Type of manuscript : Review article .

Novel Trends in Drug Delivery and Application of Curcumin in Dentistry

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Abstract

The frequent use and misuse of the currently used therapeutic agents have led to the evolution of resistant strains of common pathogens as well as increased incidence of adverse effects associated with their usage. Hence, the search for phytochemicals isolated from plants is considered as a good alternative source. The minimum number of plant species worldwide has been phytochemically investigated until date, there is a great potential for discovering novel bioactive compounds and drugs. The design and development of herbal nanoparticles have become frontier research in the nanoformulation arena. Curcumin, a hydrophobic polyphenol (diferuloylmethane) is a potent Phyto molecule obtained from turmeric (*Curcuma longa*, Family-Zingiberaceae) has a wide range of biological activities in chronic diseases and a large number of in-vitro and invivo studies in both humans and animals reported that curcumin has provoked properties like anti-inflammatory, antioxidant, antimicrobial, antiseptic, antimutagenic, hepatoprotective and immunostimulant. Due to these properties, it is quite useful in dentistry. It has a role in the treatment of periodontal diseases and oral cancers. But the clinical application of curcumin was limited due to its poor oral bioavailability, which may result from its poor water solubility, its poor pharmacokinetic profile, rapid metabolism, and rapid elimination which ultimately results in poor bioavailability upon oral administration. Therefore the introduction of novel drug delivery technologies gained the importance to achieve modified delivery of herbal drugs by increasing the therapeutic value and provides a solution towards increased bioavailability of curcumin. However, there is a scarcity of research and information in this field and much work is needed to further investigate the pharmacokinetics, enhance the delivery at the target tissue, the bioavailability, and the medicinal value of curcumin. In this review, various nanoparticles, micellar formulations, cyclodextrin inclusion compounds, and liposomes have been reported in order to improve the bioavailability, solubility, and efficacy of curcumin.

Keywords:*bioavailability, Curcumin, drug delivery system, nanoparticles.*

Introduction

Medicinal plants are used as a traditional treatment agent for numerous human diseases. Plants are the main source of different types of phytochemicals with numerous biomedical applications and can be used for the management of many diseases like diabetes, cancer, hepatotoxicity and microbial infection [1,2,3,4,5, 6,7]. Nanotechnology is a rapidly growing field and plays an important role in most of the advanced sciences, medicines, and technology areas. It led to the development of novel strategies to manipulate minute particles resulting in the production of nanoparticles .Nanoparticles prepared from plant materials such as selenium,zinc oxide ,silver are extensively explored for their therapeutic potential in many diseases [8,9,10,11,12,13,14,15]. Curcumin is a yellow-colored phenolic compound extracted from the spice herb Curcuma longa. It has attracted particular

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attention in dentistry due to its broad spectrum of biological and pharmacological activities, such as anti-inflammatory, anti-oxidant, anti-microbial,anti-tumor, anti-coagulant, anti-virus properties. Curcumin is a safe, non-toxic, and effective alternative for many new drugs[16]. Commercially available curcumin contains a mixture of 75 % curcumin,15%demethoxycurcumin, 5 %bisdemethoxycurcumin, and volatile oils. Nevertheless, the majority of the orally administered curcumin is detected in urine and feces, traces are detected in blood plasma[17]. Although 10 or 12 g/mL of orally administered curcumin in humans leads to serum curcumin level of 50 ng/ mL, it is lower than a value to achieve curcumin therapeutic effects such as controlling inflammation, cell growth, apoptosis, etc [18]. The low bioavailability of curcumin is due to its low water solubility, instability in low pH values results in difficult absorption, and limited clinical use . At the same time, after oral curcumin dosing, it is rapidly metabolized in the intestine [19].In order to overcome these limitations of curcumin by novel drug delivery systems and to improve the Curcumin bioavailability.

NOVEL DRUG DELIVERY SYSTEM OF CURCUMIN:

Solubility enhancement by manipulation of crystalline forms:

Manipulations of the crystalline state are one of the classical methods to increase solubility or the dissolution rate of insoluble curcumin [20].

Amorphous form of curcumin :

Amorphous forms non-crystalline materials and their structure similar to that of a frozen liquid. They are thermodynamically unstable and most energetic forms, which may result in higher solubility or a higher dissolution rate . Oral absorption of amorphous curcumin was studied in rats. The study reported that the absorption of the amorphous material was rather rapid, the oral bioavailability (AUC) was significantly improved.

Solid dispersions:

Solid dispersion technology transforms crystalline materials into amorphous materials. Here, an active substance (crystalline)embedded in a carrier is transformed into an amorphous form in the dispersion. This method is used to improve the dissolution and bioavailability of Curcumin[21]. A few curcumin solid dispersions were recently studied in rats. These results suggest that manipulation of the curcumin crystal itself has limited potential for absorption enhancement, while amorphous curcumin in solid dispersions led to significant increases in bioavailability [22].

Complex formation:

Cyclodextrins (CDs) are cyclic oligosaccharides that can sequester insoluble compounds within their hydrophobic cavity, resulting in improved solubility and enhanced chemical or enzymatic stability. A hydroxypropyl-β-CD inclusion compound with curcumin showed enhanced oral absorption in a rat study[23].In a rat study, cyclodextrin led to 10-20-times greater amount of total curcumin in the plasma than pure curcumin powder after oral administration**.** Bioavailability was about 0.2%, which is four times that of standard curcumin.

Phosphatidylcholine complexes :

A molecular complex of curcumin with phosphatidylcholine can be formed by refluxing in organic solvents. These carriers can increase permeability by interacting with membrane components[24]. Meriva is a product composed of complexes of curcuminoids (curcumin I, II, and III) with lecithin (mainly phosphatidylcholine). Plasma concentrations of the three components were assayed after oral administration to healthy volunteers. Of note, complex formulation increased the absorption of curcumin II much more than that of curcumin I [25]. Thus, the major plasma curcuminoid after administration of the complex was not curcumin I but curcumin II .

Nanoparticles:

Nanoparticles can provide greater penetration of membrane barriers because of their small size. Besides their size, their potential for targeting specific organs through modification makes them excellent drug carriers . The other advantages of this technology include its simplicity, ease of scale-up, and narrow particle size distribution.

Nanocrystal solid dispersion of curcumin:

It was prepared using the NanoMill-01 wet-

milling system, in which polystyrene beads micronized curcumin crystals [26]. The resulting nanosuspension was composed of curcumin, hydroxypropyl cellulose SL, sodium dodecyl sulfate (SDS), and water .

Polymeric nanoparticles:

Due to the small size and excellent biocompatibility, polymeric nanoparticles can circulate in the bloodstream for a longer time. The widely researched synthetic polymers include chitosan poly(D, L-lactide co-glycolide) (PLGA)and PEG for the curcumin nanoparticle formation [27]. These polymers can be combined to form copolymers, which could be a promising drug carrier for the site targeting and sustained action.

Solid lipid nanoparticles:

SLNs are made up of natural or synthetic lipids or lipids, such as lecithin and triglycerides, which are solid at human physiological temperature [28]. It has unique properties such as smaller size, larger surface area, the interaction of phases at the interfaces, and these are attractive for their ability to improve the performance of pharmaceuticals and other materials. Kakkar et al,2011 prepared curcumin-loaded solid lipid nanoparticles (C-SLNs) for the improvement of its oral bioavailability[29].

Liquid formulations:

Liposomes are closed spherical vesicles consisting of the lipid bilayer that encapsulate an aqueous phase in which drugs can be entrapped [30]. With the advantages of high biocompatibility, easy preparation, and chemical versatility used to improve the therapeutic activity and safety of drugs for many years [31]. So, liposomes have found wide application in enhancing curcumin's bioavailability and efficacy. All curcumin-containing formulations were effective in inhibiting cell proliferation in vitro cell culture.

Self-emulsifying drug delivery system:

It is used to solve the low bioavailability problems of poorly soluble drugs. When such a liquid system is released in the lumen of the GI tract, it disperses to form a fine (micron/nano) emulsion with the aid of GI fluid. This leads to the in situ solubilization of the drug that can subsequently be absorbed [32]. The self-micro emulsifying delivery system can significantly increase curcumin dissolution in vitro and bioavailability in vivo studies

Micelles:

The self-association of amphiphile into small aggregates (diameter less than 100 nm) is called micelles. In aqueous solution, the aggregates have a hydrophobic core surrounded by a hydrophilic layer. The hydrophobic drugs are then dissolved in the core, thus forming an aqueous solution of the drugs usually for parenteral dosage[33]. Wu et al,2011 designed a class of water-dispersible hybrid nanogels for intracellular delivery of hydrophobic curcumin[34].

DENTAL APPLICATIONS OF TURMERIC :

Periodontal problems:

Topical application: It provides relief from periodontitis and gingivitis. It is recommended to rub the gums and teeth with this paste twice daily.

Mouthwash: The chlorhexidine gluconate as well as turmeric mouthwash can be effectively used as an adjunct to mechanical plaque control methods in the prevention of gingivitis and plaque[35].

Subgingival irrigant :

A 1% curcumin solution can cause a better resolution of inflammatory signs than chlorhexidine and saline irrigation as a subgingival irrigant [36].

Pit and fissure sealant:

Pit and fissure sealant reduces the incidence of dental caries on the tooth surfaces. Acrylic monomer and one colorant selected from the group consisting of annatto extract, turmeric extract, and β-Apo-8'-Carotenal help to produce the pit and fissure sealant. [37],[38].

Anticancer properties:

Curcumin has an anti-cancer property due to its effect on biological activities of carcinogenesis including oncogene expression, cell cycle regulation, apoptosis, tumorigenesis, and metastasis [39]. It can be used in the treatment of oral cancer. It potentiates the effect of chemotherapy and enhances the effect of radiotherapy.

Precancerous lesions :

Its role in the treatment of various precancerous conditions like oral submucous fibrosis, leukoplakia, and lichen planus has also been studied . The local symptoms of burning sensation and pain were reduced and partial reversal of opening of the mouth was also observed [40].

Conclusion

Low oral bioavailability is one of the major reasons for curcumin unsuccessful in achieving therapeutic outcomes in spite of its pharmacological properties. In order to increase its absorption through the intestinal membrane, a higher concentration at the membrane surface is most important. Curcumin delivery systems with increased solubility and stability, or accessibility, in or to the GI tract, were introduced. In addition to the advances in delivery technology, simple and reproductive analytical methods should be developed. In the near future, with advances in science and technology, the therapeutic or preventive benefits of curcumin are expected to surface.

Acknowledgment: The Authors like to thank the editors and authors of the journal, which was the source for the scientific compilation of this review article.

Conflict of Interest: Nil

Source of Funding: Self

Ethical Clearance: Not Required

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