

A REVIEW ON STRATEGIES TO IMPROVE CURCUMIN SOLUBILITY: CURRENT ADVANCES AND FUTURE PERSPECTIVES

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ABSTRACT

Due to its wide range of pharmacological effects, curcumin, the primary physiologically active compound obtained from the rhizome of *Curcuma longa* (turmeric), has garnered a lot of attention, including antioxidant, anti-inflammatory, antibacterial, and anticancer characteristics. Despite its amazing therapeutic potential, Curcumin's limited absorption and poor water solubility limit its therapeutic application. Curcumin is quickly metabolically broken down in the liver and gastrointestinal system and has a comparatively low water solubility of about 0.6 µg/mL, resulting in minimal systemic availability following oral dosing. To address these constraints, Various methods of formulation have devised to boost curcumin solubility and improve its pharmacokinetic profile. These strategies include conventional techniques such as solid dispersion and use of bioenhancers, as advanced approaches including nanoparticle-based DDS, nanosuspensions, cyclodextrin inclusion complexes, and crystal engineering methods such as polymorphism and cocrystal formation. Nanotechnology-based formulations have shown special promise due to their capacity to increase medication solubility, stability, and targeted distribution. This study covers the physicochemical problems associated with curcumin, analyzes current tactics utilized to increase its accessibility and dispersion, as well as the possibility for future successful curcumin formulation development.

KEYWORDS: Curcumin, Solubility increase, Nanotechnology, Cyclodextrin complexes, Bioavailability.

1. INTRODUCTION

The rhizome of the Zingiberaceae plant *Curcuma longa* is the source of curcumin, a naturally occurring polyphenolic chemical.^[1] For ages, traditional medical systems like Ayurveda and Chinese medicine have utilized turmeric to treat a wide range of illnesses, including infections, inflammation, and digestive problems.^[2]

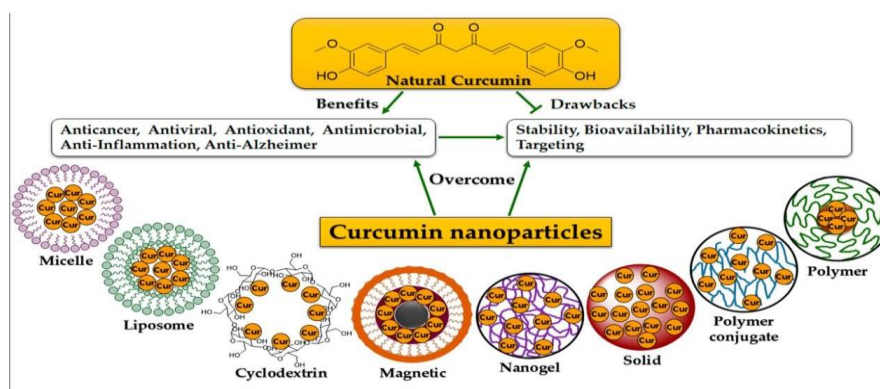


Figure 1: Curcumin Nano-Delivery Systems Overview.

Curcumin is the principal active element in turmeric and is responsible for the majority of its pharmacological action. Curcumin has gained popularity in biomedical research in recent decades due to its many therapeutic properties.

Numerous studies have shown that curcumin has antioxidant, anti-inflammatory, antibacterial, antiviral, and anticancer properties.^[3] These qualities make curcumin a prospective therapeutic agent for the avoidance and management of numerous chronic illnesses as cancer, diabetes, cardiovascular problems, and neurological diseases.^[4]

Curcumin's anticancer properties have been extensively researched both in vitro and in vivo. Curcumin has been demonstrated to impact a broad range of cancer-related molecular targets, such as growth factors, transcription factors, cytokines, and enzymes.^[5] Additionally, curcumin has been demonstrated to possess anti-inflammatory and anti-oxidative stress qualities, both of which are important in the genesis of numerous chronic diseases.

Despite its tremendous pharmacological potential, the therapeutic use of curcumin remains limited due to many physicochemical and pharmacokinetic limitations. One of the most severe constraints is its relatively low water solubility. Curcumin is essentially insoluble in water, with reported solubility values of roughly 0.6 µg/mL.^[6] Poor solubility leads to restricted dissolving in gastrointestinal fluids, which therefore decreases its absorption following oral administration.

Another key constraint is the fast metabolism of curcumin in the liver and intestinal mucosa. Curcumin undergoes significant metabolic modification into glucuronide and sulfate conjugates, resulting in fast removal from the body.^[7]

Consequently, only small quantities of curcumin are detected in plasma following oral treatment.

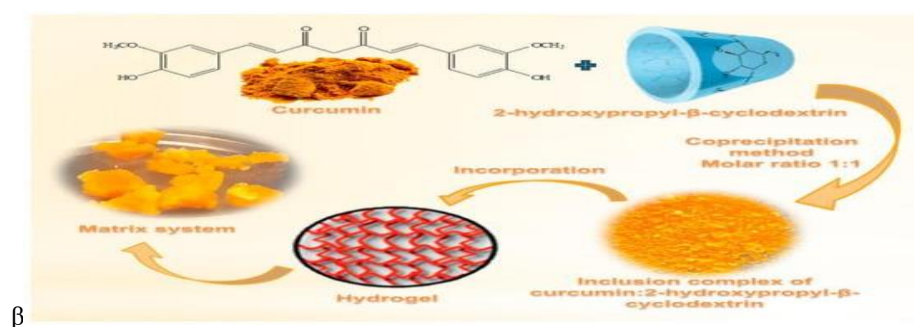


Figure 2: Solubility Enhancement Techniques section.

These constraints have inspired substantial research efforts to discover techniques that might increase the solubility, stability, and bioavailability of curcumin. Various formulation methodologies have been examined, including solid dispersion systems, nanosuspensions, cyclodextrin complexes, liposomes, polymeric nanoparticles, and crystal engineering techniques.^[8]

Among these techniques, Nanotechnology-based medication delivery methods have emerged as promising due to their capacity to improve drug solubility and cellular absorption, and enable regulated drug release.^[9] Similarly, cyclodextrin inclusion complexes and crystal engineering approaches have also indicated potential in enhancing curcumin solubility.

The current work aims to conduct a complete assessment of available approaches for improving curcumin solubility and bioavailability. The paper also analyzes the advantages and limits of various formulation processes and emphasizes future potential in the progress of effective curcumin delivery systems.

2. Physicochemical Properties of Curcumin

Curcumin, technically known as diferuloylmethane, belongs to the diarylheptanoid family of chemicals and features a unique structural structure consisting of two aromatic rings joined by a seven-carbon linker possessing α,β -unsaturated diketone activity.^[10] This chemical structure accounts for its biological function as well as its physical features.

Curcumin comes in two tautomeric forms: the keto form and the enol form. In acidic and neutral situations, curcumin mainly resides in the keto form, but in alkaline circumstances the enol form becomes more stable.^[11] These tautomeric forms alter the chemical stability and reactivity of the molecule.

Curcumin is extremely lipophilic and has limited solubility in aqueous solutions. However, it demonstrates substantially increased solubility in carbon-based turpentine such as ethanol, methanol, dimethyl sulfoxide, and acetone. The hydrophobic property of curcumin considerably inhibits reduces its absorption in the digestive system and makes it less soluble in biological fluids.

In addition to its limited solubility, curcumin is chemically unstable under physiological circumstances. Curcumin is quickly broken down in alkaline environments and is vulnerable to hydrolysis and oxidation reactions.^[12] Curcumin's stability and therapeutic efficacy are further diminished by these degradation processes.

Curcumin's quick metabolism is another important element influencing its bioavailability. The intestinal mucosa and liver undergo considerable metabolism of curcumin into glucuronide and sulfate conjugates, which are promptly removed from the body. This metabolic instability contributes greatly to the low plasma concentrations found following oral treatment.

Because of these physicochemical constraints, traditional curcumin formulations generally fail to attain therapeutic plasma concentrations. Therefore, enhancing the solubility and stability of curcumin has prominent priority in pharmaceutical research.

Several formulation strategies have been proposed to circumvent these restrictions. These include methods such as solid dispersion, nanosuspensions, liposomal encapsulation, polymeric nanoparticles, cyclodextrin inclusion complexes, and crystal engineering approaches.^[13] Each of these ways tries to increase the solubility, stability, and bioavailability of curcumin.

Conventional Strategies for Improving Curcumin Solubility

3. Conventional Solubility Enhancement Techniques

Many conventional pharmacological methods were used to increase the solubility and rate of dissolution of poorly water-soluble medications, such as curcumin, before improved nanotechnology-based delivery methods were developed. The primary goal of these methods was to raise drug wettability, surface area, and drug dispersion in an aqueous environment. The often used technologies include solid dispersion systems, the use of bio enhancers, particle size reduction, and solvent-based techniques.^[13]

These traditional procedures stay relevant because they are generally straightforward, cost-effective, and ideal for large-scale pharmaceutical manufacture. Although some of these strategies provide little improvement compared with recent nanotechnology-based approaches, they nonetheless serve a key role in increasing medication solubility and dissolving behavior.^[14]

3.1 Solid Dispersion Systems

One of the most used pharmaceutical strategies to increase the rate of dissolution of weakly water-soluble medicines. The approach involves distributing the medication in a hydrophilic carrier matrix, which increases wettability and minimizes particle agglomeration.^[15]

Chiou and Riegelman were the first to introduce the notion of solid dispersion, which they described as a solid carrier containing a dispersion of one or more pharmacologically active components. or matrix [16]. The most often used carrier materials in solid dispersion systems are polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), and hydroxypropyl methylcellulose (HPMC).

When curcumin is integrated into a hydrophilic carrier matrix, its dissolution rate rises due to greater wettability and decreased particle size. Additionally, the medication may reside in an amorphous state in the polymer matrix resulting in increased solubility.^[17]

Several research have proved the efficiency of solid dispersion strategies in enhancing curcumin solubility. For example, Kurien and Scofield showed that heat-treated curcumin demonstrated considerably higher solubility and better pharmacological activity compared with untreated curcumin.^[18] Similarly, solid dispersions of curcumin with PEG and PVP have been found to promote drug solubility and improve bioavailability.^[19]

The higher solubility found in solid dispersion systems can be due to many mechanisms including better drug wettability, decreased particle size, and conversion of crystalline drug into an amorphous form. However, solid dispersion formulations may suffer from stability concerns during long-term storage due to recrystallization of the amorphous drug.^[20]

Despite these limitations, solid dispersion remains a successful and commonly used approach for enhancing the solubility of poorly soluble medicines such as curcumin.

3.2 Use of Bioenhancers

Another major strategy for enhancing curcumin bioavailability includes the bioenhancers. Bioenhancers are compounds that enhance the absorption and bioavailability of medicines without exhibiting considerable pharmacological action of

their own.

Piperine, a natural alkaloid derived from black pepper (*Piper nigrum*), is one of the most extensively studied curcumin bioenhancers. Piperine is known to decrease medication metabolism and increase intestinal absorption of certain medicines.^[21]

Shoba *et al.* conducted a pharmacokinetic research exploring Piperine improves the bioavailability of curcumin. The results revealed that combining piperine and curcumin improved curcumin bioavailability in humans by 2000%.^[22]

This substantial rise was ascribed to the suppression of glucuronidation and improved intestinal absorption.

The method by which piperine improves curcumin bioavailability involves inhibition of hepatic and intestinal drug-metabolizing enzymes, primarily UDP-glucuronyl transferase. By inhibiting metabolic degradation, piperine improves the systemic availability of curcumin.^[23]

Because of its efficacy, piperine is typically incorporated in dietary supplements containing curcumin to increase its absorption. However, the use of bioenhancers must be carefully reviewed since suppression of drug metabolism may potentially alter the pharmacokinetics of other drugs.^[24]

3.3 Particle Size Reduction

Particle size reduction is another common method for increasing the dissolving rate of poorly soluble medicines. The Noyes-Whitney equation states that increasing the surface area of particles increases a drug's solubility rate.^[25]

Micronization and nanonization are commonly used methods to reduce pharmaceutical particle size and boost solubility. Curcumin's smaller particle size enhances the surface area accessible for dissolution, which leads to improved solubility and quicker drug release.^[26]

Standard curcumin powder has been proven to have lower solubility rates than micronized curcumin formulations. However, because curcumin is hydrophobic and has limited wettability, particle size reduction alone may not be sufficient to significantly enhance its bioavailability.^[27]

3.4 Solvent and Co-solvent Systems

Another method for increasing the solubility of poorly soluble pharmaceuticals is to utilize solvent and co-solvent systems. This procedure involves dissolving the medicine in a solvent combination to improve its solubility and formulation development.^[28]

Curcumin is more soluble in organic solvents, such ethanol, methanol, and dimethyl sulfoxide. Therefore, solvent-based extraction and formulation procedures are routinely utilized to generate curcumin formulations.^[29]

However, the organic solvents in pharmaceutical formulations may generate safety and regulatory difficulties. Consequently, the usage of solvent systems is largely confined to laboratory-scale research or extraction operations rather than final pharmaceutical products.^[30]

3.5 Limitations of Conventional Approaches

Traditional techniques to solubility improvement have both advantages and problems. Solid dispersion systems, for example, are susceptible to physical instability caused by drug recrystallization during storage. Similarly, particle size reduction strategies may not provide a significant increase in drug's solubility in highly hydrophobic compounds like curcumin.^[31]

Additionally, organic solvents, which can be dangerous and have negative effects on the environment, may be used in solvent-based processes. Researchers have therefore concentrated on innovative medication delivery methods that may enhance solubility and bioavailability.

These restrictions have led to the creation of drug delivery systems based on nanotechnology, which offer a number of benefits, such as increased drug solubility, stability, and tailored drug delivery.^[32]

Nanotechnology-Based Strategies for Improving Curcumin Solubility

4. Nanotechnology-Based Drug Delivery Systems

One of the most promising methods for increasing the solubility and bioavailability of medications that are poorly soluble in water, such as curcumin, is nanotechnology. drug delivery methods based on nanotechnology that employ nanoscale carriers to increase the solubility, stability, and targeted distribution of medications.^[32]

The typical size range of nanoparticles is 1–1000 nm. Larger surface area, a faster rate of dissolution, better drug stability, and enhanced cellular absorption are only a few benefits of nanoparticles' small size.^[33] Nanoformulations can help effectively move medications across biological membranes and greatly increase the water solubility of hydrophobic substances like curcumin.

Curcumin has been investigated using a number of nanotechnology-based delivery methods, such as polymeric nanoparticles, liposomes, nanoemulsions, solid lipid nanoparticles, and nanosuspensions. Curcumin bioavailability and therapeutic efficacy have significantly improved thanks to these cutting-edge drug delivery methods.^[34]

4.1 Polymeric Nanoparticles

One of the most researched nanocarriers for improving the solubility and bioavailability of poorly soluble medications is polymeric nanoparticles. The biodegradable polymers that make up the nanoparticles have the ability to capture and shield therapeutic compounds from deterioration.

Regarding curcumin, polymeric nanoparticles give various advantages including greater drug solubility, enhanced stability, controlled drug release, and higher cellular absorption.^[34] Commonly utilized polymers for curcumin nanoparticle compositions include:

- Poly(lactic-co-glycolic acid) (PLGA)
- Chitosan
- Polycaprolactone
- Polyethylene glycol (PEG)

Yallapu *et al.* demonstrated that curcumin nanoformulations greatly increase medication distribution and therapeutic performance in cancer therapy models.^[34] Encapsulation of curcumin in polymeric nanoparticles protects the medication

against degradation and increases its bioavailability.

Similarly, Bisht et al. created polymeric nanoparticle-encapsulated curcumin and shown better therapeutic effectiveness compared with free curcumin in pancreatic cancer models. The study demonstrated that nanoparticle administration boosted curcumin stability and accelerated cellular absorption.

The greater solubility found in polymeric nanoparticle systems is largely related to the decreased particle size and increased surface area of the medication. In addition, polymeric matrices offer prolonged drug release, which helps maintain therapeutic medication concentrations over longer durations.^[34]

Despite their advantages, polymeric nanoparticle formulations may entail complicated manufacturing methods and greater production costs compared with traditional medication formulations.

4.2 PLGA Nanoparticles

Among the numerous polymers used for nanoparticle manufacturing, poly(lactic-co-glycolic acid) (PLGA) is one of the most extensively utilized biodegradable polymers recognized by the United States (FDA) for pharmaceutical uses.^[34]

PLGA nanoparticles have various benefits including biodegradability, biocompatibility, regulated drug release, and preservation of medicines from metabolic degradation.^[35] When curcumin is encapsulated within PLGA nanoparticles, the medication is shielded against fast metabolism and degradation, resulting in increased bioavailability.

Nair et al. discovered that curcumin-loaded PLGA nanoparticles displayed considerably improved anticancer efficacy compared with free curcumin.^[35] The study indicated that nanoencapsulation enhanced medication solubility and boosted cellular absorption in cancer cells.

Furthermore, PLGA nanoparticles can give continuous release of curcumin, which helps maintain therapeutic quantities in the body for extended durations. This continuous release pattern is particularly useful for medicines like curcumin that undergo fast metabolism.^[36]

Because of these benefits, PLGA nanoparticles are usually regarded promising nanocarrier technologies for curcumin administration.

4.3 Liposomes

Liposomes are phospholipid bilayer-enclosed spherical vesicles. Liposomes can encapsulate both hydrophilic and hydrophobic drugs. Liposomal Delivery of Drugs technologies have been widely researched for enhancing the solubility and stability of poorly soluble medicines.

Curcumin can be integrated into the lipid bilayer of liposomes due to its hydrophobic nature. Liposomal encapsulation enhances curcumin solubility and protects the medication from degradation in biological settings.^[37]

Several studies have indicated that liposomal curcumin formulations boost drug absorption and improve treatment results in numerous disease types. For example, liposomal curcumin has shown promising outcomes in cancer therapy due to enhanced tumor targeting and greater drug accumulation in tumor tissues.^[38]

Additionally, liposomes can be modified with surface ligands to facilitate tailored medication delivery. This technique provides targeted administration of curcumin to specific tissues or cells, hence boosting therapeutic efficacy and decreasing adverse effects.

However, liposomal formulations may suffer from stability concerns and relatively expensive production costs, which can restrict their extensive commercial adoption.

4.4 Solid Lipid Nanoparticles

(SLNs) are another promising nanocarrier method for enhancing the solubility of poorly water-soluble medicines. These nanoparticles consist of solid lipid cores stabilized by surfactants.

SLNs provide various benefits including better drug stability, regulated drug release, and enhanced bioavailability.^[39]

Because curcumin is extremely lipophilic, it may be efficiently integrated into lipid matrices.

Studies have revealed that curcumin-loaded solid lipid nanoparticles display higher dissolving rates and better therapeutic effectiveness compared with standard formulations. Additionally, SLNs can shield curcumin from degradation and enhance its pharmacokinetic profile.

4.5 Nanoemulsions

Colloidal dispersions of oil droplets in water, typically ranging in size from 20 to 200 nm, are known as nanoemulsions. Surfactants and co-surfactants stabilize such systems.

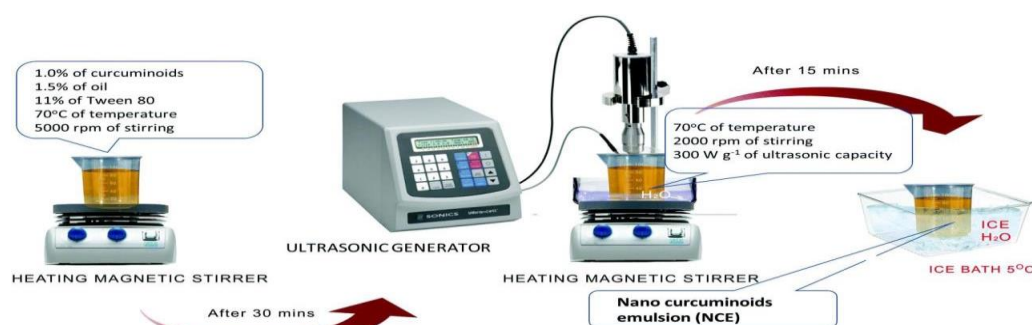


Figure 3: Nanoemulsion and Nanoparticle Preparation.

When it comes to making lipophilic medications like curcumin more soluble, nanoemulsions are especially helpful. The hydrophobic medication dissolves in the nanoemulsion's oil phase, and the tiny droplet size expands the absorption surface area.^[40]

Curcumin nanoemulsions have been proven to greatly boost medication solubility and improve oral bioavailability. In addition, nanoemulsions can boost medication permeability across biological membranes, which further enhances therapeutic efficacy.

4.6 Nanosuspensions

Nanosuspensions are homogeneous dispersions of medication particles having a size of less than 1 micron. Unlike nanoparticles, nanosuspensions contain pure medication particles stabilized by surfactants.

This approach considerably enhances the surface area of drug particles and boosts their dissolving rate.^[40] Curcumin nanosuspensions created employing high-pressure homogenization have exhibited better solubility and quicker dissolution compared with standard curcumin formulations.

Additionally, nanosuspensions can boost medication absorption by enhancing adherence of drug particles to biological membranes. This characteristic can considerably enhance the bioavailability of poorly soluble medicines.

Advantages of Nanotechnology-Based Approaches

Nanotechnology-based medication delivery systems provide various benefits compared with traditional solubility enhancement approaches. These advantages include:

1. Increased drug surface area
2. Improved dissolving rate
3. Protection against metabolic breakdown
4. Controlled drug release
5. Enhanced cellular uptake

Because of these benefits, nanotechnology-based formulations have become one of the most frequently explored techniques for enhancing curcumin solubility and bioavailability.

However, some problems remain in the creation of nanoformulations, including stability constraints, large-scale production difficulties, and possible toxicity concerns connected with nanomaterials.

Advanced Molecular Approaches, Research Gap and Future Perspectives

5. Cyclodextrin Inclusion Complexes

Cyclic oligosaccharides called cyclodextrins are frequently employed in pharmaceutical formulations to increase the stability and solubility of poorly soluble medications. Cyclodextrins can form inclusion complexes with hydrophobic compounds like curcumin because they have a hydrophilic outer surface and a hydrophobic interior cavity.

When curcumin is integrated into the hydrophobic cavity of cyclodextrins, its water solubility improves considerably. This occurs because the hydrophobic medication is sheltered within the cyclodextrin cavity while the hydrophilic outside interacts with water molecules.

Several forms of cyclodextrins are routinely employed in pharmaceutical formulations, including:

- *α -cyclodextrin*
- *β -cyclodextrin*
- *γ -cyclodextrin*
- *Hydroxypropyl- β -cyclodextrin*

Among them, β -cyclodextrin and its derivatives are the most extensively employed for curcumin formulations because of their acceptable cavity size and comparatively low toxicity.

Jacob and Nair discovered that Cyclodextrin inclusion complexes dramatically increase curcumin's solubility and stability in water. Similarly, Loftsson and Duchêne found that cyclodextrin complexes accelerate drug solubility and

improve bioavailability for various hydrophobic medicinal molecules.

In addition to enhancing solubility, cyclodextrin complexes can also boost medication stability by shielding curcumin from degradation caused by light, heat, and oxidation.

Because of these benefits, cyclodextrin-based formulations are frequently employed in pharmaceutical drug delivery systems.

6. Crystal Engineering Approaches

Crystal engineering methods are increasingly being employed to change the physicochemical characteristics of medicinal substances. Two key ways employed for curcumin are polymorphism and cocrystal formation.

6.1 Polymorphism

Polymorphism refers to the capacity of a molecule to exist in several crystalline forms that differ in molecular structure and physicochemical attributes.

Different polymorphic versions of a medication may display different:

- Solubility
- Dissolving rate stability bioavailability

Less stable polymorphic forms frequently demonstrate increased solubility and quicker dissolution compared with more stable crystalline forms.^[40]

Lu and Rohani demonstrated that polymorphism alteration of active medicinal ingredients can greatly impact medication solubility and bioavailability. In the case of curcumin, numerous polymorphic forms have been found, each having various solubility properties.

Understanding polymorphism is consequently crucial in pharmaceutical formulation development since selecting the proper polymorphic form can improve medication performance.

6.2 Cocrystals

Cocrystals are crystalline solids comprising of an active medicinal component and a co-former molecule coupled by non-covalent interactions such as hydrogen bonding or van der Waals forces.

Unlike salts, cocrystals do not entail proton transfer between molecules, which makes them useful for medications that do not readily ionize.

Sanphui *et al.* showed that curcumin cocrystals synthesized with appropriate co-formers displayed considerably enhanced dissolving rates compared with pure curcumin. Similarly, Sathisaran and Dalvi found that building curcumin cocrystals with hydroxyquinol dramatically increased solubility and dissolution behavior.

Cocrystal formation enhances drug solubility by changing the crystal lattice structure, hence lowering intermolecular forces that restrict drug dissolution.

Because of their capacity to boost solubility without affecting the chemical structure of the medication, cocrystals have received substantial interest in pharmaceutical research.

7. Research Gap

1. Although substantial progress has been made in identifying techniques to increase curcumin solubility, major research gaps remain.
2. First, many research focus on particular formulation techniques without comparing their efficacy. There is minimal comparative investigation comparing alternative solubility improvement strategies such as nanoparticles, cyclodextrin complexes, and cocrystals.
3. Second, most research assessing curcumin formulations are restricted to in vitro investigations. Only a small number of research have studied the pharmacokinetics and therapeutic benefits of these formulations in clinical settings.
4. Third, the long-term stability and safety of nanoformulations remain critical considerations. While nanotechnology-based delivery systems provide significant benefits, large-scale production and regulatory licensing may create obstacles.
5. Finally, there is little research examining hybrid delivery methods that integrate different solubility augmentation methodologies. For example, integrating nanoparticle technology with cyclodextrin complexes or cocrystal engineering may produce synergistic advantages in medication solubility and bioavailability.
6. Addressing these research gaps will be vital for moving curcumin formulations from laboratory research to clinical uses.

8. Future Perspectives

In order to achieve even larger improvements in solubility, stability, and therapeutic efficacy, future research on curcumin formulation development will concentrate on better drug delivery techniques.

The development of personalized medication delivery systems is an intriguing avenue. By using ligands or antibodies to deliver medications to sick tissues specifically, these methods improve therapy efficacy and reduce side effects.

Another innovative method is hybrid nanocarrier systems. To enhance medication delivery, hybrid nanocarrier systems integrate various nanotechnology platforms, such as lipid carriers and polymeric nanoparticles.

Piperine and other bioenhancers may continue to be crucial in enhancing the absorption and bioavailability of curcumin.

Furthermore, by forecasting the best formulation process, developments in computer simulation and artificial intelligence may aid in the development of improved drug delivery systems.

In conclusion, it is anticipated that the new pharmaceutical technology would significantly increase curcumin's medicinal potential in the future.

9. CONCLUSION

Curcumin has demonstrated therapeutic potential in the prevention and treatment of numerous diseases due to its exceptional pharmacological qualities. However, low bioavailability, rapid metabolic breakdown, and poor water

solubility severely restrict its therapeutic use.

Numerous formulation approaches have been devised to get around these limitations. These range from simple techniques like solid dispersion and particle size reduction to more advanced ones like cyclodextrin complexes, nanosuspensions, nanoparticle-based delivery systems, and crystal engineering methods.

The most promising of all these methods are formulations based on nanotechnology, which can enhance the solubility, stability, and targeted delivery of drugs.

However, issues with formulation stability, large-scale production, and clinical translation require further attention. Curcumin's successful clinical application and complete therapeutic exploitation may be made possible by further development of innovative drug delivery strategies.

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