Review Article

Therapeutic Review on Nanocurcumin

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Abstract

An active natural polyphenol compound popularly known as curcumin has found its place in food, textile and pharmaceutical industry. Due to its wide spectrum of targets, curcumin-based researches are finding extensive application in the treatment of many diseases. Therapeutic application of curcumin finds its limitation due to its poor aqueous solubility. Researchers have exploited the application of nanomaterials to enhance the bioavailability of curcumin. Nanocurcumin are extensively studied due to their applications in specific target delivery. This review is an attempt to understand the therapeutic applications of nanocurcumin from recent publications.

Key words : Curcumin, nanocurcumin, nanoparticles, micelles, liposomes, solid lipid nanoparticles.

Introduction

An Important commercial spice grown in India belongs to the family of Zingiberaceae and is commonly known as Indian Saffron. Curcumin is a polyphenolic compound which is mainly extracted from this perennial herb Curcuma longa which belongs to the family Zingiberaceae.[1] This has been used in siddha, unani and ayurvedic medicines due to its well documented health benefits. Chemically curcumin is known as (1E,6E)-1,7-bis (4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3,5-dione. It comprises of two aromatic ring systems containing o-methoxy phenolic group linked by a seven-carbon spacer consisting of an a,b unsaturated b diketone moiety. Curcumin exhibits anticancer, antiviral, anti-oxidant, anti- inflammatory, hypoglycemic, antimicrobial, and antirheumatic properties.[2]

Despite of several applications, curcumin usage as a therapeutic agent sets back because of poor solubility, poor absorption, rapid metabolism and rapid elimination. Many researchers have synthesized curcumin nanoparticles to overcome these obstacles and to improve the bioavailability. Nano curcumin was proven to possess better efficacy due to its better solubility and stability. The degradation of the loaded drug is protected in the nano size, thereby increasing the half-life.[3]

Nano curcumin

Novel curcumin nanoparticulated delivery approaches include polymeric nanoparticles, polymeric micelles, liposomes and solid lipid nanoparticles.

Polymeric nanoparticles

Biodegradability, biocompatibility and immunogenicity are the properties of biopolymers making them a versatile trait for in vitro and in vivo studies. Chitosan, carboxymethyl cellulose, poly lactic acid, poly hydroxy alkanoates, etc. are few widely used biopolymers in the drug delivery concepts. Among the different biopolymers, Chitosan based drug delivery are predominantly reported for the treatment of cancer, drug delivery to brain, pulmonary diseases, gastrointestinal diseases and in treating ocular infections (Table 1). Chitosan, a naturally occurring polysaccharide, is approved by US FDA and is the derivative of chitin, which is in turn obtained from crustacean shells of prawns or crabs. It is highly basic in nature and possesses good mucoadhesive properties. The permeation enhancing property of chitosan also facilitates the intracellular and paracellular transportation of loaded drugs. However, several factors like swelling index of the polymer, polymer degradation and diffusion property of the drug through polymer matrix governs the drug delivery at the targeted site.[4-12]

Sl. No.	Author name	Description	Therapeutic Activity
1	Rajesh Sreedharan Nair *et al.*[4]	Curcumin loaded nanoparticle using chitosan and sodium tripolyphosphate was reported. A superior release and enhanced transdermal permeation of curcumin was reported on Strat-M membrane.	An enhanced percentage cell viability was reported as a result of cytotoxic assay on human keratinocyte cells.
2	Vinod Vijayakurup *et al.*[5]	Chitosan nanocurcumin ranging from size 170 to 200 nm were reported.	Cellular uptake and cytotoxicity in lung cancer cells were reported.
3	Antony V Samrat *et al.*[6]	The demineralized extract of chitosan obtained from *Metacarcinus magister* shells was used. The curcumin loaded nanoparticles was prepared using extracted chitosan and sodium tripolyphosphate and barium chloride as chelators.	Antibacterial activity against *Pseudomonas aer ugino sa* and *Staphylococcus aureus* were studied
4	Khan MA *et al.*[7]	Curcumin loaded chitosan nanoparticles with sodium tripolyphosphate were prepared by ionic gelation method.	Increased uptake of curcumin was reported on cervical cancer cell lines like SiHa, CaSKi and HeLa.
5	Shruti Maddrla *et al.*[8]	Different formulations using chitosan, tripolyph osphate and Tween 80 were prepared by ionic gelation method and reported.	Comparison of entrapment efficiency and drug release kinetics were reported.
6	Lilli Duse *et al.*[9]	Chitosan loaded curcumin nanoparticle with good positive zeta potential was prepared .	Upon irradiation using a novel LED device (λ_{ex} = 457 nm), curcumin nanoparticles were able to generate ROS and destroy tumor cells.
7	Van Cuong Nguyen *et al.*[10]	Composite sponges using 10% curcumin, chitosan and gelatin were prepared	These composite sponges were found to enhance the formation of collagen and wound closure in vivo and therefore improved the wound healing activity
8	Thi Minh Phuc Le *et al.*[11]	Curcumin -loaded NPs have been prepared by an ionic gelation method using chitosan (Chi) and pluronic R F -127 (PF) as carriers to deliver curcumin to the target cancer cells.	Fluorescence Microscopy was used to confirm the cellular uptake of curcumin into HEK293 cells
9	Lay Hon Chuah *et al.*[12]	Curcumin loaded chitosan nanoparticles were ionically gelled with tripolyphosphate were prepared.	Enhanced A dsorption isotherm of mucin was observed on Freundlich and Langmuir models.

Table 1: Therapeutic activity of curcumin polymeric nanoparticles

Polymeric Micelles

Micelles are preferred mainly for targeting the delivery of hydrophobic drugs. Polymeric micelles prolong the circulation time of the nanoparticles in vivo thereby enhancing the cellular uptake, permeability and the retention effect. These properties are due to their composition as two layers namely inner core and outer shell. In addition to the precise delivery at the desired site, the double layer also protects the drug from GI content and overcomes the degradation and metabolism of drug. An enhanced physical stability and improved drug loading capacities can be achieved by preparing mixed micelle using co-polymers (Table 2). [13-18]

Liposomes

Liposomes are characterized by their self-assembled spherical vesicles with one or more concentric phospholipid bilayers. Liposomes can encapsulate both hydrophilic and hydrophobic components with an order of aqueous inner layer and bilipid outer layer respectively. The lipid composition of the liposomes plays an important role in controlling the various factors like zeta potential, encapsulation

Sl. No.	Author name	Description	Therapeutic Activity
1	Suping Ji *et al.*[13]	A mixed micelle was developed with Soluplus, an amphiphilic polyvinyl caprolactampolyvinyl acetate-polyethylene glycol graft copolymer and D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS 1000) for curcumin delivery. Soluplus was observed to improve the oral solubility of poorly soluble drugs. TPGS 1000 was found to enhance the drug entrapment efficiency, drug solubility and stability properties. Curcumin loaded soluplus mixed micelles were prepared by modified film dispersion method.	Absorption of Soluplus micelles were observed in the cytoplasm region of MCF-7 cells. The lower cell viability was observed and the authors have expressed that these micelles loaded with curcumin could have a significant value for the chronic breast cancer therapy.
2	Woraphatphadung T *et al.*[14]	The N-naphthyl–N,O-Succinyl chitosan and N-Octyl-N,O-Succinyl Chitosan polymeric micelle carriers were prepared by physical entrapment methods and were reported to be pH sensitive.	Anticancer activity against HT-29 colorectal cancer cells was reported. The release characteristics was found to be pH dependent and hence the name pH sensitive.
3	Fan Huang *et al.*[15]	Silver nanoparticles were prepared and decorating them in the micellar shell, which in turn is absorbed by polyaspartic acid chains in the shell.	Antibacterial activity against *Pseudomonas aeruginosa* and *S.aureus* were reported. Good biocompatibility and low hemolytic activity were achieved using these micelles.
4	Kunquan Su *et al.*[16]	Polymeric micelles of curcumin that provide sustained drug release were achieved by thin film dispersion method using Pluronic P-123.	The antitumor activity was assessed in vitro by a (3-(4,5-dimethylthiazol-2-yl) -2,5-diphenyltetrazolium bromide) assay on B16 cells. The micelles showed sustained drug release and excellent inhibitory effect on tumor cells.
5	Ornchuma Naksuriya *et al.*[17]	Polymeric micelles were prepared by fast heating method and nanoprecipitation method. It comprises of block copolymers of methoxypoly (ethylene glycol) (mPEG) and *N*-(2-hydroxypropyl) methacrylamide (HPMA) modified with monolactate, dilactate and benzoyl side groups to enhance the solubility of curcumin.	The prepared polymeric micelles formulations were found to show a significantly potent cytotoxic effect against three different cancer cell lines.
6	Xi Yang *et al.*[18]	Curcumin was encapsulated by single step solid dispersion method into monomethyl poly (ethylene glycol)-poly (ε-caprolactone)-poly (trimethylene carbonate) (MPEG-P(CL-co-TMC)) micelles.	The micelles could efficiently suppress the growth of CT26 colon carcinoma cells in vitro. They were also found to be effective in controlling the tumor growth of subcutaneous CT26 colon in vivo.

Table 2: Therapeutic activity of curcumin polymeric micelles

efficiency, stability and release properties of drugs. The phospholipids, a main constituent of liposomes is found abundant in many tissues, it promotes the delivery of drugs to most of the targeted tissues (Table 3).[19-24]

Solid Lipid Nanoparticles

Solid Lipid nanoparticles are preferred for their excellent physical stability thereby protecting the drugs from chemical degradation. They offer few ideal properties like good physical and chemical stability, reasonably small particle size and an excellent biocompatibility. Wide range of both hydrophilic and hydrophobic compounds can be incorporated. The particle size of this category ranges from 120 -200 nm and hence provides an enhanced bioavailability and high reproducibility (Table 4).[25-27]

Sl. No.	Author name	Description	Therapeutic Activity
1	Bruna Sinjari *et al.*[19]	Curcumin loaded liposomes were prepared using 1-palmitoyl 2 – phosphatidylcholine	Anti-inflammatory activities via NFkB/ERK/pERK pathway in human dental pulp treated with 2- Hydroxyethyl Methacrylate (HEMA)
2	Ng Zy *et al.*[20]	Curcumin and salbutamol liposomes were formulated using lipid hydration method	Prepared liposomes were tested on BCl-NS1 cell line to evaluate anti-inflammatory property
3	Mahmoud Hasan *et al.*[21]	Salmon lecithin is used for the preparation of curcumin loaded liposomes.	Application of nano liposomes in primary cortical neurons demonstrated the viability and formation of networks. The decrease in apoptosis rate revealed the neuroprotective role of the nanoliposomes.
4	Ce Cheng *et al.*[22]	Curcumin liposomes were prepared by a pH driven method that makes use of pH-dependent solubilization of curcumin and the self-assembly behavior of phospholipids in water.	The pH dependent preparation of liposomes overcomes the use of organic solvents when compared to other techniques.
5	Geethi Pamunuwa *et al.*[23]	Positively charged and negatively charged hybrid liposomes were prepared by thin film hydration method using egg yolk phosphatidylcholine.	The charge of the liposomes was found to have a significant effect on the skin permeation property of curcumin.
6	Yan Chen *et al.*[24]	Different kinds of curcumin loaded liposomes were prepared using Soybean phospholipids, egg yolk phospholipids, and hydrogenated soybean phospholipids.	In vitro skin permeation study and an effect on antimelanoma activity on the growth of B16BL6 melanoma cells was observed

Table 3: Therapeutic activity of curcumin loaded liposomes

S.no	Author name	Description	Therapeutic Activity
1	Bhatt H *et al.*[25]	Solid lipid nanoparticles were prepared by using glyceryl monostearate in the presence of a surfactant Poloxamer 188.	Higher apoptosis in MDA-MB 231- breast adenocarcinoma cells were reported
2	Wenrui Wang *et al.*[26]	Curcumin solid lipid nanoparticles were prepared by emulsification and low temperature solidification method.	Improved biological efficacy against breast cancer SKBR3cells in vitro was reported
3	Heba A *et al.*[27]	Curcumin solid lipid nanoparticles were prepared and dispersed in a mucoadhesive gel.	Ex vivo muco adhesion and permeation study was carried out on chicken buccal mucosa. An effective result was obtained by the short-term evaluation for the treatment of oral precancerous lesions.

Table 4: Therapeutic activity of curcumin loaded solid lipid nanoparticles

Preparation techniques of Nanocurcumins

Several methods are available for preparation of nanoparticles (Table 5). Selection of an appropriate method is important as it affects the particle size and the stability of the prepared nanoparticles. The method of preparation can be selected based on the physiochemical properties of the polymer and drug.

Conclusion

Curcumin, a natural antioxidant acts as a powerful bioactive agent. Reports on nanocurcumin reveal the increased solubility and bioavailability of curcumin. This short therapeutic review on recent publications reveals that the fabrication of curcumin as nano formulation could result in enhanced potency with optimal pharmacokinetic

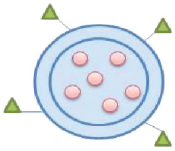
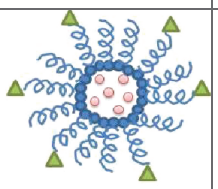
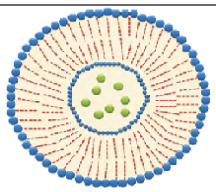
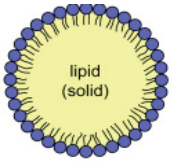
S.no	Type	Structure	Particle Size	Methods of Preparation
1	Polymeric nanoparticles[28]		10 – 1000 nm	Ionic Gelation Nano precipitation Emulsion cross linking method Spray Drying Salting Out method
2	Polymeric Micelles[29]		10 – 100 nm	Direct dissolution Dialysis Method Emulsification method Solvent Evaporation Lyophilization or freeze drying
3	Liposomes[30]		15 – 60 nm	Solvent dispersion method Detergent removal method Mechanical dispersion method
4	Solid Lipid Nanoparticles[31]		50-1000 nm	Solvent emulsification - evaporation High pressure homogenization Solvent emulsification-diffusion Melting dispersion method Double emulsion technique

Table 5: Commonly adopted methods of preparation techniques

properties. Nanocurcumin are referred as a potential therapeutic agent and finds extensive application in food and pharmaceutical industry.

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