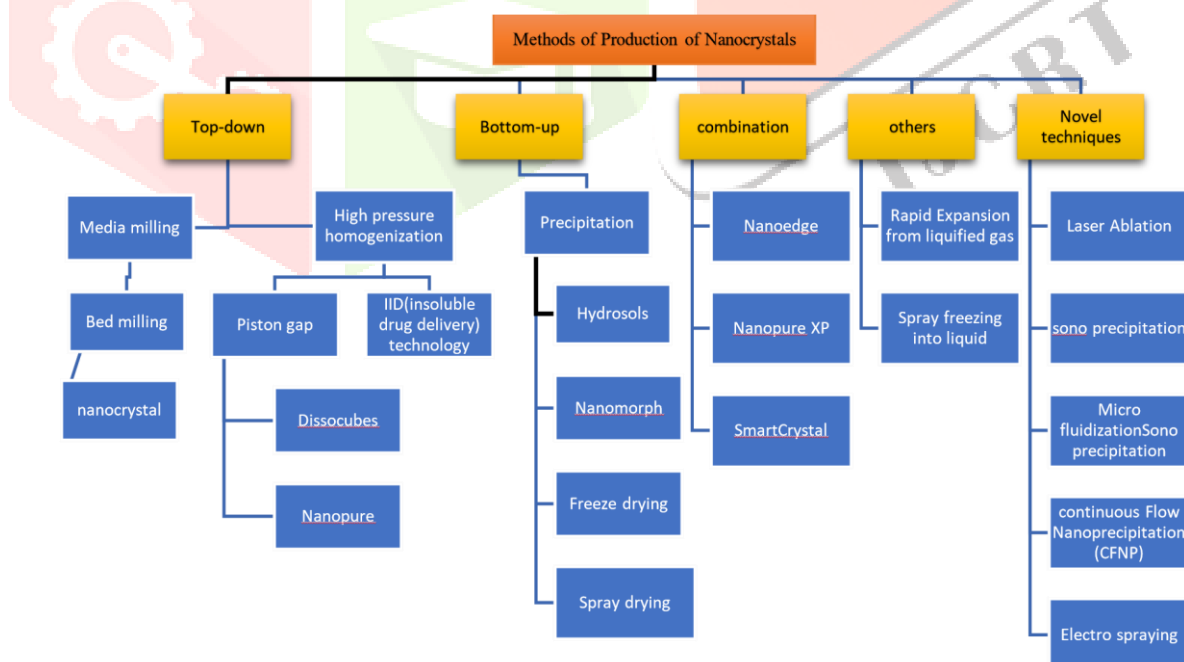


Figure 1. Methods of Preparation of Nanocrystals

5.1 Top-Down Techniques

These methods involve the size reduction of larger drug crystals to the nanoscale using mechanical forces. They are widely used due to their scalability and reproducibility.

5.1.1 Wet Media Milling (Nano-Milling)-Drug particles are suspended in a stabilizer containing liquid and milled using ceramic or zirconia beads. Mechanical shear and impact reduce the particle size to the nanometer range.

Advantages: Scalable, suitable for heat-sensitive drugs.

Application: Used in commercial nanocrystal formulations like Fenofibrate and Nanosuspensions.

Relevance to Telmisartan: Has been reported to significantly reduce particle size and improve dissolution

5.1.2 High-Pressure Homogenization-The drug suspension is passed through a narrow gap under high pressure (100–2000 bar). Cavitation and shear forces break down particles.

Advantages: No need for organic solvents, continuous process.

Limitations: High energy input, risk of thermal degradation.

5.2 Bottom-Up Techniques

These involve the controlled precipitation of drug nanocrystals from a solution, typically by altering solubility conditions (e.g., pH or anti-solvent addition)

Precipitation Method (Anti-solvent Precipitation)-The drug is dissolved in a solvent and rapidly mixed with a miscible anti-solvent, leading to supersaturation and nucleation of nanocrystals. Requires stabilizers to prevent agglomeration.

Advantages: Low energy input, simple.

Limitations: Difficult to control size, potential for aggregation.

5.3 Combination (Hybrid) Techniques

These methods integrate both top-down and bottom-up strategies to improve control over particle size, crystallinity, and production efficiency.

5.3.1 Precipitation Followed by High-Pressure Homogenization (P-H Homogenization) The drug is precipitated by anti-solvent addition to form micro- or nanocrystals (bottom-up). The suspension is subjected to high-pressure homogenization (top-down) to reduce particle size further and stabilize the crystals.

5.3.2 Sono precipitation Followed by Milling-Drug is precipitated using anti-solvent under ultrasonic waves (to control nucleation). Followed by media milling to achieve uniform nanocrystals.

5.3.3 Spray Drying + Media Milling- Drug is spray dried to obtain fine amorphous or crystalline powder. This powder is then dispersed in stabilizers and subjected to wet milling to produce nanocrystals.

5.3.4 Freeze-Drying Assisted Milling-The drug is first freeze-dried (optionally with cryoprotectants) to get a brittle powder. The dried material is then milled using high-energy media to create nanocrystals.

6. Emerging Novel Techniques for Nanocrystal Preparation

Recent advancements in nanotechnology have yielded a range of novel and innovative techniques for the preparation of drug nanocrystals. These emerging approaches overcome some of the limitations of traditional top-down and bottom-up methods—offering improved control over particle size, crystallinity, and morphology—while also ensuring better scalability and reproducibility. Such techniques are especially relevant for poorly water-soluble drugs.

(e.g., telmisartan) where enhanced dissolution and bioavailability are critical.

1. Micro fluidization

Micro fluidization is an advanced top-down technique in which a suspension is forced through microchannels at extremely high pressures. The intense shear and cavitation forces generate nanosized particles. Studies comparing micro fluidization with media milling found that micro fluidization offered advantages in processing time and size reduction. This technique has been employed for drugs and nanoparticulate systems to improve uniformity and reduce size distribution.

2. Sono precipitation

Sono precipitation combines ultrasonic energy with precipitation (typically antisolvent precipitation) to control nucleation and suppress crystal growth. The cavitation induced by ultrasound supports rapid nucleation of many small crystals before they can grow or agglomerate. It is particularly useful for

thermolabile compounds and can enhance dissolution rate by producing very fine and uniform nanocrystals.

3. *Spray-Freezing into Liquid (SFL)*

SFL is a cryogenic process that atomizes a drug solution into a cryogenic liquid (e.g., liquid nitrogen) so that freezing is nearly instantaneous. This prevents crystal growth and yields highly porous, fine particles which after lyophilization become nanocrystals with beneficial dissolution behavior. While specific full reviews for SFL in pharmaceuticals are less common, the principles of rapid freezing to control size/morphology are well-documented.

4. *Electro spraying*

Electro spraying (electrohydrodynamic atomization) uses a strong electric field to generate fine charged droplets from a drug solution, with solvent evaporation yielding nanocrystals of controlled size and morphology. It offers precise size control and pure product formation. Though widely used in material science, its application to pharmaceutical nanocrystals is emerging.

5. *Laser Ablation*

Laser ablation is a solvent-free method in which a high-energy laser is directed at a solid drug target (submerged in liquid), causing vaporization and subsequent condensation of nanoscale crystals. It enables production of high-purity nanocrystals without stabilizers or solvents. This method remains more experimental in pharmaceuticals but offers a “green” alternative.

6. *Supercritical Fluid (SCF) Technology*

Advanced SCF methods—such as Rapid Expansion of Supercritical Solutions (RESS) and Supercritical Antisolvent (SAS) precipitation—use supercritical CO₂ as solvent or antisolvent to precipitate drug nanocrystals. This enables solvent-free or low-residue processing, better particle control, and uniform size. For example, a review on SCF-assisted pharmaceutical nanocrystals highlighted its application in forming crystalline nano- and microparticles with enhanced dissolution and bioavailability.

7. *Continuous Flow Nanoprecipitation (CFNP)*

CFNP is a modern, scalable approach where precipitation occurs in a continuous flow reactor rather than a batch system. Controlled mixing of solvent and antisolvent streams under continuous flow ensures uniform supersaturation and consistent particle formation. This technique supports industrial scalability and reproducibility.

7. CURRENT MARKET FORMULATIONS

Table :2 Marketed Formulation

Brand/Generic Name	Dosage Form	Strength(s)
Telmisartan Tablets (Generic)	Film-coated tablet	20 mg, 40 mg, 80 mg
Telmisartan+ Hydrochlorothiazide	Tablet (immediate-release)	40 mg+ 12.5 mg, 80 mg + 12.5 mg
Telmisartan+ Amlodipine Besylate	Tablet (immediate release)	40 mg + 5 mg
Telmisartan+ Metoprolol Succinate (ER)	Film-coated tablet (bilayer)	40 mg + 50 mg; 40 mg + 25 mg

Telmisartan + Nebivolol	Bilayer tablet (nebivolol can be IR or ER)	40 mg + 5 mg.
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8. FUTURE PERSPECTIVE

The advancement of nanocrystal technology presents a promising future for enhancing the oral bioavailability of poorly water-soluble drugs like Telmisartan. As a BCS Class II drug, Telmisartan suffers from low solubility and variable absorption, limiting its therapeutic efficacy. Nanocrystal formulations address these issues by significantly increasing the drug's surface area and dissolution rate, leading to improved absorption and onset of action. Future developments will likely focus on optimizing production techniques such as anti-solvent precipitation and high-pressure homogenization to ensure scalability, reproducibility, and compliance with regulatory standards. Moreover, emerging hybrid methods that combine bottom-up and top-down approaches may offer better control over particle size and stability.

Another potential direction is the integration of Telmisartan nanocrystals into innovative delivery systems, such as solid dispersions, oral films, microneedles, or transdermal patches, to target specific therapeutic outcomes. Surface modification and functionalization of nanocrystals with polymers or surfactants could also improve their stability and biodistribution.

9. CONCLUSION

In conclusion, telmisartan is a BCS Class II drug characterized by poor aqueous solubility and limited oral bioavailability, which restricts its therapeutic potential. Based on the literature reviewed, nanocrystal technology appears to be a highly promising strategy to overcome these limitations. Studies reported the successful application of various top-down methods, including high-pressure homogenization and microfluidization, as well as bottom-up approaches such as solvent–antisolvent precipitation, supercritical fluid techniques, and sono-precipitation, to produce telmisartan nanocrystals with significantly reduced particle size and enhanced dissolution rates. Stabilizers and polymers have also been employed to improve physical stability, prevent aggregation, and in some cases, enable targeted or sustained drug delivery. Pharmacokinetic studies in preclinical models suggest that these nanosized formulations could improve systemic absorption and therapeutic efficacy compared to the pure drug. Although the current findings are based on previously reported research the compiled evidence strongly indicates that nanocrystal-based telmisartan formulations have considerable potential for enhancing solubility, bioavailability, and overall clinical performance. Future experimental studies are needed to validate these approaches, optimize formulation parameters, and assess safety and efficacy in humans.

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