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Novel Formulations Aspects of Curcumin for Site Specific Drug Delivery

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ABSTRACT

Curcumin, a natural polyphenolic compound from turmeric (Curcuma longa), is renowned for its health benefits, including anti-inflammatory, antioxidant, and anticancer properties. However, its clinical use is hindered by poor solubility, stability, and bioavailability. Researchers have turned to curcumin nanocomplexes, employing diverse nanocarriers and nanoparticles to address these limitations.

This abstract highlights recent advancements in curcumin nanocomplex research, emphasizing their ability to improve solubility, stability, and bioavailability. Various nanocarrier platforms, such as lipid-based nanoparticles, polymeric nanoparticles, cyclodextrin complexes, and nanoemulsions, effectively encapsulate curcumin, providing protection, controlled release, and enhanced cellular uptake, thereby enhancing its pharmacokinetic and pharmacodynamic properties.

Additionally, the abstract explores potential applications of curcumin nanocomplexes in cancer therapy, neurodegenerative diseases, cardiovascular conditions, and inflammatory disorders. Augmented bioavailability of curcumin through nanocomplexes holds promise for optimizing therapeutic efficacy, reducing dosages, and mitigating potential side effects.

In conclusion, curcumin nanocomplexes represent an innovative approach to overcome curcumin's limitations, unlocking its therapeutic potential. Ongoing research holds significant promise for the development of novel curcumin-based pharmaceuticals and nutraceuticals with improved bioavailability and clinical outcomes.

Key Words: Nanocomplex, Curcumin, Targeted drug delivery, nanocarriers.

INTRODUCTION

Curcumin as a therapeutic agent

Curcumin, is a yellowish polyphenol and predominantly derived from the rhizomes of Curcuma longa (turmeric), as well as other members of the ginger family, Zingiberaceae. The turmeric extract contains four types of curcuminoids, accounting for approximately one-six% of turmeric by dry weight. These include curcumin (60-70%), de-methoxycurcumin (20-27%), bis-demethoxycurcumin (10-15%), and cyclo-curcumin.

Chemical formula of curcumin is (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadien-3,5-dione) is a diarylheptanoid, composed of two aromatic O-methoxy phenolic groups. The two phenolic rings which are linked by two α, β-unsaturated carbonyl groups as depicted in Figure 1[1].

Turmeric has been utilized for centuries as spice and colouring agent in Indian cuisine, as well as a therapeutic agent in traditional Indian medicine. The use of curcumin as an anti-cancer agent emerged due to the abundance of epidemiological evidence linking dietary turmeric consumption with low rates of gastrointestinal mucosal cancers. Numerous experimental studies have conclusively demonstrated that free curcumin can cause cell cycle arrest and/or apoptosis in human cancer cell lines derived from various solid tumors, such as colorectal, lung, breast, pancreatic and prostate carcinoma, among others[2].

NANOCOMPLEXES

Nanocomplexes can be synthesized using different biopolymers and methods. One approach is the layer-by-layer assembly using electrostatic coating of biopolymers. Electrostatic interactions between partially positively charged proteins and negatively charged biomolecules can be enhanced by adjusting the pH of the solution around the isoelectric point of the protein molecule. Thermally induced partial denaturation of proteins can also enhance hydrophobic interactions with biopolymers, allowing for self-aggregation of protein molecules and simultaneous adsorption of polysaccharide molecules[3].

Nanocomplexes of Curcumin have been prepared to enhance its bioavailability and therapeutic

efficacy. These nanocomplexes can be prepared using various materials such as liposomes, micelles, nanoparticles & cyclodextrins. They have been shown to improve the solubility, stability & delivery of curcumin to its target sites[4].

Various studies have indicated that the effectiveness of curcumin nanocomplexes in various disease models. For instance, curcumin-loaded liposomes have been proved to have anti-inflammatory effects in models of acute lung injury & rheumatoid arthritis. Curcumin nanoparticles have also been shown to have anticancer effects in models of breast and lung cancer[5].

In addition, curcumin nanocomplexes have been shown to have potential therapeutic uses in neurodegenerative disorder such as Alzheimer's and Parkinson's disease. Curcumin-loaded nanoparticles have been indicate to improve memory and cognitive function in animal models of Alzheimer's disease[6].

This preparation shows a facile and effective nano-encapsulation strategy to improve water dispersibility, stability & even bioactivities of poorly soluble nutraceuticals (with an emphasis on curcumin, a typical poorly soluble nutraceutical with a lot of health benefit), through nano-complexation with food proteins[7].

Overall, curcumin nanocomplexes have shown great promise in enhancing the bioavailability and therapeutic efficacy of curcumin. However, future studies are needed to fully understand the mechanism of actions underlying their effects and to optimize their formulation for clinical use[8].

Polyelectrolyte complexes

Polyelectrolyte complexes (PECs) are the association complexes formed between two different charged particles (e.g. polymer-polymer, polymer-drug and polymer-drug-polymer). These are formed/developed due to electrostatic interaction between two different charged polyions. This avoids the use of chemical cross linking agents, thereby reducing the possible toxicity effects and other undesirable effects of the chemicals. The polyelectrolyte complexes formed between a poly acid and poly base are little affected by the pH variation of the dissolution medium[9].

Polyelectrolyte complex nanoparticles can be used for the encapsulation and delivery of natural antioxidant curcumin to carcinoma cells. Chitosan/Alginate nanoparticles show curcumin encapsulation efficiency of 69% and exhibit sustained release of curcumin in-vitro. Anticancer activity of curcumin loaded Chitosan/Alginate nanoparticles towards MCF-7 cells (Human Breast cancer cell line with Estrogen, Progesterone and Glucocorticoid receptors) is studied using MTT assay (a colorimetric assay for measuring cell metabolic activity). Intracellular uptake of the drug encapsulated nanoparticles is confirmed by fluorescent imaging[10].

In recent years, self-assembly of proteins with natural or synthetic polyelectrolytes to form complexes (polyelectrolyte complex) with drug candidates has drawn increasing attention[11]. PEC formation leads to particles with dimensions on a colloidal level, generating optically homogeneous and stable nano-dispersions. In addition, such methods have the advantage of not necessitating sonication and organic solvents during preparation, therefore minimizing possible damage to drug candidates[12].

Protein-polysaccharide nanocomplexes have gained more and more attention, as the complexes of different types of materials is usually superior to single biopolymers. Different complexation techniques, such as single or multi-steps of methods to form complexes or conjugates, that have been utilized in the past few years to fabricate nanocomplexes for curcumin delivery were summarized and explained, along with detail introduction on various encapsulation mechanisms, such as pH driven and anti-solvent methods. In addition, the encapsulation and delivery 9efficiencies of nanocomplexes synthesized using different types of biopolymers[13].

Background of PEC Formation

The mixing of solutions of polyanions and polycations leads to the spontaneous formation of interpolymer complexes under release of the counterions. Complex formation can take place between polyacids and polybases, but also between their neutralized metal and halogenide salts. For free polyelectrolyte chains the low molecular counterions are more or less localized near the macroions, in the case of high charge densities, particularly because of counterion condensation. The driving force of complex formation is mainly the gain in entropy due to the liberation of the low molecular counterions[14].

The formation process of polyelectrolyte complexes may be divided into three main classes

1. Primary complex formation
2. Formation process within intracomplexes
3. Intercomplex aggregation process

The first step is realized through secondary binding forces such as Coulomb forces immediately after mixing oppositely charged polyelectrolyte solutions. This reaction is very rapid. The second step proceeds within the order of an hour and involves the formation of new bonds and/or the correction of the distortions of the polymer chains. The third step involves the aggregation of secondary complexes, mainly through hydrophobic interactions. Such an aggregation is influenced by many factors, e.g., the structure of the polymer components and the complexation conditions. The final aggregates of the polyelectrolyte complexes are insoluble in ordinary solvents, and the molar ratio of the repeating units of the polymer components in the aggregates is almost unity[15].

Curcumin, a hydrophobic polyphenol shows anticancer activity towards prostate cancer, lung cancer, bone cancer, head and neck cancer, breast cancer and gastrointestinal cancer. In addition to the anticancer potential, curcumin possesses anti-oxidant, anti-inflammatory and anti-microbial properties. Regardless of all these desirable properties, curcumin is not extensively used for cancer therapy because of its poor aqueous solubility, stability and rapid metabolism For overcoming these limitations, different nano-formulations such as polymeric micelle liposomes, nano-gels have been developed[10].

Methods of preparation of nanocomplexes

Homogenization method

Polyelectrolyte nanoparticles were prepared by mixing and homogenization. Briefly, cationic electrolyte was dissolved in acetic acid solution (1%, v/v) with high speed stirring until completely dissolved. The solution was filtered (filter pore size 30~50 μm) to remove the insoluble substances. Anionic electrolyte solution was prepared by dissolving it in the distilled water, adjusting the same pH to cationic electrolyte solution. Afterwards, Anionic electrolyte solution was added drop wise to cationic electrolyte solution at equal volume at 800 r/min for 30min using an IKA RW 20 digital overhead stirrer. Curcumin was first dissolved in ethanol together with 1% Tween 80 at a certain weight ratio. After dissolution, the mixture was dispersed into the cationic solution followed by the addition of anionic electrolyte, as described for polyelectrolyte nanoparticles preparation. The system was then attached to a rotary evaporator for removing the ethanol. The final samples were transferred in vials under nitrogen bed and stored in the refrigerator (at 4°C in the dark) until use[11].

Ultrasonication method

Curcumin-loaded nanocomplexes were prepared via a precipitation-ultrasonication method with modifications. curcumin, PVPK30, and soy lecithin were dissolved in acetone, distilled water, and distilled water, respectively, at concentrations of 10 mg/mL. PVPK30 and soy lecithin were mixed in the volume ratios of 1:0.5, 1:1, and 1:2 to a total volume was 6 mL. Then 0.6 mL curcumin acetone solution was added into the mixed solution with ultrasonication for 2 min (20.6235 kHz, 340 W), followed by evaporation of acetone at 60 ◦C under vacuum until no organic solvent remained. The resultant nanocomplexes were defined as K30-L1:0.5, K30-L1:1, and K30-L1:2,respectively[12].

Simple vortex mixing method

Complex cationised gelatin /Alginate polyelectrolyte complex was prepared by simple mixingof cationised gelatin and Alginate. Solutions of sodium alginate(0.1% and 0.2%,w/v) and cationised gelatin (0.1% and 0.2%, w/v) were pre-pared in distilled water. Polyelectrolyte complex was prepared by the addition of aqueous solution of Alginate to cationised gelatin at room temperature under vigorous vortexing for 5 min. Polyelectrolyte complexes ofdifferent compositions were prepared by varying the volume of Alginate and CG. PEC combination which shows the lowest size was centrifuged at 15,000 rpm for 20 min to separate the nanoparticles. Curcumin was dissolved in acetone (1 mg/mL) and added to0.1% solution of cationised gelatin. Complex formation was performed. Solution of Alginate (1 mL, 0.1%) was added to the curcumin containing cationised gelatin solution (3 mL) and vortexed for 5 min. Drug loaded nanoparticles were separated by centrifugation as mentioned above and was dried under vacuum[10].

Applications of curcumin polyelectrolyte nanocomplexes for different drug delivery

Polyelectrolyte complexes enhances anti-diabetic activity of curcumin

Low bioavailability, poor aqueous stability and lack of appropriate delivery systems delimit the chemotherapeutic effect of curcumin. In this study, curcumin was encapsulated in chitosan-based polyelectrolyte complexes and its anti-diabetic activities were assessed using in vitro a-amylase inhibitory assay and in vivo anti-hyperglycaemic effect in alloxan-induced rats. Inhibition of these carbohydrate metabolizing enzymes delay the breakdown of carbohydrate, increase transit time and decrease postprandial glucose excursion levels in diabetic conditions using in silico molecular model showed that curcumin had a better inhibitory capacity towards a-amylase activity than quercetin and many other natural compounds.

In this study, results showed that the efficacy of sub-therapeutic non-encapsulated dosage of the phytodrug in hyperglycaemic rats was enhanced via nano-encapsulation in chitosan tripolyphosphate drug delivery carriers. The physicochemical and biopharmaceutical properties of the excipient used in the development of the drug delivery carriers greatly influenced the bioavailability, release and efficacy of such drugs. Glucose lowering effect of curcumin encapsulated in chitosan-tripolyphosphate formulations supplemented with alginate was enhanced by 30% compared to those prepared with chitosan only.

It is reported that insulin-loaded in chitosan-alginate nanoparticles produced by ionotropic pre-gelation followed by polyelectrolyte complexation and administered orally to hyperglycaemic rats reduced glucose levels by two-folds compared to oral administration of insulin or those physically mixed with empty nanoparticles[16].

Curcumin nanocomplexes for treating cancer

Curcumin nanocomplexes segregated to provide nanoparticles after dispersion in water and showed potential to stabilize curcuminoid contents for at least 12 months in the storage conditions used. Acute and chronic toxicity studies were conducted to confirm the safety of Curcumin nanocomplexes. A single low or medium dose of Curcumin nanocomplexes is safe in both mice and hamsters. Likewise, low and medium daily CNCs doses are safe for long-term administration. We observed that Curcumin nanocomplexes treatment have the potential to produce toxicity in high-dose treatments, but most abnormal parameters returned to normal levels by 28 days after the final dose[17].

This study encapsulated the naturally available nutraceutic agent, curcumin, in PLGA nanoparticles, investigated their kinetics of degradation in vitro and studied the drug release in HER2-positive MCF7 breast cancer cells. Our study demonstrates that PLGA nanoparticles are able to release curcumin intracellularly inducing time- and dose-dependent inhibition of proliferation via a G2/M block even at low concentrations of drug. The cytotoxic behaviour was actually triggered by specific cell cycle arrest

caused by free curcumin released in the cytoplasm, while PLGA nanoparticles proved to be completely innocuous toward cells in absence of drug. As the therapeutic dosages commonly required for curcumin-based treatments of inflammatory and cancer diseases are extremely high due to a poor bioavailability of this molecule in vivo, our results suggest a great potential of PLGA-based nano-formulation of curcumin for the treatment of malignant breast cancer[18].

Anti-inflammatory activity of curcumin nanocomplexes

Inflammatory bowel diseases are characterized by chronic and relapsing inflammation of the gastrointestinal tract. Current treatment strategies for Inflammatory bowel diseases are insufficient, expensive and associated with high toxicity. In the search for alternatives that could help in the management of Inflammatory bowel diseases without causing serious side effects, natural compounds have been considered. Curcumin is a natural, inexpensive compound with anti-inflammatory properties. Concurrently, silver can suppress microbial activity and promote wound healing. Taking into account the properties of both compounds, we decided to combine, with the use of nanotechnology, silver and curcumin to synergistically enhance their activity. We obtained two formulations: a complex of curcumin and silver (i) nanoparticles (nAg) and a complex of curcumin nanoparticles and silver (i) nanoparticles. They assessed the anti-inflammatory effect of the formulations in vitro in LPS-stimulated RAW264.7 macrophages and in vivo in a mouse model of dextran sulfate sodium (DSS)-induced colitis. In vitro, both formulations inhibited the release of nitric oxide and in vivo the complexes alleviated colitis. In conclusion, our research showed that combining curcumin with nAg enhances curcumin's anti-inflammatory properties and that using nanocurcumin instead of curcumin further enhances this effect. Curcumin and silver (i) nanocomplexes may become a new treatment option in Inflammatory bowel diseases [19].

Nanocomplexes composed of glycyrrhizic acid derived from the root of the licorice plant (Glycyrrhiza glabra) were formulated for the delivery of curcumin . Glycyrrhizic acid / curcumin nanocomplexes demonstrated high intracellular uptake into macrophages (RAW264.7 cells), consequently reducing the release of the pro-inflammatory cytokine tumor necrosis factor-α. Furthermore, glycyrrhizic acid / curcumin nanocomplexes successfully reduced the levels of serum pro-inflammatory cytokines and splenomegaly in a rheumatoid arthritis model[20].

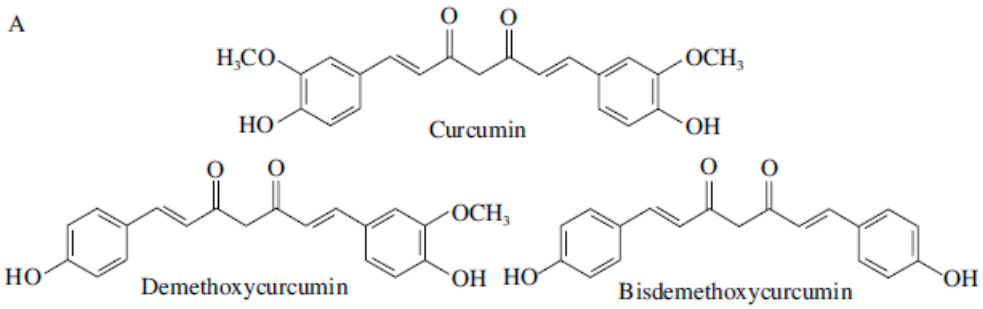

Fig 1: Structure of curcumin, de-methoxycurcumin and bis-demethoxycurcumin.

Polyelectrolytes	Category (Based on the charge type)
Natural Polyelectrolytes	
Nucleic acids	Poly-anion

Poly (L-lysine)	Poly-cation
Poly (L-glutamic acid)	Poly-anion
Carrageenan	Poly-anion
Alginates	Poly-anion
Hyaluronic acid	Poly-anion
Chemically modified biopolymers	
Pectin	Poly-anion
Chitosan (deacetylation of chitin)	Poly-anion
Cellulose – based	Poly-anion or Poly-cation
Starch – based	Poly-anion or Poly-cation
Dextran – based	Poly-anion or Poly-cation
Synthetic polyelectrolytes	
Poly (vinylbenzyl trialkyl ammonium)	Poly-cation
Poly (4-vinyl-N-alkyl-pyridimiun)	Poly-cation
Poly (acryloyl-oxyalkyl-trialkyl ammonium)	Poly-cation
Poly (acryamidoalkyl-trialkyl ammonium)	Poly-cation
Poly (diallydimethyl-ammonium)	Poly-cation
Poly (styrenesulfonic acid)	Poly-anion
Poly (vinylsulfonic acid)	Poly-anion
Poly (acrylic or methacrylic acid)	Poly-anion
Poly (itaconic acid)	Poly-anion
Maleic acid/ diallyamine copolymer	Poly-ampholytic

Table:1 Important Polyelectrolytes[9]

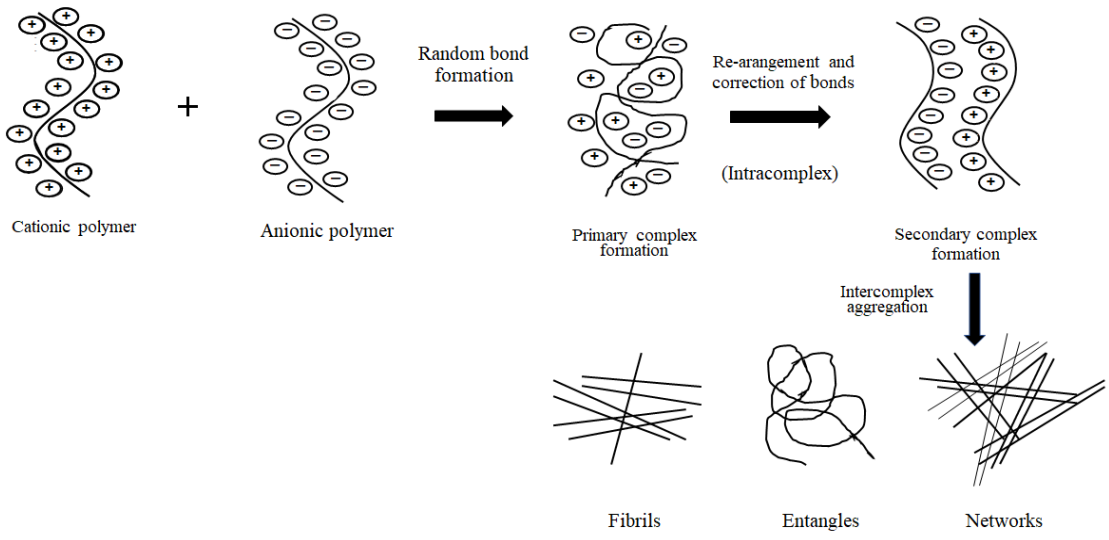

Fig 2: Structural representation of Polyelectrolyte complex formation

Nanoforms	Size	Activities
Curcumin loaded Solid-lipid nanoparticles (Cur-SLNs)	60 nm	Prevents Lipopolysaccharide induced sepsis
Zinc oxide–curcumin core–shell nanoparticles (ZnO–Cum)	~45 nm ZnO core ~12 nm curcumin shell	Antibacterial activity (including the antibiotic resistant bacteria)
Curcumin-TA-metal complex • Cur@TA-Fe III • Cur@TA-Cu II	• 200 nm • 160 nm	Antibacterial activity
Nano-micelle containing curcumin (Sina Curcumin ®)	10 nm	• Antidiabetic activity • Decrease in insulin resistance • Improvement in lipid profile
Nanocurcumin	300nm	• Antidiabetic • Anti-inflammatory (STZ induced inflammation) • Protects pancreatic beta cells
NANOCUR-MF Nanocurcumin combined with magnetic field	34–359nm 8MT magnetic field	• Anticancer • Antimicrobial • Antitumor
Curcumin-reduced gold nanoparticles (AuNP's-Cur)	26nm	• Anticancer • Antitumor

Table:2 Different types of nanocurcumin and their activities[21-27].

Disease Targeted	Outcome of Study
Coronavirus disease 2019	Nanocurcumin modulated increase in rate of inflammatory cytokines in COVID-2019 patients.
Coronavirus disease 2019	Symptoms of COVID-2019 resolved faster in group administered with Nanocurcumin and improved recovery rate.
Metabolic syndrome	Levels of Brain-derived neurotrophic factor, IL-10, serum concentrations of malondialdehyde decreased.
Oral lichen planus	Decrease in reticular-erosive-ulcerative (REU) score observed.
Knee Osteoarthritis	Reduced levels of Collagenase-2 and NO
Human lung cancer	Significantly inhibited the migration ability of A549 cells; promote intracellular ROS overproduction and induced apoptosis.
Migraine	Significant reduction in serum levels and expression of IL-17 mRNA
Migraine	PTX3 gene expression and serum levels were both significantly less
Human Glioblastoma	Enhancement in cytotoxicity against U87MG cell lines

Table:3 Recent Findings with Use of Nanocurcumin[28-36].

Some of the latest research conducted in past years (2019–2021) have been cited in this table

CONCLUSIONS

curcumin nanocomplexes emerge as a groundbreaking solution to the inherent obstacles associated with harnessing the therapeutic potential of curcumin across various medical applications. Whether through encapsulation within nanocarriers or fusion with nanoparticles, these nanocomplexes have showcased impressive capabilities in elevating curcumin's solubility, stability, and bioavailability. Leveraging an array of nanocarrier platforms, ranging from lipid-based nanoparticles and polymeric nanoparticles to cyclodextrin complexes and nanoemulsions, researchers have effectively tapped into curcumin's healing properties while addressing its inherent limitations.

Moreover, the versatility of curcumin nanocomplexes extends their utility across a broad spectrum of medical domains, encompassing cancer treatment, management of neurodegenerative disorders, cardiovascular health, and the alleviation of inflammatory conditions. The enhanced bioavailability achieved through these nanocomplexes not only amplifies therapeutic effectiveness but also holds the potential to reduce required dosages, potentially mitigating unwanted side effects.

As research within the realm of curcumin nanocomplexes continues to evolve, there is a growing sense of optimism regarding the development of pioneering pharmaceuticals and nutraceuticals that unlock the full potential of curcumin. These advancements are poised to enhance patient outcomes and introduce innovative avenues for addressing multifaceted health challenges. Curcumin nanocomplexes represent a promising paradigm shift in delivering this natural compound, ultimately harnessing its complete therapeutic potential to benefit healthcare and overall well-being.

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