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Challenges of Curcumin Bioavailability: Novel Aerosol Remedies

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Nanoparticles are promising aids for drug delivery for previously challenging diseases, and many incurable ones. Curcumin (diferuloylmethane) is a pleiotropic molecule having various target molecules in the body. Despite its effects, curcumin-based drugs are not readily available in the market because of their low bioavailability. Although dietary intake and knowledge about the potential of curcumin are high in countries like India, studies indicate that the bioavailability problem still persists. However, administration of curcumin through inhalation has received little consideration. In this review we discuss the potential of curcumin, approaches made to overcome the bioavailability challenges, and novel approaches that could be applied in order to deliver curcumin in a pressurized metered dose inhaler (pMDI).

Keywords: Nanoparticles, Curcumin, Bioavailability, Drug delivery, pMDI.

The modern world is facing the threat of life threatening diseases like cancer and cardio-vascular diseases. Most of these are attributable to life style changes and negligence of ancient medicine where food is often used as medication. Curcumin ($C_{21}H_{20}O_6$), the active component of *Curcuma longa* Linn., is an important traditional medicine, and a delicacy of Asian countries. Curcuminoid, the commercial name of *C. longa* extract, contains 77% curcumin, 18% demethoxycurcumin and 5% bismethoxycurcumin. Most of its physical and chemical properties have been described [1]. Though curcumin is highly pleiotropic and has therapeutic potential, it has not been a highly pronounced candidate drug because of its poor oral bioavailability. Studies show that large amounts of curcumin are needed to produce measurable physiological changes in humans [2].

A number of technologies have been applied to improve curcumin bioavailability, like natural and synthetic analogs, and nanoparticles. However, these have not solved the problem and curcumin bioavailability and its *in vivo* mode of action remain an enigma [3]. Lungs provide enough surface to volume ratio for the absorption of high doses of drugs and make them available for systemic delivery [4]. Despite their large surface area, lungs have limited impediment to drug delivery. Another advantage is that the drug can be in any form, solid, liquid or aerosol, provided that it has the critical surface area that the lung can absorb [5]. Inhalers are non-invasive devices which can deliver drugs through the pulmonary route. They can principally target, but are not limited to, the lungs. The pulmonary route is a promising means for the delivery of drugs for both systemic and local treatment [6]. Unfortunately, not much research has been reported on the potential aerosol route for delivering curcumin. Curcumin can be encapsulated in hydrogels for controlled release of the drug through propellant driven metered dose inhalers (pMDI) [7]. The current review not only aims at exploring the difficulties related to conventional delivery systems, but also the possibilities of a novel aerosol delivering system for curcumin.

Potential of curcumin: Curcumin (diferulomethane), dubbed as Indian 'solid gold', is widely used in cuisines throughout Asia. Historically, knowledge about curcumin dates back two millennia. Ancient Hindu literature mentions its use in religious ceremonies and culinary preparations [8]. Curcumin research is ever increasing since its anti-microbial activity was reported in 1949 [9]. Curcumin possesses three important functional groups, a phenolic, diketo and o-methoxy. These are directly attributable for its biological activities, like free radical scavenging, Michael's acceptor, which induces phase II enzymes like hemeoxygenases [10-11]. The therapeutic potential of curcumin is immense. It acts as an anti-inflammatory agent against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases [12]. Cole and coworkers explained the neuroprotective effects of curcumin [13]. It has multi-targeting ability which is revealed by its interaction with inflammatory molecules, cell survival proteins, protein kinases, protein reductases, glyoxalase I, xanthine oxidase, proteasome, HIV1 integrase, HIV1 protease, sarco (endo) plasmic reticulum Ca^{2+} ATPase, FtsZprotofilaments, carrier proteins, and metal ions [14]. Curcumin also regulates histone deacetylases, histone acetyltransferases, DNA methyltransferase I, and miRNAs, which are involved in the epigenetic control of the genome [15]. The transcription of a number of proinflammatory molecules {for example, interleukins (IL 1, 2, 6), TNF-α, monocyte chemotactic protein 1} are under the direct control of nuclear factor kappa B (NF-κB). Aberrant activation of these molecules manifests many clinical conditions, including cancer and cachexia. Inhibition of NF-κB provides novel insights into anti-inflammatory therapy for these diseases [14]. Curcumin inhibits NF-κB mediated activation of the inducible nitric oxide synthase (iNOS) pathway. In normal cells, NF-κB will be bound to inhibitory kappa-B alpha (IκB-α) and cannot bind to DNA. In some cancers and activated immune cells, IκB-α is phosphorylated and degraded, activating NF-κB. Curcumin inhibits the phosphorylation of IκB-α, thus stopping iNOS synthesis. This confers protection against certain cancers and inflammation [16]. Curcumin, as evident from dietary intake, is highly biocompatible. The LD_{50} value of curcumin shows that it is non-toxic, even above 2 g/kg body weight of mouse and rat [17]. One clinical study of patients with high-risk or pre-malignant lesions, demonstrated that curcumin is not toxic to humans up to 8 g/day when taken orally for 3 months [18]. Due to the hydrophobicity of curcumin, water soluble analogs were the 'need of the hour' during the past decade, and there are now more than 100 papers describing curcumin analogs. Nanobiotechnology presents new vistas for efficient drug targeting and delivery. Even a pleiotropic drug like curcumin can be efficiently targeted and delivered. When conjugated with or encapsulated in nanoparticles,

curcumin retains its properties and can act as a potential drug against various cancers [19]. Curcumin is proven as a promising candidate drug for treating various diseases, including external cancerous lesions and pancreatic cancer, although the results have been obtained from a limited subset of patients undergoing clinical trials. A list of human clinical trials has been tabulated [20]. Curcumin analogs, curcumin containing liposomes, micelles, phospholipid complexes, prodrugs, and PEGlyation have been prepared and characterized [10].

Oral delivery of curcumin: the challenges: Despite grams of curcumin being taken through food, its bioavailability is very low. In one dose escalation study, curcumin administered at 8 g to healthy individuals was undetectable in serum and could be found only in small amounts when administered at 12 g [21]. Hydrophobicity of curcumin is one of the reasons for its poor bioavailability [9], the other being its rapid conversion into glucouronides and sulfates *in vivo* [22-24]. Glucouronides of curcumin certainly show some biological activity, like inhibiting the assembly of microtubule proteins under cell-free conditions [25]. Certain metabolites, like tetrahydrocurcumin (THC), show improved anti-oxidant activity, but poor inhibition of NF-κB and induction of phase II enzymes [10]. This, along with results obtained from various experiments on oral administration of curcumin for treating pulmonary fibrosis [26-28], cannot unambiguously explain curcumin bioavailability and its role in curing the disease [29]. The effective concentration of curcumin for treating various diseases has been reviewed [30]. These concentrations can never be reached *in vivo* if curcumin is administered orally. For example, the IC_{50} of curcumin against HIV type I integrase is 40 μMM^{-1} [14]. Curcumin cannot be detected in blood of healthy individuals, even if administered in doses of 10-12 g [31]. Sensitive procedures like LC-MS/MS cannot detect free curcumin in either plasma or cell culture medium when administered by the intra peritoneal cassette system, with a plasma half life for curcumin of 111 min and area under the curve of 0.4 μM*h [2]. Many phase II clinical studies reveal the same [32-34]. Hence, it can be concluded that oral curcumin cannot elicit biological reaction *in vivo* because of its poor bioavailability.

Approaches to overcome the challenges: The first effort for improving curcumin bioavailability was made by mixing turmeric powder with milk during ancient times [20]. Freeze dried rhizome powders mixed with milk at a concentration of 200 mg/kg, when administered to streptozotocin induced diabetic rats increased HDL levels (P<0.05) and decreased blood glucose considerably (P<0.001) [35]. Curcumin dissolved in corn oil or in combination with piperine, when administered to rats treated with benzo(a)pyrene (BaP), reduced BaP-induced oxidative insult and clastogenicity compared with curcumin alone [36]. This improvised bioavailability of curcumin is because of its solubility in milk and corn oil. Biopiperine® (containing 2 g curcumin and 5 mg piperine) was shown to improve bioavailability by two times. This improved method and various synthetic curcumin analogs are reviewed elsewhere [10]. Curcumin can be dissolved in hot water; solubility increases from 0.6 μg/mL to 7.4 μg/mL, without affecting its biological activity [37]. Hydrophilic curcumin metabolites, like THC, have been tried and showed improved bioavailability.

Curcumin can be effectively delivered by loading it into liposomes or nanoparticles, forming self-microemulsifying drug delivery systems (SMEDDS), cyclodextrin inclusions, and solid dispersions, as well as the latest reported technologies such as nadodisks and nanotubes. They all have their own advantages and disadvantages, for example, the rapid uptake of curcumin conjugated liposome by reticulo endothelial cells and its diminished half life in circulation, the inherent toxicity of surfactants used in preparing microemulsions, and toxicity associated with long time usage of synthetic polymer [38-39] synthesized curcumin nanogels, which are water dispersible and can be used for photothermal therapy. The nanogel is made up of a Ag/Au bimetallic complex conjugated with hydrophobic polystyrene, which is encapsulated in a hydrophilic, thermosensitive, polyethylene glycol analog. Ag/Au can absorb near infrared (NIR) light, which can be exploited for heating this thermosensitive outer layer and thus releasing the drug load. THERACURCUMIN (TC, made up of 10%, w/w, curcumin, 2% other curcuminoids, 46% glycerin, 4% gum ghatti, and 38% water) is a micron sized particle with mean diameter of 0.19 μm. When administered at a 30 mg dose level, TC increased the AUC_{0-6h} of curcumin 27.3 fold compared with free curcumin [40]. NanoCurc™, a polymer of *N*-isopropylacrylamide, vinylpyrollidone and poly(ethyleneglycol)monoacrylic acid containing curcumin, was found to block tumor growth and metastases of pancreatic cancer in the mouse model [41]. A modified cyclodextrin, hydroxypropyl-β-cyclodextrin, increased the solubility of curcumin and its analogs and showed increased anti-angiogenic properties in colitis rat models, which can be used effectively against cancer and inflammatory diseases [42].

Poly-lactic-co-glycolic acid (PLGA) encapsulated curcumin showed reduction of cystic fibrosis symptoms in mouse through a nasal potential difference study [43]. Though free curcumin was not detected in blood, it is the widely used procedure for PLGA-curcumin preparations. PLGA encapsulated curcumin increases the oral bioavailability in some rat models [44-45]. Chitosan encapsulation provided superior bioavailability compared with free curcumin in *Plasmodium yoelii* infected mice [46]. Eudragit® S-100 is an anionic copolymer based on methacrylic acid and methyl methacrylate, which dissolves above pH 7, hence releasing drugs into the gastro intestinal tract. It is routinely used to coat the drug delivery system for colon targeting. Zhang and his group [47] successfully synthesized Eudragit® S-100 coated calcium pectinate microspheres of curcumin, from which the *in vitro* release of curcumin in the presence of rat cecal extracts was superior to that of unconjugated curcumin. Curcumin encapsulated in cell derived exosome improved its solubility and inhibited septic shock induced by bacterial LPS [48]. When loaded onto apotransferrin (a protein that is effectively endocytosed by receptors expressed in HIV infected cells), curcumin effectively inhibited HIV I *in vitro*. The apotransferrin-curcumin complex, named nanocurcumin [49], nanoparticles mediated delivery systems are costly and may produce side effects when administered to humans, since most nanoparticles described so far have been validated only *in vitro*, in cell lines and pre-clinical models. Also, intra-venal, oral administration of drugs at appropriate concentration is difficult because each individual metabolizes drugs differentially. Hence an efficient, cheaper and easier means, like aerosol delivery, is needed.

Aerosol mediated delivery of curcumin: Aerosol drug delivery is cheaper, effective and has fewer side effects when compared with systemic delivery. This method has been widely used from time immemorial, for example, asthma cigarettes made of *Datura stramonium* [50]. Fifty years of research has yielded delivery systems like pMDI, DPI and nebulizers. Hess [51] reviewed inhalers and nebulizers that were used for treatment of asthma, while the different formulations like spray drying and double emulsion that can be successfully used in these devices are reviewed elsewhere [6]. Additionally, aerosols can be functionalized, for example wheat germ agglutinin functionalized PLGA nanoparticles containing anti-tuberculosis drugs like rifampicin, isoniazid and pyrazinamide are effectively targeted to the lung [52]. We are in the age of intelligent nebulizers (iNeb) with

adaptive aerosol delivery (AAD) systems which can deliver drugs according to the tidal volume and breathing pattern of individuals so that no drug is wasted [53]. iNeb can be used successfully to deliver drugs, even protein like interferon γ [54]. Akita APIXNEB, another AAD device, is used for the delivery of α-antitrypsin (AAT) to AAT deficient patients with increased peripheral delivery of the protein without much loss by exhalation [55]. Lungs are provided with immune system cells called alveolar macrophages which uptake and digest aerosols bigger than 50 μm in diameter. Information about lung geometry and breathing patterns that depends upon age and body weight is well established in developing animals [56]. These advances imply that aerosol therapy can be administered to patients ranging from new born to the old-aged and makes aerosol delivery superior to oral and intra-venal delivery. Despite these advances, only two papers deal with aerosol mediated delivery of curcumin. Both used swellable chitosan microparticle encapsulated curcumin for delivery through pMDIs. These microparticles, when deposited on the lung surface, swell and release about 35% of the encapsulated curcumin in 24 hours [7]. A similar preparation has been shown with good *in vitro* bioactivity [57]. Hence, further research in the field of aerosol mediated curcumin delivery could find an effective solution for the decade old problem of curcumin bioavailability.

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