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A REVIEW ON PREPARATION METHODS OF CURCUMIN NANOPARTICLES

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Abstract: **Generally nanoparticles size ranges from 1 to 100 nm with one (or) more dimensions. Generally nanoparticles classified into inorganic, organic and particles based on carbon in scale that has properties improved compared to larger size of respective materials. They show properties which are enhanced such as strength, sensitivity, high reactivity, stability, surface area etc., due to their smaller size. They were synthesized by various methods for research and commercial uses which are classified into three types-chemical, physical and mechanical processes which had sawn a vast improvement. We have prepared this paper to present a review on nanoparticles, their types, characterization, synthesis methods and applications in field of environment.**

Keywords: **Applications, Characteristics, Evaluations, Formulations, Nanoparticles, Types.**

1. INTRODUCTION

Nanoparticles are the fundamental components of Nano technology. Nano particles size ranges from 1 to 100nm which are made up of metal, metal oxides, organic matter, and carbon. Nanoparticles differ from various dimensions, to shapes and sizes apart from their material. Surface can be irregular with surface variations or a uniform. Among nanoparticles some are crystalline or amorphous with single or multi-crystal solids either agglomerated or loose.In the process of synthesizing new drugs, most drug candidates are insoluble or poorly soluble in water which causes a huge downfall for the pharmaceutical industry. One of the main reasons for a drug insolubility is its complex and large molecular structure. It has been reported that over 65% of new active pharmaceutical ingredients (APIs) are either poorly soluble in water or insoluble. Due to their low aqueous solubility properties and high permeability, they are categorized as class II of the Biopharmaceutics Classification System (BCS), where the dissolution step is the rate limiting factor in drug absorption. The pharmaceutical industries are now facing a challenge to improve the dissolution characteristic of poorly water soluble drugs which is the key factor in enhancing drug bioavailability. For instance, they help to increase the stability of drugs/proteins and possess useful controlled release properties. This review predominately focused on synthesis of different types of nanoparticles using chemical, physical and biological methods. However, chemical and physical methods are expensive and harmful but biological method is simple, non-toxic, rapid and eco- friendly. It also explains about the characteristics of nanoparticles and concluded with various applications. [1]

Nanoparticles (NPs) are categorized into the following classes based on their shape, size, and chemical characteristics.

2. CHARACTERSTIC FEATURES OF NANOPARTICLES

characteristic features like optical properties, catalytical activities, have huge surface area and good thermal properties mechanical strength electrical conductivity vary than that of bulk material.

Colour: At nanoscale this optical property behaves differently. Elemental gold has nice shining yellow colour, but nanoparticles of gold show red colour.

Catalytic activity: Since the surface area of nanoparticles is large they show increased catalytic activity. They are usually heterogenous catalyst that means catalysts are solid form and the reactions occur on the surface of the catalyst. These catalysts can be easily separated and recycled. For example: Pd, Pt metal nanoparticles used in hydrogenation reactions. Ti02, ZnO are used in photo-catalysis. Gold in bulk is unreactive but the nanoparticles of gold behave as very good catalyst for organic reactions.

Surface area: High surface-to-volume ratio is a very important characteristic of nanoparticles. Bulk material if subdivided into a group of individual nanoparticles, the total volume remains the same, but the collective surface area is largely increased. With large surface area for the same volume, these small particles react much faster because more surface area provides more number of reaction sites, leading to more chemical reactivity. Explanation of increase in surface area with decrease in particle size.

Thermal strength: The melting point of nanomaterial changes drastically with size.

For example : Sodium clusters (Nan) of 1000 atoms melts at 288 K, 10000 atoms melt at 303 K and bulk sodium melts at 371 K.

Mechanical strength: The mechanic al strength of nano clusters increase the hardness of the metal. For example : nanoparticles of copper and palladium clusters with diameter in the range of 5-7 nm have hardness up to 500 r. greater than the bulk metal.

Electrical conductivity: At nanoscale level the electrical conductivity changes.

For example: Carbon nanotubes behave as a conductor or semiconductor whereas carbon is non-conductor. [8]

3. APPLICATIONS OF NANOPARTICLES

Considering the unique properties discussed in this Section, NPs can be used in variety of applications. Some important of these are given below.

Applications in drugs and medications: Nano-sized inorganic particles of either simple or complex nature, display unique, physical and chemical properties and represent an increasingly important material in the development of novel nano-devices which can be used in numerous physical, biological, biomedical and pharmaceutical applications. NPs have drawn increasing interest from every branch of medicine for their ability to deliver drugs in the optimum dosage range often resulting in increased therapeutic efficiency of the drugs, weakened side effects and improved patient compliance. Iron oxide particles such as magnetite (Fe3O4) or its oxidized form maghemite (Fe2O3) are the most commonly employed for biomedical applications. The selection of NPs for achieving efficient contrast for biological and cell imaging applications as well as for photo thermal therapeutic applications is based on the optical properties of NPs. Mie theory and discrete dipole approximation method can be used to calculate absorption and scattering efficiencies and optical resonance wavelength for the commonly used classes of NPs i.e. Au NPs, silica-Au NPs and Au nanorods. The development of hydrophilic NPs as drug carrier has represented over the last few years an important challenge. Among the different approaches, polyethylene oxide (PEO) and polylactic acid (PLA) NPs have been revealed as very promising system for the intravenous administration of drugs. Superparamagnetic iron oxide NPs with appropriate surface chemistry can be used for numerous in vivo applications such as MRI contrast enhancement, tissue repair, and immunoassay, detoxification of biological fluids hyperthermia, drugs delivery and cell separation. All of these biomedical applications require that the NPs have high magnetization value, a size smaller than 100 nm and a narrow particle size distribution. The detection of analytes in tissue sections can be accomplished through antigen-antibody interactions using antibodies labeled with fluorescent dyes, enzymes, radioactive compounds or colloidal Au.

Applications in manufacturing and materials: Nanocrystalline materials provide very interesting substances for material science since their properties deviate from respective bulk material in a size dependent manner. Manufacture NPs display physicochemical characteristics that induce unique electrical, mechanical, optical and imaging properties that are extremely looked-for in certain applications within the medical, commercial, and ecological sectors. NPs focus on the characterization, designing and engineering of biological as well as non-biological structures < than 100 nm, which show unique and novel functional properties. The potential benefits of nanotechnology have been documented by many manufacturers at high and low level and marketable products are already being mass-produced such as microelectronics, aerospace and pharmaceutical industries. Among the nanotechnology consumer products to date, health fitness products from the largest category, followed by the electronic and computer category as well as home and garden category. Nanotechnology has been touted as the next revolution in many industries including food processing and packing. Resonant energy transfer (RET) system consisting of organic dye molecules and noble metals NPs have recently gamed considerable interest in bio photonics as well as in material science. The presence of NPs in commercially available products is becoming more common.

Applications in electronics: There has been growing interest in the development of printed electronics in last few years because printed electronics offer attractive to traditional silicon techniques and the potential for low cost, large area electronics for flexible displays, sensors. Printed electronics with various functional inks containing NPs such as metallic NPs, organic electronic molecules, CNT sand ceramics NPs have been expected to flow rapidly as a mass production process for new types of electronic equipment. Unique structural, optical and electrical properties of one dimensional semiconductor and metals make them the key structural block for a new generation of electronic, sensors and photonic materials. The good example of the synergism between scientific discovery and technological development is the electronic industry, where discoveries of new semiconducting materials resulted in the revolution from vacuumed tubes to diode sand transistors, and eventually to miniature chips .The important characteristics of NPs are facile manipulation and. reversible assembly which allow for the possibility of incorporation of NPs in electric, electronic or optical devices such as ‘‘bottom up” or ‘‘self-assembly” approaches are the bench mark of nanotechnology.

4. TYPES OF NANOPARTICLES

Nanoparticles can be classified in various types based on their structures, sizes or physical and chemical properties. A few of them are carbon-based nanoparticles, lipid-based nanoparticles, and polymeric nanoparticles.

Carbon-based Nanoparticles:

These nanoparticles contain carbons. It includes two main materials: carbon nanotubes (CNTs) and fullerenes. CNTs are graphene sheets that are rolled into a tube. These materials are mainly used for structural strengthening as they are 100 times stronger than steel. CNTs are classified into single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs). CNTs are one of a kind in a way as they are thermally conductive along the length and non-conductive over the tube.

Fullerenes are the allotropes of carbon. Their structure is like a hollow cage as shown in the Figure 1.below having sixty or more carbon atoms. The structure of C-60 is called Buckminsterfullerene, which looks like a hollow football. In these structures, carbon units are having a pentagonal and hexagonal arrangement.

Ceramic Nanoparticles:

They are inorganic solids made up of oxides, carbides, carbonates, and phosphates. These types of nanoparticles are having chemical inertness and high heat resistance. These are useful in drug delivery for many diseases like bacterial infections, glaucoma, and cancer.

Metal Nanoparticles:

These nanoparticles can synthesize by chemical, electrochemical, or photochemical strategies. By chemical methods, we can get metal nanoparticles by reducing the metal-ion precursors in solution by chemical reducing agents. These can adsorb small molecules and have high surface energy. They are widely used in research areas, detection and imaging of biomolecules, environmental and bio-analytical applications.

Semiconductor Nanoparticles:

They are having properties like those of metals and non-metals. They are found in the periodic table in groups II-VI, III-V or IV-VI. Some examples are InP, InAs GaP, GaN, germanium and silicon etc. These are used in electronics devices, photo-optics, photo catalysis, and water splitting applications.

Lipid-Based Nanoparticles:

They are generally spherical in shape and having a diameter ranging from 10 to 100nm. It comprises of a strong center made of lipid and a network containing soluble lipophilic particles. The outside layer of these nanoparticles is stabilized by surfactants and emulsifiers. These nanoparticles have applications in the biomedical field as a drug carrier and delivery and RNA release in cancer therapy. [3]

5. ADVANTAGES OF NANOPARTICLES

1. Ease of modifying nanoparticle surface properties and particle size to target drugs both passively and actively after parenteral administration2.

2. Using nanosized quantum dots based on immunofluorescence to label particular bacteria, which makes it easier to identify and get 1rid of them8.

3. Nanotechnology is a growing field in many industries, including aquaculture, and it has numerous applications in areas like nutrition. [4]

6. DISADVANTAGES OF NANOPARTICLES

1. Because of their small size and high surface area, nanoparticles are highly reactive in the cellular environment.

2. When used for drug delivery, non-biodegradable particles may accumulate at the site of the drug delivery, causing a chronic inflammatory response2.

3. Because nanoparticles have limited targeting capabilities, it is not possible to stop the therapy. [4]

7. PREPARATION METHODS OF CURCUMIN NANOPARTICLES

a. Single Emulsion-Solvent Evaporation Technique.

b. Thin Film Hydration Method.

c. Micro Emulsion Method.

d. De-solvation Method.

e. Agitation and Sonication Method.

f. Cross Linking Method.

g. Freeze Dried Anti Solvent Crystallisation And High Pressure Homogenizer Method.

h. Co-Precipitation Method.

i. Electro spraying Method.

a. Single emulsion solvent evaporation technique: Curcumin loaded nanoparticles were prepared by using single emulsion solvent evaporation technique. In glass tube, to take 100-200 mg of PLGA polymer was dissolved in 5 ml of dichloromethane (DCM), then 10 or 20 mg curcumin powder dissolved in solvent mixture and intermittent vortex for 30 min. The mixture of drug/polymer was added in glass tube containing 10 ml of aqueous PVA solution. After, adding the drug/polymer mixture in PVA solution then vortex for more 10 sec at high speed. This polymer mixture was emulsified in ice water bath for 7 min at 40 % amplitude by using probe sonicator. This emulsified mixture was poured into 30 ml of 0.5% aqueous solution under magnetic stirring. Dichloromethane was evaporated under high magnetic stirring at 800 rpm for 3 hrs. The nanoparticles were collected by using centrifugation at 20,000 rpm for 15 min and washed for 3 times with distilled water. Then supernatants were collected, pellets of the nanoparticles was re-suspended in 5 ml distilled water.

b. Thin Film Hydration Method: The drug loaded lipid nanoparticles was prepared by using a thin film hydration method. In this technique, lipid phosphatidylcholine, cholesterol, curcumin are mixed in the methanol and chloroform desired ratio. Then rotatory evaporator apparatus are used for evaporation of solvent mixture under the reduced pressure at 45°C for 15min at 70 rpm speed. In the solvent mixture containing elements are removed by vacuum pumping for 3 to 4 hrs then thin film is formed. Finally, thin film of drug loaded lipid nanoparticles are hydrated for 1 hrs by using pH 7.4 phosphate buffer solutions. This lipid mixture are sonicated for probe sonication and filtrated by 0.45 µm membrane filter and finally well appropriated drug loaded lipid nanoparticles are formed and store at 4°C. Schematic diagram of lipid loaded Curcumin nanoparticles by thin film hydration method.

C. **Micro emulsion-sonication Method:** The Curcumin nanostructure lipid carriers (NLC) are prepared by using Micro emulsion method. In this method, sonicator is used. The lipids of steric acid (SA) and capric triglycerides (CA) are heated to 75 °C, the surfactants of tween 80 and plutonic F127 are added in melted lipid solution until the solution is clear. Another 1 ml of distilled water and non- ionic surfactants are heated to 75 °C and to melted lipid solution containing curcumin under the continuous stirring. The formed emulsion are added in 2 to 4 °C cold water then they are solidified and the solidified emulsion are homogenised at 8000 rpm for 5 min. Finally well distributed curcumin nanostructure lipid carriers are formed. Schematic diagram of lipid loaded Curcumin nanoparticles by Micro emulsion method.

d. Desolvation Method: The curcumin nanoparticles are prepared by using the desolvation technique. In this technique aqueous polysaccharide solution of ethanol precipitation are used for the preparation of curcumin polysaccharide nanoparticles. Essentially absolute ethanol is a desolving agent and curcumin as the active substances with arranged concentration of absolute ethanol, and 0.1% of tween 20 emulsifying agent is used. To dissolve 5mg/ml of chitosan, 0.1% tween 20 in deionised water and continuous stirring for 1 hour at 90°C. Then the desolving agent of absolute ethanol is added drop wise to the chitosan solution under mixing at 70°C. The nanoparticles formed suspension is centrifuged at 10,000 rpm for 2 min. After centrifugation to separate large particles, supernatant are collected and again centrifuge for 15,000 rpm for 15 min, then resulting nanoparticles precipitate are washed with 1 ml of desolving agent of absolute ethanol and to remove free curcumin. Certainly, the formed nanoparticles are re-suspended in deionised water and freeze dried to form a well distributed polysaccharide curcumin nanoparticles. Schematic diagram of polymer loaded Curcumin nanoparticles by desolvation method.

e. Agitaton and Sonication Method: The curcumin nanoparticles are obtained by two methods one as Agitation and second as sonication. In agitation method, 0.05g mL−1 of curcumin are added in ethanol then 100 ml of this solution are added in predefined volume of deionised water. Then this solution is agitated for 2 hrs at 200-1000 rpm for 50°C. After agitation this solution is lyophilised to obtain a yellow colour TY] powder of curcumin nanoparticles. The nanoparticles are obtained from ethanol and agitation process is known as NEA. In sonicaton process, 0.10 gmL−1 of curcumin are added in ethanol then 100 ml of this solution are added in predefined volume of deionised water. Then this solution was sonicated (120W) for 2 hrs at 50°C. After sonication this are lyophilised to obtain well distributed yellow colour curcumin nanoparticles and second part are maintained as solution. The nanoparticles are obtained from chloroform and sonication is known as NES. Schematic diagram of Curcumin loaded nanoparticles by Agitation method.

f. Cross-linking Method: The curcumin loaded human serum albumin (HSA) nanoparticles are prepared by cross-linking method. Firstly, to prepare the human serum albumin nanoparticles and then to load the curcumin in human serum albumin nanoparticles and to form curcumin loaded HSA nanoparticles. In this method, 1% solution human serum albumin added in 2 ml of phosphate buffer saline and to prepare different concentration of di-thiothretol (DTT 1-10 mm) and Sodium deoxycholate (NaDS 5-30 mm). Then this solution was incubated for 1 hrs at 30 °C. After, incubation of this solution 1 ml of ethanol was added drop by drop to the solution and constant stirring. After the addition of ethanol the solution are again incubated for 10 min at 37 °C, then solution are stored at room temperature for 2 hrs. Thereafter, dialysis is performing for 24 hrs under the constant stirring and to remove the unbound or unreacted DTT and NaDS using PBS dialysing agent. After dialysis, take 0.2-2 mg of curcumin mix in 1 ml of ethanol and they are added in alternately to HSA nanoparticle solution. This solution is equilibrated for 15 min and then performs the dialysis process for 12 hrs to remove the unbounded or unreacted curcumin. Finally curcumin loaded human serum albumin (HSA) nanoparticles are form. Schematic diagram of HSA loaded Curcumin nanoparticles by cross-linking method.

g. Freeze Dried Anti Solvent Crystallisation And High Pressure Homogenizer Method: Stabilizer loaded curcumin nanoparticles are prepared by anti-solvent crystallisation method. In this method, 1 gm of curcumin was added in 20 ml of acetone and to dissolve. Then this solution are added in the 200 ml of aqueous solution containing different weight concentration of stabilizer such as PVP, HPMC at a rate 5 ml per/min by using a burette. Then this solution was stirred for 600 rpm for 25 °C, the final concentration of curcumin and stabilizer suspension is formed in different ratio. Then the final suspension are instantly freeze dried at -70°C for 48 hrs, then to form stabilizer loaded curcumin nanoparticles by freeze dried anti-solvent crystallization method. In high pressure homogenizer, prepared suspension of curcumin and stabilizer in different ratio are homoginzed. In 1st step the pressure are adjusted at 500 bars, pass the suspension for 5 times in a homogenizer and final step pressure are adjusted for 1000 bars, pass the suspension for 10 times in a homogenizer. The final obtained suspension is instantly freeze dried at -70°C for 48 hrs, then. To form stabilizer loaded curcumin nanoparticles freeze dried anti solvent crystallisation method followed by high pressure homogenizer. Schematic diagram of Stabilizer loaded Curcumin nanoparticles by anti- solvent crystallisation method.

h. Co-Precipitation Method: Amorphous Calcium Phosphate (ACP) loaded curcumin nanoparticles are formed by co-precipitation method. In this method firstly, calcium nitrate are dissolved in 29 ml of deionized water to form 1 mm aqueous solution. Then ammonium hydrogen phosphate was added drop by drop in this and to form a white suspension. The raw materials are arranged in calcium and phosphate ration at 1.5 and pH maintained for 8 by the addition of 1 M Sodium hydroxide solution at 30°C, then formed nanoparticles are washed with deionized water and to remove any other ions and samples are centrifuged and freeze dried. After forming a ACP nanoparticles then, 5 mg/ml of curcumin are loaded in calcium nitrate solution then, mixture are stirring for 1 hrs under slowly addition of sodium hydrogen phosphate then mixture are stirring again for 15 min at 30°C, resulting suspension are centrifugated to form a ACP loaded curcumin nanoparticles. Schematic diagram of ACP loaded Curcumin nanoparticles by co-precipitation method.

i. Electro spraying Method: The nanoparticles are prepared by the Electro-spraying technique. In this technique, curcumin as the active ingredient, zein, chitoson, piperazine as the biopolymer used for preparing curcumin, piperazine as the biopolymer used for preparing curcumin, piperazine loaded zein, chitoson nanoparticles. In the preparation of nanoparticles, firstly to prepare zein unloaded micro particles then unloaded zein nanoparticle without addition of curcumin, chitosan, piperazine.

Preparation of zein unloaded micro and nanoparticles: Zein are dissolved in 70 % ethanol water v/v ratio and continuously stirring at room temperature up till dissolve completely.

Preparation of curcumin loaded zein nanoparticles: After the development of zein concencentraton, the different weight ratio of curcumin are added to zein solution (curcumin: zein) ratio ranges from 1:10, 1:20. Then curcumin are dissolved in 70 % ethanol and needed relation of zein to curcumin solution (1:10, 1:20, and 1:30). [5]

8. EVALUATION OF NANOPARTICLES

Particle size: The two most crucial factors in the characterisation of nanoparticles are the particle size distribution and shape. Electron microscopy is used to measure size and morphology. Nanoparticles are primarily used for medicine delivery and targeting. The release of drugs has been found to be influenced by particle size. Larger surface areas are offered by smaller particles. The majority of the drug that has been placed onto them will therefore be exposed to the particle surface, resulting in rapid drug release. Contrarily, medicines slowly spread across bigger particles.

Zeta-potential: The surface charge property of nanoparticles is frequently described using the zeta potential of a nanoparticle. It exhibits how electrically charged particles are and is affected by both the particle's makeup and the medium in which it is disseminated. It has been demonstrated that nanoparticles having a zetapotential higher than 30 mV are stable in suspension because the surface charge prevents the particles from aggregating.

Particle shape: Before being evaluated, the nano suspension is characterised by SEM and then lyophilized to produce solid particles. The solid particles have a platinum alloy coating, by means of a sputter coater.

Drug entrapment: efficiency Ultracentrifugation was used to remove the nanoparticles from the aqueous medium for 30 minutes at 50C at 10,000 rpm. A decanter was used to collect the resultant supernatant solution. In phosphate buffered saline pH7.4 dispersed to thoroughly eliminate the un-entrapped drug molecules. The technique was performed again. The

difference between the total amount of drug used to generate the nanoparticles and the amount of drug present in the aqueous medium was used to calculate the amount of drug entrapped in the nanoparticle. Drug entrapment efficiency is given by the following equation, Amount of drug released from the lysed nanoparticles.

Transmission electron microscopy: Transmission electron microscopy (TEM) operates on different principle than SEM. yet it often brings same type of data. The sample preparation for TEM is complex and time consuming because of its requirement to be ultrathin for the electron transmittance. The dispersion of nanoparticles is applied on films or grids of support. To enable and ensure that nanoparticles can withstand the instrument vacuum after treatment, they are either fixed by plastic embedding or a negative staining substance such phosphotungstic acid or its derivatives, uranyl acetate, etc. the sample can also be heated to liquid nitrogen temperatures after being embedded in vitreous ice. When a beam of electrons passes through an incredibly thin sample and interacts with it as it does so, the surface features of the sample are discovered. [7]

9. MARKETED FORMATIONS OF NANOPARTICLES

CURCUMIN NANO FORMULATIONS IN INFLAMATTORY DISEASES

Curcumin-Loaded Nanocarriers in Pulmonary Ailments:

It has been reported that CUR-loaded phospholipid vesicles can significantly improve CUR's anti-inflammatory properties, enhancing its overall therapeutic efficacy. In this light, new CUR-loaded phospholipid vesicle formulations and studies testing their potential in treating pulmonary disorders, such as asthma or chronic obstructive pulmonary diseases, have progressively increased. For instance, formulated and used glycerosomes, which are vesicles containing high amounts of glycerol employed for CUR lung delivery through aerosol therapy. In this study, glycerosome formulation was improved by adding sodium hyaluronate or trimethyl chitosan chloride to ameliorate vesicle stability and performances during aerosolization process. The improved polymer-glycerosomes could deliver CUR in the last stages of the next-generation impinger to a better extent than regular glycerosomes. Moreover, glycerosomes in general and polymer-glycerosomes in particular, significantly improved CUR effectiveness by (i) inhibiting proinflammatory cytokine production (IL-6 and IL-8) and protects oxidatively stressed A549 cells in vitro and (ii) increasing CUR deposition in the deeper respiratory tract *vivo*. Similarly, formulated chitosan- and hyaluronan-coated liposomes for CUR pulmonary delivery and addressed carriers' influence on its effectiveness against oxidative stress. CUR incorporation in liposomes or polymer-coated liposomes significantly promoted CUR lung deposition and improved its antioxidant power, a phenomenon likely due to vesicles' ability to interact with cells and release CUR in the cytoplasm. CUR-loaded liposomes were also tested as an antiasthmatic system, leading to a significant reduction of inflammatory markers, such as IL-6, IL-8, IL-1β, and TNF-α compared to positive control. In this regard, the lower CUR-tested dosage (1 μg/mL) reduced the inflammatory markers release to a better extent than higher doses, which is not surprising considering that natural compound-beneficial effects are now recognized to be influenced by several factors, including dose and redox environment. Other studies also demonstrated that CUR liposomal formulations effectively reduced the expression of proinflammatory markers (IL-6, IL-8, and TNF-α) in human synovial fibroblasts and mouse macrophages (RAW264.7) stressed with LPS. Cytokine storm, which refers to the increased secretion of cytokines such as IL-1β, IL-6, TNF-α, and IL-18, is a characteristic of COVID-19 patients with lung damage. In this regard, a clinical trial performed on COVID-19 patients indicated the ability of a nanomicellar form of CUR to significantly decrease the mRNA expression and cytokine secretion levels of IL-6 and IL-1β, which may ameliorate disease's clinical manifestation and promote overall recovery.

Curcumin-Loaded Nanocarriers in Skin Ailments

Curcumin has also been incorporated in phospholipid vesicles tailored for skin applications. Hyalurosomes, a new class of phospholipid vesicles immobilized with sodium hyaluronate, have been specifically formulated to treat skin wound-associated inflammatory and oxidative processes. Thanks to their peculiar structure and viscosity, hyalurosomes vesicles could incorporate a high CUR amount and retain it over 3 months of storage. CUR-loaded hyalurosomes significantly improved CUR antioxidant activity being able to effectively protect keratinocytes from oxidative stress and even promoting cell proliferation. Hyalurosomes also promoted CUR accumulation in different skin strata and wound healing *in vivo* in a mouse model of 12-O-tetradecanoylphorbol-13-acetate- (TPA-) induced lesions by inhibiting edema and MPO activity.

CUR-loaded phospholipid vesicles have also been used to reduce psoriasis-associated inflammatory and oxidative processes. In this regard, vesicles facilitated lipophilic payload penetration in different skin layers, ensuring its delivery the damaged site. Recently, formulated hyaluronic acid-enriched ethosomes as topical systems for the treatment of psoriasis. In this work, hyaluronic acid was added to vesicle surface in as it can interact with CD44 protein, which is overexpressed in inflammation- and oxidative stress-associated diseases and can be considered a potential targeting system capable of increasing both CUR skin retention and efficacy. As expected, the CUR cumulative amount detected in the skin following hyaluronic acid-modified ethosome application was very high. This result may be due to the ethosomal bilayer's high flexibility that may overcome the stratum corneum barrier and reach the deepest skin strata, especially in the dermis, where psoriatic skin lesion-associated inflammatory cytokines, such as IL-17 and -22, are mainly located. *In vitro* results were confirmed by confocal observation of CUR accumulation in the skin, which was more evident in the deeper skin strata when hyaluronic acid-associated liposomes were used. In particular, the CUR-associated fluorescence was preferentially located in the epidermis, where CD44 is highly expressed in psoriasis-like skin, thus promoting improved CUR accumulation at the site.

10. CONCLUSION

Raw turmeric rhizomes are processed to obtain turmeric powder with 6.47 ± 0.01% curcumin percentage. Curcumin is successfully extracted from turmeric powder using the soxhlet extraction method, and the extractability of curcumin is 5.16 ± 0.44%. The mechano-chemical fabrication method is used to synthesize nanocurcumin from the extracted curcumin. When curcumin and nanocurcumin are dispersed in water, curcumin is not soluble in water, while nanocurcumin is freely dispersed. However, there is no change between the chemical structures of curcumin and nanocurcumin. According to the results, the particle size of nanocurcumin increases with the flow rate and the curcumin concentration of the stock solution, while it decreases with the sonication time. TEM and SEM images provide evidence of spherical and smooth surface morphology and the size range between 100 and 200 nm. In contrast, the other analytical techniques such as UV−visible spectroscopy, FTIR, and XRD further confirm the characteristic features of nanocurcumin synthesis. The present study is the first evidence to synthesize nanocurcumin, using the natural turmeric rhizome as the raw material, bringing a new insight on natural substances such as turmeric.

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