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Review Article

A Review of Different Approaches for Improving Curcumin Bioavailability

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Abstract

The creation and development of herbal nanoparticles have moved to the forefront of nanoformulation research. Curcumin is the most essential bioactive component of curcuma longa, a plant that has been utilized in traditional medicine for centuries. This chemical contains therapeutic properties that can be utilized to prevent and treat a wide range of ailments. Curcumin has proven therapeutic efficacy in the treatment of a range of human ailments, however, it has a limited bioavailability, which appears to be due to poor absorption, rapid metabolism, and rapid systemic clearance. As a result, nanotechnology is a revolutionary concept that can be used to curcumin solubility, stability, and bioavailability issues. This review examines contemporary developments in chemical and pharmaceutical technologies, as well as the utilization of innovative materials for medical applications.

Keywords: Curcumin, Nanotechnology, Nanoformulation, Bioavailability

Introduction

Turmeric (Curcuma longa L., a perennial herb in the Zingiberaceae family) contains curcumin, a powerful natural antioxidant with a wide range of biological applications. It can be found in tropical and sub-tropical areas all around the world. It is widely grown in asian countries, particularly India and China, and is frequently used as a home cure for several maladies in Ayurveda, Unani, and Siddha medical systems. According to human and mouse research, when curcumin is consumed orally, it has a decreased bioavailability when it passes through intestinal digestion. Curcumin nanoparticles, liposomes, micelles, and phospholipid complexes, as well as curcumin nanoparticles, liposomes, and micelles, can all help with circulation, permeability, and metabolic resistance. Nanotechnology is being investigated as a potential means of increasing curcumin's efficacy. Medication delivery and tissue targeting are extremely successful using nanotechnology-modified substances.[1] It features keto-enol tautomerism, with a dominant keto form in acidic and neutral media and a stable enol form in alkaline media. Its chemical name is bis-alpha-unsaturated -diketone, or diferuloylmethane.[2] Curcumin has a wide range of uses, including antibacterial activity[3], anti-inflammatory[4], anti-oxidant[5], pro-apoptotic[6], chemopreventive[7], chemotherapeutic[5], anti-proliferative [6,8], wound healing, anti-nociceptive[9], antiparasitic[10], antimalarial[11], diabetes[12], obesity, neurologic, psychiatric disorders[13], cancer[4], and chronic illnesses affecting the eyes, lungs, liver, kidneys, gastrointestinal[14], and reproductive system[15] and as nanotechnology advances, nanoparticles will become more significant in new drug delivery systems. Nanoparticle formulation will provide new ways to improve solubility, stability, bioavailability, pharmacological activity, and the ability to avoid physical and chemical degradation. As a result, combining curcumin with nanotechnology provides a solution for increased bioavailability and therapeutic efficacy.[16]

Problems with Curcumin Bioavailability

Low intrinsic activity, poor absorption, high rate of metabolism, inactivity of metabolic products, and/or rapid excretion and clearance from the body are all reasons for the lower bioavailability of any substance within the body. Curcumin has been shown in studies to have high intrinsic activity and, as a result, usefulness as a therapeutic agent for a

variety of illnesses. However, investigations on curcumin absorption, distribution, metabolism, and excretion over the last three decades have demonstrated poor absorption and quick metabolism of curcumin, severely limiting its bioavailability.[17] Curcumin bioavailability issues such as low blood levels, limited tissue distribution, apparent quick metabolism, and short half-life are discussed in depth in this section.[18]

Serum concentration –

One of the most notable findings in curcumin research is the discovery of incredibly low serum levels.[19] Wahlstrom and Blennow used Sprague– Dawley rats in their 1978 study to investigate the absorption, distribution, and excretion of curcumin. Curcumin was poorly absorbed from the gut, as evidenced by the presence of negligible quantities of curcumin in the blood plasma of rats after oral administration of 1 g/kg of curcumin.[18]

Tissue distribution –

Curcumin's biological action is dependent on its uptake and distribution in bodily tissues.[19] These results imply that curcumin pharmacokinetics found in tissues following i.p. treatment cannot be directly compared to those observed after gavage or food ingestion, according to Ravindranath et al.[18]

Metabolites –

Curcumin metabolism in rodents and humans has been studied in several ways. Curcumin is susceptible to conjugations such as sulfation and glucuronidation at diverse tissue sites once it is absorbed. The first biodistribution study showed the metabolism of the major part of curcumin given to rats orally. The liver was identified as the primary organ involved in curcumin metabolism.[19]

Half-Life-

Curcumin clearance from the body, or systemic elimination, is another significant element that influences its biological action.[18]

Methods of Preparations:

1. Coacervation techniques
2. Nanoprecipitation method
3. Spray drying method
4. Single emulsion method
5. Solvent evaporation method
6. Micro emulsion
7. Wet milling method
8. Thin-film hydration method
9. Solid dispersion method
10. Emulsion polymerization method
11. Fessi method
12. Ionic gelation method
13. Ultrasonication
14. Antisolvent precipitation method

Coacervation techniques

In this method of manufacture, the polymer is dissolved in a suitable solvent (e.g., dichloromethane, ethyl acetate, or acetonitrile), and the herbal drug (curcumin) is suspended directly in the polymeric solution and homogenized properly. Nanoparticles are collected via centrifugation. [20] It's a budget-friendly option. The biggest drawback of this method is the massive amount of solvent required. Chirio et al. developed curcumin-loaded nanoparticles using this technique.[16]

Nanoprecipitation method

Nanoprecipitation is also known as the solvent displacement method. The needed polymer is suspended in a suitable solvent to produce a polymeric solution, which is then mixed with the herbal medication in this method (curcumin). After that, the drug-polymer solution is added to water and continuously agitated, resulting in precipitation. Using heated airflow, the solvent is then allowed to evaporate.[21] Because of the use of spray drying, amorphous drugs were created, which may partially crystallize during processing. In this method of synthesis, curcumin and polymer are combined in the same solvent or a mixture of solvents. Chin et al. developed starch nanoparticles to control curcumin release.[19]

Spray drying method

Curcumin nano-crystals can be made via spray drying. A Mini spray-dryer is used to dry curcumin nano-suspensions with a medicine concentration of 10% (w/w) for this purpose. [22] The spray-dried curcumin nanocrystals are promptly collected after the process. Yallapu et al. developed curcumin-encapsulated PLGA nanoparticles.[18]

Single emulsion method

Curcumin nanoparticles are typically made with a single emulsion method. This method produces curcumin nanoparticles by dispersing them in a suitable solvent and then homogenizing or ultrasonifying them at high speeds to create an emulsion. Additionally, the emulsion's solvent is evaporated by continuous magnetic stirring at room temperature or reduced pressure.[23] Before being lyophilized, the solidified nanoparticles are ultrasonicated and collected, then washed with distilled water to remove any additives. Curcumin-loaded poly (lactic-co-glycolic acid) (PLGA) nanoparticles are potentially a possibility. Sari et al. (2013) used this method to manufacture curcumin nanoparticles.[16]

Solvent evaporation method

The evaporation of a solvent consists of two main steps: The evaporation of the dispersing solvent used to dissolve curcumin in the formation of a drug-polymeric solution a solid mass is created as a result. The emulsion is turned into a nanoparticle suspension by evaporating the solvent. This method avoids the low temperatures required for solvent evaporation and thermal deposition.[24] the following are a few drawbacks: The reagents used in this method are very expensive; selecting the correct solvent is difficult, and evaporating organic solvent takes a long time. Curcumin nanoparticles loaded with PLGA (Polylactic acid-co-glycolic acid) are created using this approach.[16, 18]

Microemulsion

Making nanoparticles via a microemulsion is regarded to be the best method. The surfactants used in this method are hydrophobic for water-soluble drugs and hydrophilic for oil-soluble meds. A microemulsion is generated by mixing a little amount of surfactant with curcumin, oil, and water. It results in the formation of a turbid solution, which in most cases appears as minute droplets. Curcumin nanoparticles are made more surface stable using a variety of surfactants. This method is straightforward and can be used to deliver medications at a low cost of energy.[25] Certain elements, such as temperature and pH change, have an impact on the microemulsion process

for making phospholipid-based curcumin encapsulated microemulsions.[16]

Wet milling method

Curcumin nanoparticles can be made using the wet-milling method. Curcumin is dispersed in a dispersing solvent that is appropriate for curcumin. The ultrasonication technique is used to further agitate the resultant solution. Curcumin nanoparticles are synthesized using distilled water.[26] The generated nanoparticles are collected after centrifuging the resultant solution. Giat et al. employed wet milling to create nano curcumin.[16, 18]

Thin film hydration method

In this manufacturing approach, herbal medicine (curcumin) and surfactants are allowed to interact in a suitable organic solvent under sonication conditions. The solvent is allowed to evaporate at a particular pressure. After that, distilled water is added in a sonication condition, and the resulting nanosuspension is centrifuged to obtain curcumin nanoparticles. [27] Using this method, Moorthi et al. (2012) demonstrated the production of curcumin nanoparticles.[19]

Solid dispersion method

In this way, the matrix and hydrophobic drugs like curcumin are mixed. A matrix can be amorphous or crystalline. This method can be used to dissolve an intractable hydrophobic medicine. This method, which is both rapid and scalable, is used to make curcumin nanoparticles. Curcumin nanoparticles were created by Moorthi et al. (2012) using a solid dispersion method.[16]

Emulsion polymerization method

Organic and continuous phase emulsion processes can both be used to make curcumin nanoparticles. The surfactant is ultrasonically dissolved in pure water, followed by the dissolution of curcumin in a suitable solvent and the addition of the solution to the surfactant. Moorthi et al used this method to make curcumin nanoparticles, and piperine was combined with curcumin to boost the biological activity of the resulting curcumin nanoparticles.[19]

Fessi method

In this method of manufacture, curcumin is dissolved in a suitable solvent under sonication conditions. The resultant solution is then stirred constantly while being blended with pure water and a surfactant. Curcumin nanoparticles can be made spontaneously using this method. Moorthi et al., 2012 used this method to create curcumin nanoparticles. This is a simple and basic method for producing nanoparticles.[16, 18]

Ionic gelation method

Curcumin, a hydrophobic medicine, is dissolved in a solvent with 100 percent curcumin solubility and then added to the polymeric solution while stirring constantly. This method involves cross-linking a polymer with a medicine such as curcumin. Chabib et al. (2012) described the fabrication of curcumin nanoparticles using chitosan as a polymer.[28] This polymer improved the solubility and stability of curcumin nanoparticles.

Ultrasonication

This method is most commonly employed with drugs that aren't particularly water-soluble. Curcumin is first dissolved in an organic solvent, and the resulting solution is then added to a polyelectrolyte solution that has been ultrasonically agitated for multiple time intervals[29], with the curcumin nanoparticles collected. Zhang et al. (2011) employed this ultrasonication method to make curcumin nanoparticles.[19]

Antisolvent precipitation

An antisolvent precipitation process is used to make the water-insoluble medicine. Curcumin is dissolved in an organic solvent and then slowly added to deionized water while stirring continually. Curcumin nanoparticles can be made using this method.[30] This technique of synthesis has the benefit of being appropriate for the production of poorly soluble curcumin nanoparticles.[19]

Types of Curcumin Nano-Drug Delivery Systems

1. Liposomes
2. Polymeric Nanoparticles
3. Solid lipid nanoparticle
4. Polymeric micelles
5. Magnetic nanoparticles
6. Nanogels
7. Gold Nanoparticles
8. Silver Nanoparticles
9. Niosomes
10. Cyclodextrin
11. Implant delivery system
12. Cur-PLGA-NPs.

Liposome

Liposomes are nanoscale spherical artificial vesicles created from natural phospholipids and cholesterol. These vesicles have been reported as immunological adjuvants and drug transporters. Liposomes are increasingly being used in the pharmaceutical industry to carry medications, vaccines, and enzymes for disease prevention and treatment. Liposomes have been used to study chemotherapeutic medications for cancer treatment, vaccines for immunological protection, radiopharmaceuticals for diagnostic imaging, and nucleic acid-based medicines for gene therapy.[31] Liposomes are spherical vesicles having a lipid bilayer encasing an aqueous phase that can be used to encapsulate medications.[32] Because of their high biocompatibility, ease of synthesis, chemical diversity, and simple modification of pharmacokinetic parameters by changing the chemical composition of the bilayer components, they have been used to improve the therapeutic effectiveness and safety of pharmaceuticals for many years. As a result, liposomes are frequently employed to boost curcumin bioavailability and effectiveness. To increase curcumin solubility, Rahman et al. produced beta-cyclodextrin curcumin inclusion complexes that trapped both native curcumin and the complexes into liposomes independently.[33] All curcumin-containing formulations were effective at inhibiting cell proliferation in vitro cell culture. Using several liposomal formulations, Chen et al. studied the stability of curcumin in phosphate-buffered saline, human blood, plasma, and culture medium. [34] Liposomal curcumin was more stable in phosphate-buffered saline (PBS) than free curcumin (PBS).[35] Curcumin-loaded flexible liposomes (CUR-SLs) with silica coatings and curcumin-loaded flexible liposomes (CUR-FLs) without silica coatings were produced, and bioavailability of CUR-SLs and CUR-FLs was shown to be 7.76- and 2.35-fold higher than curcumin suspensions, respectively.[36,37] The fluidity of the lipid bilayers and the small size of the liposomes make oral absorption easier. [19,38]

Liposome Preparation:

Researchers looked at several total lipid curcumin ratios (weight/weight) ranging from 10:1 to 4:1 before settling on a constant ratio of 10:1. The lyophilization process consisted of several stages. Curcumin was initially dissolved in DMSO at a 50 mg/mL concentration. In tert-butanol (20 mg/mL), the lipid (e.g., DMPC) was dissolved. The two solutions were mixed and passed through a 0.22 M filter for sterilizing. Aliquots of this solution were placed in lyophilization vials.The vials were frozen in a dry ice acetone bath and lyophilized for 24 hours to remove any DMSO and tert-butanol. The vials were held at a constant temperature of 20 degrees Celsius. In certain tests, the lipid formulation comprised DMPC or DMPC/DMPG. [39]

Polymeric Nanoparticles

Lipids, proteins, and carbohydrates, as well as a variety of natural and synthetic polymers, can be used to make NPs, which range in size from 10 to 1000 nm. For distribution, a medication is dissolved, entrapped, encapsulated, or attached to an NP matrix. Depending on the method of preparation, NP, nanospheres, or nanocapsules can be obtained. NP systems are being used to examine a variety of biomedical applications. NP systems have lately gained popularity for enhancing the therapeutic index of encapsulated pharmaceuticals by sheltering them from enzymatic degradation, changing pharmacokinetics, lowering toxicity, or permitting controlled release over extended durations, as discussed previously. Because of their small size and high biocompatibility, polymeric nanoparticles can circulate in the bloodstream for long periods, allowing for more targeted therapy. [36] Synthetic polymers such as chitosan, poly(D, L-lactide co-glycolide) (PLGA), and PEG have been widely explored for curcumin nanoparticle synthesis. Polymers can also be combined to make copolymers, which could be useful for site targeting and long-term action.[19]

Solid Lipid Nanoparticles (SLNs)

SLNs are made up of natural or synthetic lipids or lipids, such as lecithin and triglycerides, and are solid at human physiological temperatures. SLNs offer unique properties that make them appealing for boosting the performance of nutraceuticals, pharmaceuticals, and other materials, such as a smaller size, a larger surface area, and phase interaction at interfaces. Lipophilic substances can be solubilized by a solid lipid core matrix in solid lipid nanoparticles. Surfactants aid in the stability of the lipid core (emulsifiers).[40] All formulation excipients must be Generally Recognized as Safe (GRAS) to achieve and maintain a solid lipid particle following injection. The melting point of lipid nanoparticles must be higher than body temperature (37°C).Kakkar et al. developed curcumin-loaded solid lipid nanoparticles (C-SLNs) to improve their oral bioavailability. Dadhaniya et al. studied the adverse effects of a new solid lipid curcumin particle in rats.[19]

Polymer Micelles

Micelles are lipid molecules with a relatively narrow size range of 10 to 100 nm that create a spherical shape in aqueous solutions, making them more stable in biological fluids when diluted.[41] Micelles' functional properties are based on amphiphilic block copolymers that create a nanoscale core/shell structure in aqueous circumstances. Polymeric micelles can transport water-insoluble drugs like curcumin, improving their efficiency by directing them to certain cells or organs.[42] As a result, fewer drugs accumulate in healthy tissues, toxicity is decreased, and greater doses can occasionally be administered. Liu et al. created curcumin-loaded biodegradable self-assembled polymeric micelles for long-term release to overcome curcumin's limited water solubility. Raveendran et al. also looked at making curcumin-loaded micelles with an amphiphilic Pluronic/ polycaprolactone block copolymer, which was found to be successful at boosting curcumin's water solubility. The micellar technique can be used to solubilize, stabilize, and distribute curcumin precisely.[19]

Magnetic Nanoparticles

In magnetic drug targeting, a drug is conjugated with a magnetic material under the influence of an external magnetic field. Drug-loaded magnetic nanoparticles can gather in desired tissue regions under the influence of an external magnetic field, and the drug can then be controlled to release from the particles. Yallapu et al. constructed magnetic drug carriers with a pluronic polymer (F127) shell for the controlled delivery of curcumin.[43] Tran et al. created a nanosized magnetofluorescent Fe_3O_4-curcumin compound with entrapped curcumin and a chitosan or oleic acid outer shell. The Fe_3O_4-curcumin compound demonstrated a high-loading cellular uptake that was visible by magnetic and fluorescent methods, and it was also shown to be a good candidate for a dual (optical and magnetic) imaging probe.

Nanogels

Nanogels are three-dimensional polymer chain networks cross-linked by covalent bonds that may be modified to generate biocompatible and degradable gel networks. Because of their smaller particle size (10–200 nm), biodegradability and/or biocompatibility, extended half-life, high stability, greater drug loading and/or trapping, and immune system protection, nanogels offer a lot of potential for systemic drug administration. Goncalves et al. used a self-assembled dextrin nanogel as a curcumin delivery technique, using dynamic light scattering and fluorescence experiments. Chemical functional groups, cross-linking density, surface-active and stimuli-responsive components, and surface-active and stimuli-responsive components can all be altered to get distinct nanogel properties. It developed a family of water-dispersible hybrid nanogels for intracellular delivery of hydrophobic curcumin.[19]

Gold nanoparticles

Because of their optical and electrochemical distinctiveness, gold nanoparticles are a powerful technology in nanomedicine applications. The stability of AuNPs and their propensity to combine with biomolecules are two of their most prominent qualities. AuNPs are being investigated as critical drug delivery vectors due to some of their qualities, such as reduced cytotoxicity, configurable surface properties, and in vivo stability. They're also simple to make and put to use. Rajesh et al. conjugated curcumin with AuNPs and increased curcumin solubility using polyvinyl pyrrolidone (PVP), a well-known drug carrier.[44] In a work by Singh et al., curcumin was bound to the surface of AuNPs to increase its bioavailability.[45] Manju and Sreenivasan have developed a simple method for making water-soluble curcumin-conjugated AuNPs that can be utilized to target many cancer cell types. Curcumin targeting and long-term release, as well as significant antioxidant activity, are likewise caused by AuNPs.[9]

Silver Nanoparticles

Because of its excellent efficacy, silver is often utilized as an antibacterial agent. Silver nanoparticles with surface plasmon resonance have been discovered to exhibit amazing optoelectronic properties. They have been shown to have superior antimicrobial activity when compared to other silver antibacterial agents. To improve the use of sodium carboxymethyl cellulose silver nanocomposite films for antibacterial applications, new film-silver nanoparticle

curcumin complexes have been developed.[46] Furthermore, silver nanoparticles may protect cells against HIV-1 infection and aid wound healing, as well as play an important anti-inflammatory, antiviral, and anticancer role. Aside from long-term therapeutic effects and sustained release, the combination of silver nanoparticles and curcumin has several other advantages, including anti-inflammatory, anti-infection, anti-cancer, and wound healing properties.[19]

Niosomes

Niosomes are microscopic lamellar structures formed when cholesterol is combined with a nonionic surfactant of the alkyl or dialkyl polyglycerol ether class and hydrated in aqueous conditions. They resemble liposomes in structure and can be used as a viable alternative to liposomal drug carriers. Niosomes are a promising drug delivery vehicle that is less toxic and boosts drug therapeutic index by confining drug activity to target cells due to their non-ionic nature. The properties of the vesicle formulation are various and changeable.[47] Changes in composition, size, lamellarity, trapped volume, surface charge, and concentration can all affect vesicle characteristics. The vesicles could act as a storage facility for the drug, slowly releasing it. Niosomes are osmotically active, stable, and improve the stability of the entrapped medication. They improve the oral bioavailability of poorly absorbed medications by increasing skin penetration.

Cyclodextrin

Cyclodextrins (CDs) are uncommon molecules with a "pseudo-amphiphilic" structure that are used in pharmaceutical and related sectors. From the enzymatic degradation of starch, glucosyltransferase produces cyclic oligomers of -1,4D-glucopyranoside, or CDs. Noncovalent inclusion complexes can be formed with a wide range of guest molecules using CDs with lipophilic inner chambers and hydrophilic outer surfaces.[48] Internally, CDs have a hydrophobic domain that can take water-insoluble chemicals, while the exterior hydrophilic surface makes it easier to dissolve.[49] They've been employed in the production of liposomes, microspheres, microcapsules, and nanoparticles, among other delivery vehicles. Insoluble drugs' solubility and dissolution are improved using CDs, increasing their bioavailability.[50] They also improve the permeability of insoluble, hydrophobic drugs by allowing the drug to be available at the surface of the biological barrier (e.g., skin and mucosa) from the moment it divides into the membrane, without harming the lipid layers of the barrier.[51] It's crucial to use just enough CD to solubilize the medication in the aqueous media in these cases, as too much can impair drug availability. Cyclodextrins can boost drug bioavailability by stabilizing medicine molecules at the biomembrane surface. [52] For example, CD-enhanced insulin bioavailability following nasal administration is mostly due to its stabilizing effect. Because the medicine dissolves in the mucosa and enters the systemic circulation, sublingual drug delivery is one of the most successful ways for avoiding hepatic first-pass metabolism.[53] Several lipophilic pharmaceuticals' bioavailabilities in sublingual formulations have been reported to be improved by complexing poorly water-soluble medicines with cyclodextrin.[19,54]

Implant delivery system

Whether in the shape of millions, pellets, or microspheres, drug-loaded polymer implants can deliver drugs for extended periods. Increased patient compliance leads to improved therapeutic outcomes, especially for chronic drugs, thanks to this subcutaneous implantation. In the realms of contraception and hormone therapy, this procedure is well-known. Non-degradable polymeric matrix and biodegradable polymeric matrices are the two types of polymeric delivery technologies now in use. Non-degradable biometrics are made of silicone or polymer (ethylene-co-vinyl acetate).[55] The Norplant delivery system employs this technique of contraception. Vadhanam et al. used the technology to give ellagic acid in a breast cancer model over 28 weeks, exhibiting efficacy while using 130-fold less chemical via Silastic implants than the dietary strategy (500 ppm). Mechanical failure, which could result in dosage dumping in reservoir systems and continuous dose reductions in solid-drug dispersion matrices, is a risk with this technology, even though it can deliver for long periods. Another disadvantage of this method is the risk of fibrous growth around the implants, which could make removal difficult at the end of the treatment period.[19]

Conclusion

Traditional medicine is the oldest kind of health care in the world. Curcumin is a naturally occurring chemical that helps people avoid developing chronic illnesses. Curcumin solubility, stability, and bioavailability are all difficulties that can be solved with nanotechnology. This review discusses the numerous problems, preparation methods, and several types of curcumin nano-drug delivery systems of curcumin nanoparticles, as well as its novel approach. However, in vitro and in vivo studies account for the majority of curcumin's recognized effects. Curcumin has yet to be approved for the treatment of any disease in humans. As a result, the promise of nanotechnology-based medicine may become a reality with tremendous effort and additional research.

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Conflicts of Interest

The author does not have any conflicts of interest.

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Authors Contribution

RRC and SDJ: Conceptualization, Methodology, Writing-Original draft preparation, Writing- Reviewing and Editing, **VHT and ASJ:** Visualization, Investigation, **KVG and ASJ:** Conceptualization, Writing- Reviewing and Editing.

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