Improving the bioavailability of curcumin: is micro/nanoencapsulation the key?

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“CUR is a promising molecule with a wide range of pharmacological effects, such as antimicrobial, anti-inflammatory, anticancer and wound healing, as well as effects in chronic diseases, such as Alzheimer’s disease and diabetes. However, its physicochemical properties are not favorable to the development of new pharmaceutical forms”

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During the last decades, substances from secondary metabolism of a number of plants and their derivatives have been investigated due to their important biological activities and advantages in pharmacological therapy. Among them, polyphenols compose a group of substances showing a variety of simple and complex chemical structures and can display multiple phenolic functional groups [1]. Curcumin (CUR), a yellow phytopolyphenol present in the rhizomes of turmeric (*Curcuma longa* Linn), has displayed multiple biological properties. This plant belongs to the ginger family (Zingiberaceae) being found in subtropical and tropical regions of India, China and Latin America. The dietary spice turmeric is extensively utilized in curries and mustards exhibiting 2–5% of curcuminoids: demethoxycurcumin, bisdemethoxycurcumin and cyclocurcumin [2–5].

Turmeric has been considered an important therapeutic agent in Chinese and Indian traditional medicine for supporting the blood, liver, joints, immune system and digestive tract [2,6]. CUR was isolated from turmeric, identified and purified almost two centuries ago by Vogel and Pelletier. In 1910, Milobedzka and Lampe identified its chemical structure. The biological properties of CUR were determined in the mid-twentieth century [5,7].

CUR is safe even at high doses (12 g per day) in humans, but displays low aqueous solubility (3.12 mg/l at 25°C) [8], poor absorption, apparent rapid metabolism and rapid systemic elimination, resulting in problems of bioavailability [9]. Many approaches have been investigated to improve the CUR bioavailability, such as the use of adjuvant that interferes with glucuronidation, the use of structural analogs of CUR and also the use of technological strategies. Among them, the micro/nanoencapsulation has emerged as one of the most investigated strategies.

Pharmacological properties

CUR is considered as a pleiotropic molecule and multiple biological effects have been reported, such as the antimicrobial, anti-inflammatory, antioxidant, anticancer and some effects against diabetes [6,10]. Its antioxidant activity is due to the phenolic functional group with hydrogen that possesses donating ability [10]. Moreover, some articles have reported the action of CUR in Alzheimer’s disease by inhibiting and reduction A β oligomers and lowering cell cytotoxicity, suppression of inflammation and oxidative damage, as well as, improving cognitive deficits [11].

CUR also exerts potential activity in metabolic diseases such as diabetes by increasing of insulin sensitivity as well as hypoglycemic and hypocholesterolemic effects. These effects are consequences of suppression of blood pressure and blood glucose, maintenance of pancreatic β -cell volume and normalization of cholesterol, phospholipids levels and triglyceride [3].

The cardioprotective effect of CUR has been evaluated by inhibition of the generation of free-radical and enhanced activities of detoxifying enzymes (glutathione-S transferase) *in vivo* [12]. The electrocardiographic and

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histopathological data from an animal model of cyclophosphamide-induced cardiotoxicity have been improved after 10 days of CUR administration in combination with piperine [12].

Extensive evidences have demonstrated CUR as a therapeutic and chemopreventive drug in cancer. A wide range of cancer cells, including liver, pancreatic, cervical, stomach, colon and breast cancer had their generation, transformation, proliferation and metastasis attenuated or suppressed by CUR [1]. The molecular mechanism of CUR in cancer seems to be related to the suppression of induction of early growth response-1 gene product (EGR-1), protein tyrosine kinase cascades and MAPK pathway [1]. CUR antiproliferative potential has been associated with traditional anticancer drugs such as paclitaxel and cyclophosphamide [13]. CUR could sensitive cells towards apoptosis and its modulatory role in expression of protein kinase C (PKC), nuclear factor- κ B (NF- κ B) and histone deacetylase (HDAC) in breast cancer has been investigated [13].

CUR antimicrobial properties have also been investigated, and the mechanism is related to the interaction between methoxy and hydroxyl groups from CUR and the prokaryotic cytoskeletal protein (FtsZ), a cell division initiating protein [14]. Furthermore, the yellowish appearance of CUR makes it a potential photosensitizer in photodynamic therapy of various diseases, such as infections and cancer [5,15].

Physicochemical properties

CUR is also known as diferuloylmethane or (1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione [5]. Its structure ($C_{21}H_{20}O_6$; MW 368.385 g/mol) is composed of two aromatic rings with hydroxyl and methoxyl groups in the *ortho* position, which are connected by seven carbons with two α,β -unsaturated carbonyl groups. It displays three possible forms, a β -diketonic and two isomers in an equilibrating *keto-enol* tautomeric form [16]. Between pH 3 and 7, the enol form is more stable and predominant, due to the planar conformation. However, the conformation is dependent of solvent properties, temperature and polarity [17].

CUR is highly lipophilic, displays log P 3.29, and has demonstrated photosensitivity, low solubility in aqueous solutions and under alkaline conditions (pH > 7), which makes them susceptible to degradation because of the formation of phenylate anion, increasing the production of CUR radicals [5,16].

Thus, the physicochemical properties of CUR are a challenge for the development of new drug-delivery systems. Since the high lipophilicity of CUR limits the bioavailability, the therapeutic efficacy and clinical applicability of CUR are hampered. Considering the Biopharmaceutical Classification System of drugs, CUR is classified as a class II drug, showing poor aqueous solubility but high permeability. A very low plasma concentration and no significant therapeutic activity are reported after the oral administration of CUR (8–12 g daily) [9]. Thus, there is a huge necessity for the development of carriers that can deliver CUR to the target site [1,6,10,16].

Micro/nanostructured systems containing CUR

The development of carriers in order to solubilize or encapsulate CUR has grown really fast during the last decade. These carriers can improve solubility, stability, as well as precise and selective delivery of CUR to the target site and, consequently, improve the pharmacokinetics [4,10]. In an attempt to solve the physicochemical CUR drawbacks, many carriers have been developed such as micro/nanoparticles or capsules, micro/nanoemulsions, nanovesicles, lyotropic liquid vesicles and foams, among others.

Micro/nanoparticulate systems containing CUR have demonstrated successful improvement in wound healing, antioxidant, anti-inflammatory, tissue regenerating, as well as, Alzheimer's disease [6,8,18]. These formulations have been prepared using synthetic and natural polymers such as derivatives of cellulose, acrylic acid, lactic acid, glycolic acid, chitosan, gums, resins and gelatin, as well as lipid components such as stearic acid [4]. Therefore, the development of micro/nanoparticulate systems could improve the stability to light degradation, for example. In addition, it could provide biodegradability and biocompatibility, as well as high encapsulation efficiency and adequate surface potential [4–6]. Considering that CUR has demonstrated a wide range of pharmacological effects, some authors have developed particulate systems for an extensive variety of applications such as bladder [4], brain [11] as well as skin [6].

The colloidal systems called micro/nanoemulsions are used to encapsulate, solubilize and deliver hydrophobic drugs. Nanoemulsions display the property of thermodynamic stability, and they are transparent, while the microemulsions do not exhibit this property, and they are not transparent. During the development of emulsion-based systems, some parameters should be meticulously controlled, such as emulsion droplet size, oil composition, volume fraction, incorporation of CUR in the apolar phase and type of interfacial materials. These characteristics display huge importance, since they interfere in the stability, release and bioaccessibility of the nano/microemulsions. Once

the emulsion-based systems exhibit small droplet size, the drug could cross the intestinal lumen as well as the cutaneous barrier [5,16].

The spherical vesicles, comprised by at least one phospholipid bilayer, called liposomes, have been widely employed as CUR-delivery systems. These vesicles are able to carry hydrophilic and hydrophobic drugs, since they are structured in a polar core surrounded by an apolar region. In addition, liposomes containing CUR have been reported to present low toxicity, biodegradability and biocompatibility [5,19].

Moreover, CUR has been incorporated in other drug-delivery systems, such as lyotropic liquid crystal systems, foams, micelles, hydrogels and nanofibers [19]. The lyotropic liquid crystal systems, classified as lamellar, cubic or hexagonal mesophases, can be administered in mucosal or topical delivery. The lipid-surfactant mesophases have the ability to absorb water from the physiologic liquids, thicken, and turn to gel phases in which the drugs could be released in a modified way [5]. The foams composed of porous silk fibroin scaffold have been loaded with CUR in order to provide quick healing of burns or wounds or to be employed as soft tissue replacements after postsurgical chemotherapy [19].

Conclusion

CUR is a promising molecule with a wide range of pharmacological effects, such as antimicrobial, anti-inflammatory, anticancer and wound healing, as well as effects in chronic diseases, such as Alzheimer's disease and diabetes. However, its physicochemical properties are not favorable to the development of new pharmaceutical forms due to the high hydrophobicity, light and pH instability that impair the absorption and bioavailability. Consequently, in the attempt to solve this problem, new strategies have been developed like micro/nanoencapsulated systems, vesicles and colloidal systems. Nevertheless, substantial gaps should be filled, since there is a lack of comparison between the performance of many formulations developed to deliver CUR in a specific aim, lack of toxicity and availability data of CUR in each drug-delivery system and lack of human and preclinical studies in order to evaluate the bioavailability. Therefore, only after these gaps are filled are we going to know if micro/nanoencapsulation is really the key for the improvement of the CUR bioavailability.

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