REVIEW ARTICLE e-ISSN: 2349-0659 p-ISSN; 2350-0964

A Review on Curcumin and its Use as Novel Drug Delivery System

Shweta Vashist[1]*, Sujata Sharma[1], Jyoti Kumari[2], Manoj Gadewar[1], Sahil Arora[3]

Abstract

Curcumin is a principle compound obtained from turmeric, that is, *Curcuma longa* which is Indian rhizomatous medicinal plant from the family Zingiberaceae. Curcumin is yellow pigment commonly used as a spice in food processing industry. Curcumin, Demethoxycurcumin, and Bisdemethoxycurcumin are the major active constituents of the turmeric and are collectively known as curcuminoids. In recent studies, it has been demonstrated that curcumin has a variety of biological activities, pharmacological performances, provide protection, and promotion of health. This paper reviews the current research progress on its versatile bioactivity, such as antioxidant, anti-inflammatory, and immune-regulatory activities, cancers, diabetes, liver, and cardiovascular systems. The curcumin belongs to biopharmaceutical classification system Class IV that indicates low solubility and low permeability. The systemic bioavailability of orally administered curcumin is low in humans and only traces of it have been found in the liver. Here, we emphasized its broad therapeutic activity in treating life-threatening diseases by improving solubility as well as permeability with the help of novel drug delivery system.

Keywords: Anticancer, Antioxidant, Bioavailability, Curcumin, Curcuminoids, Health benefits

Asian Pac. J. Health Sci., (2022); DOI: 10.21276/apjhs.2022.9.3.30

Introduction

In recent time, there is no single drug delivery system, which fulfill all the criteria but with the advancement of technologies the attempts have been made to achieve all the priorities with in a single approach for that we are focusing on sustained and controlled release formulation along the natural origin of drug for safe and effective management of many life-threatening diseases. In the novel time researchers want to introduce the dosages form that does not bring any kind of side effects and have the maximum possibility of curing the disease completely. On behalf of these researchers, we focus on the curcumin which is safe as well as natural origin. Hence, in this paper, we try to introduce curcumin proniosomes that has its great importance in today's world.[1] The curcumin which is natural origin obtained from turmeric its iupac name is Curcumin, 1, 7-bis (4-hydroxy- 3-methoxyphenyl) -1, 6- heptadiene-3, 5-dione), having small molecular weight, hydrophobic polyphenolic compound, isolated from the rhizomes of *Curcuma longa*, family Zingiberaceae.[2] Curcumin has many beneficial effect and having long list of its application in every field such as as food additive, cosmetic, and as a traditional herbal medicine, curcumin a drug effective in various respiratory conditions (asthma, bronchial hyperactivity, and allergy) other disorders including anorexia, coryza, cough, hepatic diseases, cancer, Alzheimer, Parkinson's, and sinusitis.[3] In biopharmaceutical classification system (BCS) curcumin belongs Class IV means poor solubility and poor permeability but because of its abundant list of merits we try to formulate curcumin proniosomes.[4] In many of studies, it is reported that high dose of curcumin up to 12 g/day is safe. On oral administration no amount of curcumin was observed while high amount was observed in feces because of high rate of metabolic excretion.[5] Proniosomes are dry formulation of water soluble particles which are coated with surfactant and the drug molecules are encapsulated within the vesicular structure of proniosomes, that prolong the existence of drug in the systematic circulation and enhances the penetration into tissue and reduce toxicity. The proniosomes are prepared by the modification in niosomes which literally help to formulate novel drug delivery system.[6] They are rehydrated immediately before use on agitation in hot aqueous media to produce the immediate results within minutes. Proniosomes are physically stable during the storage and transport.[7]

[1]School of Medical and Allied Sciences, K.R. Mangalam University, Sohna, Haryana, India.

[2]School of Medical and Allied Sciences, IIMT University, Meerut, Uttar Pradesh, India.

[3]Department of Pharmaceutical Science, Chandigarh University, Chandigarh, India.

Corresponding Author: Shweta Vashist, School of Medical and Allied Sciences, K.R. Mangalam University, Sohna Road, Gurugram 122103, Haryana, India. E-mail: shwetavashist55@gmail.com

How to cite this article: Vashist S, Sharma S, Kumari J, Gadewar M, Arora S. A Review on Curcumin and its Use as Novel Drug Delivery System. Asian Pac. J. Health Sci., 2022;9(3):148-153.

Source of support: Nil

Conflicts of interest: None.

Received: 09/12/2021 **Revised:** 12/01/2022 **Accepted:** 16/02/2022

Description of Curcumin

Curcumin, 1,7-bis (4-hydroxy- 3-methoxyphenyl) -1,6- heptadiene 3,5-dione), is having a small molecular weight, natural hydrophobic polyphenolic compound, isolated from the rhizomes of *C. longa*, family Zingiberaceae. The structural formula of curcumin was first described in 1910 by LaWmpe and Milobedesk. It shows its solubility in Ethanol, Ketone, Acetic acid, Chloroform, Dimethylsulfoxide, acetone while insoluble in water and ether.[8] The Source of curcumin which in Figures 1and 2.[9]

Various Curcuminoids are found in Curcumin

The curcuminoids founds are about 5% bisdemethoxycurcumin, 15% demethoxycurcumin, and 80% Curcumin.[10] On chemical

analyses have shown that turmeric contains carbohydrates (69.4%), moisture (13.1%), protein (6.3%), fat (5.1%), and minerals (3.5%). The essential oil (5.8%) obtained by steam distillation of the rhizomes contains a-phellandrene (1%), sabinene (0.6%), cineol (1%), borneol (0.5%), zingiberene (25%), and sesquiterpines (53%), curcumin (3-6%) is responsible for the yellow color.[11] The Figure 3 shows major curcuminoid found in turmeric.[12]

Uses of Curcumin

1. Curcumin having rich amount of potassium which keeps you healthy
2. Curcumin having collagen protein which maintain skin elasticity and keep joints healthy
3. Curcumin is used as a dietary supplement
4. Curcumin is used in cosmetic formulation
5. Curcumin is used in Ayurveda formulation
6. Curcumin is used in many life-threatening diseases.[13]

Routes of Administration of Curcumin

Curcumin is a natural compound that has a list of therapeutic activity that is why it is used in current scenario. Due to its less side effects, it is used in novel drug delivery systems which can be administered by many ways: Topical, oral, and inhalational depending on the use.[14]

Pharmacokinetics

In many of the Pharmacokinetic studies in animals its demonstrated that 40–85% of oral dose of curcumin passes through the gastrointestinal (GI) tract remains unchanged and undergoes rapid metabolic reduction that resulting in poor bioavailability. Example: On oral dose administration of 0.1 g/kg into rat yields 2.25 μg/ml of free curcumin in plasma,[15] while on 40 mg/kg i.v dose in rat completely disappear from plasma.[16]

Bioavailability of Curcumin

In many of research papers, we studied that curcumin belong to BCS Class IV category and it observed that systemic bioavailability of orally administered curcumin is low in humans. In many of researches on human and animals the clear result indicates on oral administration of curcumin the trace elements of it and its metabolites were observed in systemic circulation as well as in liver,[17] Piperine has been reported to increase the bioavailability of curcumin.[18] The further researches in mice with novel drug delivery systems, the nano-particulate curcumin results show more bioavailability and had a longer half-life than native curcumin.[19] THERACURMIN, a nano-particulate curcumin, in their result also shows improved bioavailability in humans. They also compared various published reports that clearly emphasized on the plasma curcumin levels in human subjects after oral intake of gets increases.[20]

BCS

The BCS is used for determining the exact value of drug solubility and its permeability through the membrane. Before the development and designing of new formulation researchers follow this system to obtain the future goals. This system is broadly divided into four major classes on the basis of high/low solubility and permeability of the drug but now this system is guided by USFDA and WHO.[21] The Biopharmaceutical classification system in Figure 4.[22]

Solubility

According to the guidance of USFDA and WHO a drug is considering to be highly soluble when the highest dose (if the API appears on the WHO Model List of Essential Medicines) or highest dose strength of any market formulation as an oral solid dosage form (if the API does not appear on the WHO Model List of Essential Medicines) which is soluble in 250 ml or less then in aqueous media over the pH range of 1.2–6.8.[23]

Permeability

The extent of absorption of a drug substance in humans is directly the measurements of the rate of mass transfer across the intestinal membrane. A drug substance is considering highly permeable when the extent of absorption is observed/determined to be 90% or more. All this is guided in the BCS.[24]

Types of BCS

This BCS is classified into four major categories on the basis of solubility and permeability of drug from the intestinal membrane, as shown below.

- Class I: High Solubility - High Permeability
- Class II: Low Solubility - High Permeability
- Class III: High Solubility - Low Permeability
- Class IV: Low Solubility - Low Permeability.

Therapeutic Properties of Curcumin

Anti-inflammatory Activity

Curcumin has listed of beneficial activity one of it is anti-inflammatory activity.it has natural origin with potent benefits. It acts in managing the anti-inflammatory activity by suppressing the activation of transcription factor NF-kB, because the factor produces inflammatory gene. Curcumin also act by controlling the regulation of cyclooxygenase-2 enzyme.[25]

Anti-obesity Activity

Curcumin was significantly recorded as a main aspect in treating the obese patients. Several clinical trials have been resulted on curcumin obesity effects. In a most recent study, it is reported that on oral administration of curcumin 1.6 g/day with 8 mg piperine significant reduction in body mass index, body fat, and body weight. These studies were also in nonalcoholic fatty liver disease patients and show nearly the same result.[26]

Anti-Alzheimer Activity

Many investigations have been done to identify the effect of curcumin on Alzheimer's disease patients. The main cause of Alzheimer's disease is increased in Aβ40 levels in serum or Aβ-deposits as a plaque in the brain. Now in recent studies curcumin shows remarkable results on Alzheimer's disease patients with curcumin (100 mg/day) stated significant improvements in Neuropsychiatric Inventory after 12 weeks'

Figure 1: Source of curcumin

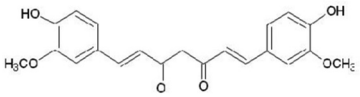

Figure 2: Structure of curcumin

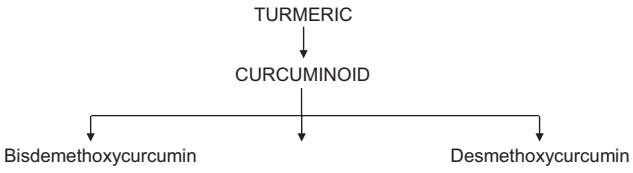

Figure 3: Three major curcuminoid in turmeric

	High solubility	Low permeability
High permeability	Class 1 High solubility High permeability	Class 2 Low solubility High permeability
Low permeability	Class 3 High solubility Low permeability	Class 4 Low solubility Low permeability

Figure 4: Biopharmaceutical classification system

treatment. Recent findings, on novel curcumin formulations (Longvida® and Theracurmin) in low doses (80–180 mg/day), were ensure a higher bioavailability, improved memory good acute, and chronic activities immediately after a single dose, while after 4-week administration enhanced memory, mood, and alertness.[27]

Anticancer Property of Curcumin

Curcumin is considering to be a very potent anticancer agent. Cancer is a result of successive alterations resulting in apoptosis, uncontrolled cell proliferation of cells. Curcumin can suppress the cancer of the skin, oral cavity, mammary gland, intestine, colon, etc. In many of studies, it is highlighted that cancer is cured by inhibit cell proliferation, inhibits cytochrome P450 isoenzymes, inhibits cell-cycle-related proteins like (PCNA, cyclin E, p34cdc2) and last but not least by Induction of gluthathione S-transferase activity.[28] The Curcumin response against apoptosis is represented in Figure 5.

Anti-oxidant Activity

Curcumin has been shown to improve systemic markers against oxidative stress it can modulate the activity of those agents which is responsible for the oxidative stress are glutathione, catalase, and superoxide dismutase enzymes and free radicals. Curcumin protect biomembranes against peroxidative damage, it means free radical mediated chain reaction which is reason of cell damage. Curcumin attribute its activity by hunting the reactive free radicals. Curcumin having variety of functional groups including the B-diketo group, carbon–carbon double bonds, and phenyl rings containing varying concentration of hydroxyl and methoxy groups which make the curcumin high recommendable agent against oxidative stress.[29]

Anti-diabetic Activity

Curcumin is a naturally occurring compound and has received most attention in managing most of the diseases. On considering these parameters, its contribution is also seen in managing the diabetes. Diabetes is the consequence of hyperglycemia and changes in energy metabolism. Diabetes in association with depletion of cellular antioxidant defense mechanism systems and enhanced the production of reactive oxygen species.[30] Curcumin improves the function of the endogenous antioxidants which improves glucose-lowering activity and also stimulation of the pancreas to produce and secrete more insulin that will assist to manage the diabetes.[31]

Anti-pancreatitis activity

The curcumin is a prominent active substance which exhibits many activities and one of them its anti-inflammatory activity against pancreatitis. The mechanism through curcumin performs its activity by inhibiting the activation of factor NF-κB, as well as inhibiting mRNA, it is a key regulator of inflammation. The pancreatitis correlates with the inflammatory responses. The blockage of key signals of the inflammatory responses improves the condition of pancreatitis patient.[32]

Anti-rheumatoid Activity

Rheumatoid arthritis is a joint disorder that more commonly observed in old age persons. A randomized, controlled trial is performed; curcumin was recommended in patients with rheumatoid arthritis. Curcumin 1200 mg daily given to the patient and found effective in improving S joint swelling, morning stiffness, and other joint disorders.[33]

Curcumin against Bacterial Activity

Curcumin and the oil fraction both are having the property to suppress the growth of several bacteria such as *Streptococcus*, *Staphylococcus*, and *Lactobacillus*. The aqueous extract of turmeric rhizome has antibacterial effects. Curcumin also prevents the growth of *Helicobacter pylori* strains.[34] The Figure 6 represent schematic illustration of curcumin health benefits.[35]

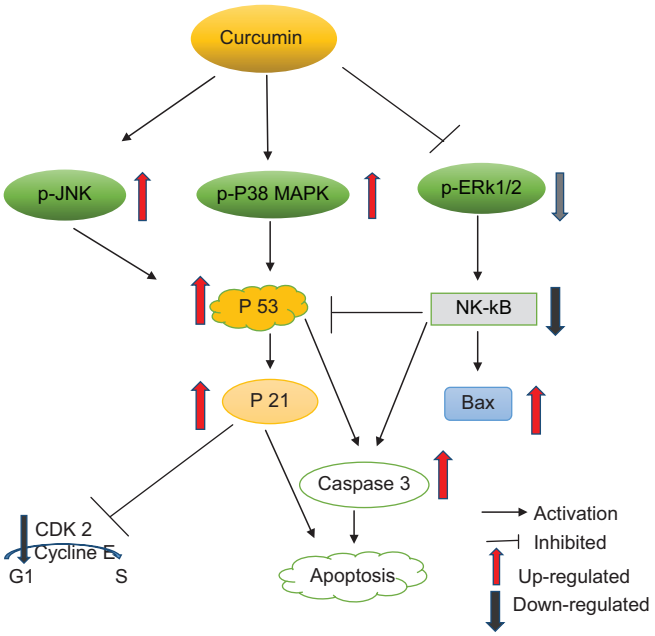

Figure 5: Representation of curcumin response against apoptosis

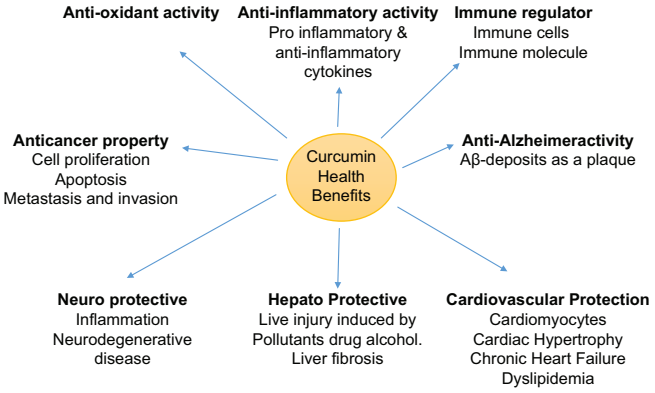

Figure 6: Representation of curcumin health benefits

Curcumin against Covid-19 Induced Inflammation

During COVID-19 people faces different of health issue some of them faces respiration issues, hyper inflammation, condition and many more. After their study it observes, it's all because of cytokine blast which consider the main reason behind this hyperactive condition. Now during this pandemic, we focus to manage this life-threatening infection with natural sources and this time we show our trust on curcumin because of its list of benefits with low side effects. Here, different dosages form of curcumin are formulated and used but nanocurcumin produce remarkable responses. Curcumin affect productivity of interleukin (IL)-6 and IL-1β cytokines also works on mRNA expression.[36] On further studies researchers observe that on modulation by curcumin, also reduces the level of IL-17, IL-21, IL-23, and granulocyte-macrophage colony-stimulating factor, that is, Th17 mediated factors.[37]

Advancement in Curcumin Formulation

Preparation of Nanosuspension

Curcumin belongs to Class IV category of drug in BCS that indicate low solubility and low permeability. The systemic bioavailability of orally administered curcumin is low in humans and only traces of it have been found in the liver. Here, we emphasized its broad therapeutic activity in treating life-threatening diseases by improving solubility as well as permeability with the help of novel drug delivery system. For this purpose, curcumin nanosuspension is prepared to achieve more prominent delivery and activity of curcumin. Curcumin nanosuspension was formulated by high-speed homogenization technique. First, the mixture of drug and solvent is prepared and then this mixture is added into the another mixture of surfactant and solvent 1:15 and homogenize at speed of 10,000 rpm for 10 min. Further, the mixture was magnetically stirred about 4–5 h to remove the organic solvent completely after that samples were immediately transferred to a vial and subjected to probe sonication at 90 W for 10 min and the temperature must be controlled using a water bath.[38,39]

Preparation of Curcumin Niosomes

Curcumin niosomes in an another advancement in curcumin formulation to improve the effectiveness of this poor solubility and poor permeability drug. Curcumin niosomes are prepared by thin-film hydration method they contain nonionic surfactant and cholesterol. The nonionic surfactant and cholesterol were mixed with 20 mL chloroform in a rotatory evaporator and immersed in a water bath at 60°C after that curcumin drug was added into it with solvent. Now evaporate the solvent and a thin film form which further dissolved in 20 mL of phosphate buffer, then placed in a water bath at 60°C and rotated at 120 rpm to hydrate the layers.[40,41]

Preparation of Curcumin-loaded Self-emulsifying Drug Delivery Systems

SEDDS are isotropic mixtures of oil, surfactant, co-surfactant, and drug that rapidly form fine oil-in-water (o/w) nanoemulsions when introduced into aqueous medium under mild agitation.[39] In the human body, the agitation required for formation of nanoemulsions is provided by digestive motility of the GI tract. The curcumin loaded SEDDS were prepared by dissolving curcumin in mixtures with variable ratio of oil, surfactant, and co-surfactant. Then mix then by gentle stirring until a clear solution was obtained. The weight ratio of surfactant to co-surfactant varied from a range of 3:1 to 7:1, whereas the percentage of the oil phase was confined, that is, a range of 5–25%.[42,43]

Preparation of Curcumin-loaded Liposomes

In the present study, liposomes were used as a drug delivery system to improve the stability, bioavailability and anticancer activity of lipophilic Cur. So far, a number of liposomal formulations of Cur have been reported by others groups. Curcumin loaded liposomes is a novel advancement in the medical science. Curcumin liposomes were formulated using the extrusion technique. In this method, lipids and curcumin were dissolved in chloroform to get stock solutions. Then curcumin was mixed with 40 mg of lipid and

chloroform was removed from the samples through evaporation process, so a thin lipid film obtained. That film further dissolved in a mixture of cyclohexane and methanol (99:1, v/v) and freeze-dried for 8 hours at low pressure. Now the films were hydrated by addition of 1.5 ml of NaCl at 64°C, in a water bath, with gentle mixing. Finally, sonicated liposomal suspensions for 8 minutes at 64°C and extruded 10 times through Nucleopore plycarbonate filters with pore sizes of 400 and 100 nm and we get curcumin loaded liposomes.[44]

Preparation of Curcumin Nanosponges

Nanosponges are the newest technology which facilitate on targeted drug delivery for extended period of time for those drugs which have low solubility and permeability problem. Nanosponges are nano size particle having a tiny sponge like structure. This system of delivery belongs to the BCS second classes of drug which also improves the bioavailability related factors.[45] The curcumin loaded nanosponge were formulated by emulsion solvent diffusion method. The nanosponge preparation contains varying concentration of Eudragit L-100 with polyvinyl alcohol DCM also. First, Eudragit L-100 was taken and dissolved in dichloromethane this mixture was added into aqueous solution of polyvinyl alcohol and with constant stirring at 1200 rpm for 2 h and add curcumin. Now filter the product and dried in an oven at 40°C for 24 h. Then finally dried curcumin loaded nanosponges were obtained.[46]

Preparation of Microspheres

Microspheres are one of the multiparticulate delivery systems which are prepared to produce prolonged or controlled drug delivery, as well as to improve bioavailability and stability and to achieve target drug delivery. Curcumin microspheres were formulated by solvent evaporation technique, where Eudragit S 100 was dissolved in a mixture of Propan-1-ol and Chloroform (1:2) at 28°C, that is, room temperature and with constant stirring add curcumin. Then pour 100 ml of water containing 0.02% of sodium lauryl sulfate at 1000 rpm for 90 min. Finally collect, filter, and wash the mixture. Then washed microspheres dried at room temperature to make them rigid.[47]

Discussion

The present review is based on the advancement of curcumin in the field of pharmaceutics that includes various parameters and techniques which have glorious research in future here we compare various properties of curcumin with each other and studded its application in managing life threatening diseases by the ability of high loading capacity of drug in the novel formulation.

Conclusion

Curcumin has received worldwide attention because of its multiple health benefits. many Researchers suggests that curcumin can help in the managing many of health issues such as cancer, inflammation, diabetes, oxidative stress, Alzheimer's disease, obesity, and many more. However, curcumin belong to BCS Class IV category means having low solubility and low permeability problem to overcome this issue when curcumin is combined with piperine, then bioavailability of curcumin increases. The further researches with novel drug delivery systems, the nanoparticulate curcumin results show more bioavailability and had a longer half-life than native curcumin.

Acknowledgment

The authors are thankful to family and I would like to thank my Mentor Ms. Aarti Bhati for his expert advice and encouragement throughout this review.

References

1. Aggarwal BB, Sung B. Pharmacological basis for the role of curcumin in chronic diseases: An age-old spice with modern targets. Trends Pharmacol Sci 2009;30:85-94.
2. Araújo CC, Leon LL. Biological activities of *Curcuma longa* L. Mem Inst Oswaldo Cruz 2001;96:723-8.
3. Tirkey N, Kaur G, Vij G, Chopra K. Curcumin, a diferuloylmethane, attenuates cyclosporine-induced renal dysfunction and oxidative stress in rat kidneys. BMC Pharmacol 2005;5:15.
4. Sharma RA, Steward WP, Gescher AJ. Pharmacokinetics and pharmacodynamics of curcumin. Adv Exp Med Biol 2007;595:453-70.
5. Lazaro ML. Anticancer and Carcinogenic properties of curcumin: Considerations for Its clinical development as a cancer chemo preventive and chemotherapeutic agent. Mol Nutr Food Res 2008;52 Suppl 1:S103-27.
6. Deepika S, Rizwana K, Sharma B. A review on proniosomes drug delivery: An innovative approach. World J Pharm Res 2020;9:1322-33.
7. Walve JR, Rane BR, Gujrathi NA. Proniosomes: A surrogate carrier for improved transdermal drug delivery system. Int J Res Ayurveda Pharm 2011;2:743-50.
8. Bharat AB, Indra BD, Ichikawa H, Ahn KS, Sethi G, Sandur SK, *et al*. Curcumin Biological and Medicinal Properties. 2006. p. 297-368.
9. Yin S, Zheng X, Yao X, et al. Synthesis and Anticancer Activity of Mono Carbonyl Analogues of Curcumin.Journal of Cancer Therapy;2013:4,113-123.
10. Parize AL, Stulzer KH. Evaluation of chitosan microsphere contains curcumin cross linked with sodium tripolyphosphate. Quim Nova 2012;35:1127-1132.
11. Bagchi A. Extraction of curcumin. IOSR J Environ Sci Toxicol Food Technol 2012;1:1-16.
12. Xiao-Yu Xu, Meng X, Li S, et al. A Review Article: Bioactivity, Health Benefits, and Related Molecular Mechanisms of Curcumin: Current Progress, Challenges, and Perspectives.Nutrients;2018:10,1553.
13. CFR Code of Federal Regulations Title 21. Available from: https://www.accessdata.fda.gov
14. Ahmed S, Anuntiyo J, Malemud CJ, Haqqi TM. Biological basis for the use of botanicals in osteoarthritis and rheumatoid arthritis. eCAM 2005;2:301-8.
15. Pan MH, Huang TM, Lin JK. Biotransformation of curcumin through reduction and glucuronidation in mice. Drug Metab Dispos 1999;27:486-94.
16. Ireson C, Orr S, Jones DJ, Verschoyle R, Lim CK, Luo JL, *et al*. Characterization of metabolites of the chemo-preventive agent curcumin in human and rat hepatocytes and in the rat *in vivo*, and evaluation of their ability to inhibit phorbolester-induced prostaglandin E2 production. Cancer Res 2001;61:1058-64.
17. Pandey A, Srivastava R, Shukla A Kumar et al. Physico-Chemical Studies onMolecular Interactions of Curcumin with Mono and Divalent Salts at DifferentTemperature. Int J of Smart Home.2011;7-23.
18. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: Problems and promises. Mol Pharm 2007;4:807-18.
19. Mohanty C, Sahoo SK. The *in vitro* stability and *in vivo* pharmacokinetics of curcumin prepared as an aqueous nanoparticulate formulation. Biomaterials 2010;31:6597-611.
20. Kanai M, Imaizumi A, Otsuka Y, Sasaki H, Hashiguchi M, Tsujiko K, *et al*.

Dose escalation and pharmacokinetic study of nanoparticle curcumin, a potential anticancer agent with improved bioavailability, in healthy human volunteers. Cancer Chemother Pharmacol 2012;69:65-70.
21. Brahmankar DM, Jaiswal B, Sunil A. Book of Biopharmaceutical and Pharmaceutics: A Treatise. New Delhi: Vallabh Prakashan; 2016. p. 29.
22. Chavda HV, Patel CN, Anand IS.A Review: Biopharmaceutics Classification System.Systematic Reviews in Pharmacy. 2010.
23. FDA/CDER. Guidance for Industry, Waiver of *in-Vivo* Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. Washington, DC; 2000.
24. World Health Organization. Multisource (Generic) Pharmaceutical Products: Guidelines on Registration Requirements to Establish Interchangeability. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, Fortieth Report. Geneva: World Health Organization. WHO Technical Report Series, No. 937, Annex 7; 2000. p. 347-90.
25. Jurenka JS. Anti-inflammatory properties of curcumin, a major constituent of *Curcuma longa*: A review of preclinical and clinical research. Altern Med Rev 2009;14:141-53.
26. Di Pierro F, Bressan A, Ranaldi D, Rapacioli G, Giacomelli L, Bertuccioli A. Potential role of bioavailable curcumin in weight loss and omental adipose tissue decrease: Preliminary data of a randomized, controlled trial in overweight people with metabolic syndrome. Preliminary study. Eur Rev Med Pharmacol Sci 2015;19:4195-202.
27. Cox KH, Pipingas A, Scholey AB. Investigation of the effects of solid lipid curcumin on cognition and mood in a healthy older population. J Psychopharmacol 2015;29:642-51.
28. Kuttan R, Bhanumathy P, Nirmal K, George MC. Potential anticancer activity of turmeric (*Curcuma longa*). Cancer Lett 1985;29:197-202.
29. Wright JS. Predicting the antioxidant activity of curcumin and curcuminoids. J Mol Structure (Theochem) 2002;591:207-17.
30. Tesfamariam B. Free radicals in diabetic endothelial cell dysfunction. Free Radic Biol Med 1994;16:383-91.
31. Mahesh T, Balasubashini MS, Menon VP. Photo irradiated curcumin supplementation in streptozotocin-induced diabetic rats: Effect on lipid peroxidation. Therapie 2004;59:639-44.
32. Yu WG, Xu G, Ren GJ, Xu X, Yuan HQ, Qi XL, *et al*. Preventive action of curcumin in acute pancreatitis in mouse. Indian J Med Res 2011;134:717-24.
33. Deodar SD, Sethi R, Srimal RC. Preliminary study on antirheumatic activity of curcumin (diferuloyl methane). Indian J Med Res 1980;71:632-4.
34. Chattopadhyay I, Kaushik B, Bandyopadhyay U, Banerjee RK. Turmeric and curcumin: Biological actions and medicinal applications. Curr Sci 2004;87:44-58.
35. Sharifi-Rad J, Rayess YE, Rizk A et al. A Review: Turmeric and Its Major Compound Curcumin on Health: Bioactive Effects and Safety Profiles for Food, Pharmaceutical, Biotechnological and Medicinal Applications. Front Pharmacol. 2020; 11: 01021.
36. Valizadeh, H, Abdolmohammadi-Vahid S, Danshina S, Gencer MZ, Ammari A, Sadeghi A, *et al*. Nano-curcumin therapy, a promising method in modulating inflammatory cytokines in COVID-19 patients. Int Immunopharmacology 2020;89:107088.
37. Tahmasebi S, El-Esawi MA, Mahmoud ZH, Timoshin A, Valizadeh H, Roshangar L, *et al*. Immunomodulatory effects of nanocurcumin on Th17 cell responses in mild and severe COVID-19 patients. J Cel Physiol 2020;236:5325-38.
38. Samar AA, Maha AH, Ali SA, Kadria AE. Nanosuspension: An emerging trend for bioavailability enhancement of etodolac. Int J Polym Sci 2015;938594.
39. Vandana BP, Abhijit AD, Kulkarni RM. Nanosuspensions: A promising drug delivery strategy. J Pharm Pharmacol 2004;56:827-40.
40. Nair SC, Kumar BS, Krishna R, Ps L, Vasudev DT. Formulation and evaluation of niosomal suspension of cefixime. Asian J Pharm Clin Res 2017;10:194.
41. Ravalika V, Sailaja AK. Formulation and evaluation of etoricoxib niosomes by thin-film hydration technique and ether injection method. Nano Biomed Eng 2017;9:242-8.
42. Kim HJ, Yoon KA, Hahn M, Park ES, Chi SC. Preparation and *in vitro* evaluation of self-microemulsifying drug delivery systems containing idebenone. Drug Dev Ind Pharm 2000;26:523-9.
43. Amit AK, Vandana BP. Design and evaluation of self-emulsifying drug delivery systems (SEDDS) of nimodipine. AAPS PharmSciTech 2008;9:191-6.
44. Stewart JC. Colorimetric determination of phospholipids with ammonium ferrothiocyanate. Anal Biochem 1980;104:10-4.
45. Khade PH, Talware AC. Cyclodextrin based nanosponges used as solubility enhancing agent. Int J Pharm 2104;45:157.
46. Patel NM, Soniwala MM. Influence of release enhancer on release of Venlafaxine HCL from glyceryl behenate matrix tablet. Indian Drugs 2008;45:104.
47. Vohra SY, Patil CC. Development and characterization of Stavudine microspheres prepared using different polymers. J Pharm Res 2009;2:953-7.