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Curcumin: The Golden Spice In The Treatment of Rheumatoid Arthritis

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ABSTRACT

Curcumin, an orange-yellow colored component of turmeric is a diarylheptanoid. It is the principal curcuminoid obtained from the rhizomes of the *Curcuma longa* plant (*Zingiberaceae*). It is a polyphenol product obtained from turmeric. It is been used in some medicinal preparation and even as a food-coloring agent. By the *in vivo* and *in vitro* studies it is confirmed that curcumin has antiviral, anti-arthritic anticancer, anti-amyloid, anti-inflammatory and antioxidant properties. The present article highlights the role of curcumin in the treatment of rheumatoid arthritis (RA). It emphasizes on the oral, transdermal and parenteral routes of drug delivery systems and the emerging trends related to these delivery systems such as solid dispersions, cyclodextrin inclusion compounds, solid lipid nanoparticles, liposomes, micro nano emulsions, transdermal patches, topical gel and proniosomes etc.

Keywords: Rheumatoid arthritis, Curcumin, Drug delivery, Treatment.

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INTRODUCTION

Since ages, rheumatic diseases have affected mankind the most common inflammatory conditions in developing countries [1, 2]. Rheumatoid arthritis is a systemic inflammatory disorder which is caused due deposition of uric acid crystals in the joints mainly the diarthrodial joints which leads to chronic inflammation, granuloma formation and joint destruction. It is a disease associated with extravascular immune complex as well as a disorder of cell mediated immunity. According to the World Health Organization (WHO) [3], over 150 diseases and syndromes are related to orthopedic, rheumatic and musculoskeletal.

Consequently biologically active compounds derived from plants are useful in combating diseases [4]. In India, Ayurvedic medicine, the 'science of life' which is a natural system of treatment, has been practiced for several years and emphasizes on rejuvenation of our body systems, prevention of disease and increasing human life span through natural therapies [5]. Synthetic drugs such analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs) and corticosteroids are used for the treatment of rheumatoid arthritis. Since these drugs possess side effects there is a need for the herbal drugs which could overcome all the problems caused by the synthetic drugs. Among the herbal drugs curcumin which is a component of turmeric shows extensive therapeutic potential against rheumatoid arthritis. As folklore medicine turmeric is used for the treatment of rheumatoid arthritis, skin cancer, chronic anterior uveitis, small pox, wound healing, conjunctivitis, chicken pox, urinary tract infections, liver ailments, jaundice, menstrual difficulties, digestive disorders, and colic; for abdominal pain and distension .It is also used as an antiseptic and as an antibacterial agent by many South Asian countries [6, 7].

CURCUMIN: THE GOLDEN SPICE

As a traditional medicine curcumin has been used for many centuries in countries such as India and China [8]. *Curcuma longa* is a member of the *Zingiberacae* (ginger) family of botanicals and is a perennial plant that is native to Southeast Asia [9]. It is chemically a yellow polyphenol, diferuloylmethane extracted from the rhizomes of *Curcuma longa* [10].

Curcumin chemical structure was determined by Roughley and Whiting in the year 1973 and was first isolated in 1815. According to the FPO/WHO Specifications, synonyms of curcumin are turmeric yellow, diferuloylmethane, Kurkum, and C.I. Natural Yellow [11-14]. It has been identified as 1,6-heptadiene- 3,5-dione-1,7-bis (4-hydroxy-3-methoxyphenyl)-(1e,6e) or diferuloylmethane. Curcumin is not soluble in ether and water but soluble in alkali, ketone, acetic acid, ethanol, and chloroform, acetone, and dimethyl sulfoxide[15] .The molecular formula of curcumin is C21H20O6, its molecular weight is 368.37 g/mol, and melting point is 183.8 °C [16, 17]. Curcumin occurs in two tautomeric forms, keto and enol. In the solid phase the enol form is more stable and in solution form it can cross the blood–brain barrier easily [18, 19].

Scientific Research has shown curcumin to be a molecule which is capable of interacting with numerous molecular targets involved in inflammation [20].

Phytoconstituents

Turmeric is comprised of a group of three cur- cuminoids such as curcumin (diferuloylmethane), bisdemethoxycurcumin and demethoxy- curcumin. It is even present as volatile oils namely tumerone, atlantone, and zingiberone. There may be presence of proteins, sugars and resins. The complex of curcuminoid is also known as the Indian saffron [21]. Curcumin is a lipophilic polyphenol which is insoluble in water but is stable in the acidic pH of the stomach [22].

Plant morphology

Turmeric plant possesses underground rhizomes which possess segmented skin and finger like projections. The rhizome in the centre is mostly thickened like a tuber and has several roots .The rhizomes are fleshy and branched. Turmeric is usually grown as annual crop and is a perennial proved leafy and erect herbaceous plant. It needs warm and slightly humid atmosphere and requires temperature between 20-30° C and also a significant amount of rainfall. It is 60-90 cm in height. The flowers are yellow in colour and grouped together dense with size range of 10-15 cm in length. The blade of leaf is thin, ovate, sheath like with long petiole and entire margin. The leaves are oblong, broad and narrowed towards the base. They are slight green in colour, 8-14 cm wide and 35-40 cm long. Above the ground the plant bears no fruits and the primary rhizome is ovate, known as "bulb" and the secondary one are cylindrical in shape [23]. Rhizomes are yellow in colour with an orange line inside the rhizomes. But externally rhizomes are scaly and brownish [24].

ORAL DRUG DELIVERY

Oral administration of curcumin was effective as cortisone or phenylbutazone for acute inflammation and one-half as effective in cases of chronic inflammation [25]. Oral administration of *Curcuma longa* significantly reduced the inflammatory swelling compared to controls in rates with Freunds adjuvant induced arthritis whereas in monkeys, it inhibited neutrophil aggregation associated with inflammation. *C. longa*'s anti-inflammatory properties inhibited both biosynthesis of inflammatory prostaglandins from arachidonic acid as well as neutrophil function during inflammatory states [26]. In humans the systemic bioavailability of orally administered curcumin is low only traces of it have been found in the liver and portal circulation [27]. Oral administration of curcumin at doses between 36 and 180 mg/day is safe for human usage even if it is taken up to 4 months [28]. The small amount of the curcumin taken orally enters the plasma and that enters the bloodstream is rapidly conjugated via glucuronidation and sulfation to inactive products in the liver. Antony and co-workers [29] stated that curcumin, at a dose of 2000 mg/day, was well tolerated by all the study volunteers without even mild adverse reactions. Different phase-I clinical trials, conducted separately by Shoba *et al*.[30] and Cheng *et al*.[31] indicated that curcumin is well tolerated in human subjects when taken at doses as high as 12,000 mg/day [30, 31]. These results were confirmed by Lao and coworkers [32]. The acceptable daily intake of curcumin as an additive has been defined by the WHO as 0-3 mg/kg body weight [33]. Curcumin is less absorbed from the GIT and it is rapidly metabolized [34, 35].

In order to enhance the action of curcumin the novel drug delivery methods were being introduced.

Solid dosage forms

Solid dosage forms such as polymorphs enhanced the solubility and dissolution rate. Solid dispersions transformed crystalline to amorphous material. Dispersion in hydroxypropyl methylcellulose acetate succinate (HPMC-AS) at a dose of 20mg/kg gave a Cmax of 147 ng/ml (Tmax=60 min). The bioavailability was 10.7% compared with intravenous injections [35]. Another dispersion with polyethylene glycol 660 12-hydroxy stearate at a dos e of 50mg/kg gave a Cmax of 90 ng/ml (Tmax=15 min) and rapid absorption was observed. The AUC of the dispersion was five-times higher than that of a standard crystalline suspension [36]. The last example is a dispersion of curcumin in cellulose acetate, at the same dose which gave a Cmax of 187 ng/ml. The AUC of this dispersion was eight-times higher than that of a standard crystalline suspension.

Cyclodextrins (CDs) are cyclic oligosaccharides consisting of six to eight sugar molecules in a cyclic structure. They sequester insoluble compounds within their hydrophobic cavity, which results 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 [37-40]. Compared with a curcumin suspension, its Cmax (370 ng/ml) was about nine-times higher at a 500 mg/kg dose. In a rat study, CAVAMAX™ W8 led to 10-20-times greater amount of total curcumin in the plasma than pure curcumin powder after oral administration. Curcumin after hydrolysis of the plasma was assayed with glucuronidase and sulphatase. Bioavailability was about 0.2%, which is four times that of standard curcumin. Phosphatidylcholine complexes were prepared by refluxing curcumin with phosphatidylcholine in organic solvents. Phospholipid complexes, liposomes and micelles reduces the hydrophobicity of curcumin; these carriers can also increase the permeability by interacting with membrane components

These are in the sub- micron size range and consist of biocompatible and biodegradable materials, such as triglycerides and fatty acids [41]. SLNs are composed of polysorbate 80 (45.45%), soy lecithin (0.58%) and Compritol 888 ATO™ (7.27%) which were prepared by micro emulsification. The SLNs at a dose of 50mg/kg were administered to the rats and the Cmax was as high as 14.3 µg/ml and the AUC was 39 times higher than that of a control curcumin solution [42]. After hydrolysis with glucuronidase it was assayed. Another SLN composed of poloxamer 188, glyceryl monostearate, soy lecithin, medium chain triglyceride (MCT) and curcumin was evaluated and the particle size was found to be 129 nm. The SLNs at a dose of 80mg/kg were administered to rats. These SLNs gave a significantly higher Cmax (565 ng/ml vs. 279 ng/ml), shorter Tmax (0.5 h vs. 1.0 h) and greater AUC (820 mg/l h vs. 344 mg/l h) compared with a crystalline curcumin suspension [43]. LONGVIDA™, which is composed of turmeric root extract, soy lecithin docosahexaenoic acid, stearic acid, ascorbyl esters, is formulated as LNPs. The curcumin content by weight is 20-30%. In healthy volunteers, 650 mg of the product (130-260 mg curcumin) gave a Cmax of 22 ng/ml (Tmax=2 h). In patients with arthritis, 2000 mg of the product (400-800 mg curcumin) gave a Cmax of 32 ng/ml (Tmax=3.5 h) [44].

Liposomes are a well-established delivery system incorporating poorly soluble drugs .Curcumin-loaded liposomes made with lecithin (SLP-PC70), with an average size of 253 nm, were prepared and orally administered to rats [45]. At 100 mg/kg, the Cmax was 319 ng/ml (Tmax=30 min), while the Cmax of a control curcumin crystal suspension was 65 ng/ml (Tmax=2 h). The AUC was 5-fold higher than the control. In this study, curcumin was assayed after hydrolysis with glucuronidase and sulphatase. Curcumin-loaded silica-coated liposomes (157 nm in size) were prepared to protect the particles in the harsh environment of the GI tract showed higher stability against artificial gastric fluid and more sustained drug release in artificial intestinal fluid [46]. In a study on rats, a 50 mg/kg dose gave a Cmax of 450 ng/ml (Tmax=2 h) and an AUC that was 7.8-fold higher than that of a standard curcumin suspension. The rationale for the use of liposomes is shown in Figure 1.

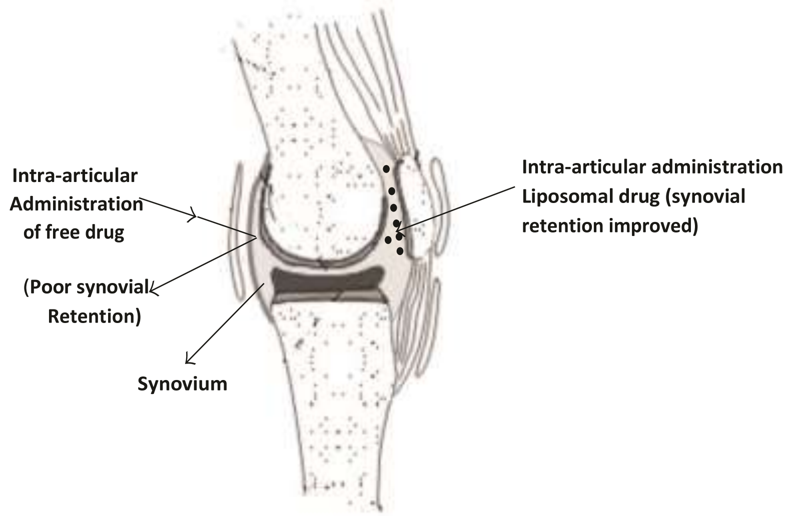

Figure 1: Rationale for the use of liposomes in rheumatoid arthritis

Micron (nano) emulsions are the colloidal, optically isotropic, transparent or slightly opalescent formulations which consists of surfactant, co- surfactant oil and water. A formulation of nano emulsion was prepared in aqueous solution which composed of composed of Capryol 90, Cremophor RH40 and Transcutol P. The solubility of curcumin 32.5 mg/ml and the droplet size was 27.3 nm [47]. When compared with the suspension at a dose of 200 mg/kg, the microemulsion had a substantially increased Cmax (3.57 μg/ml; Tmax=138 min) and an AUC (690.5 μg/ml min), while the control, at a dose of 100 mg, had a Cmax of 0.83 μg/ml (Tmax=1.5 h) and an AUC of 153.2 μg/ml min. The bioavailability in the emulsion was 22.6-fold higher than that in the control suspension. A micron (nano) emulsion with a droplet size of 218 nm was prepared using curcumin, oil (MCT), surfactant (Span 20, monostearin, modified starch, Tween 80) and water [48]. The bioavailability of this microemulsion was studied in mice at a dose of 197 mg/kg. The Cmax was 29.9 μg/ml (Tmax=1 h) and the bioavailability was nine-times higher than that of unformulated curcumin. Another emulsion of drop size 69nm containing curcumin of concentration 100mg/ml, PEG 600 and Cremophor was prepared. At a dose of 1.8 g/kg in mice, the Cmax was 4.73 μg/ml (Tmax=20 min) [49]. In another example of an emulsion composed of PEG 400, polyethylene glycol, ethanol, Tween 80 and water was prepared with an average drop size of 176 nm. With a 20 mg/kg dose administered to rats, the Cmax was 451 ng/ml. By virtue of its size and chemical composition it is possible to retain the drug in the synovial cavity in the form of liposomes [50, 51].

Another formulation of phytosomes were prepared which were basically microspheres consisting of curcumin (Cur-PS-CMs). Curcumin was encapsulated using ionotropic gelation which had a particle size of 23.21 ± 6.72 μm and drug loading efficiency of 2.67 ± 0.23.The invitro release at different pH was carried out for both and the release for curcumin phytosome microspheres was found to be slower .Whereas the pharmacokinetic studies in rats showed a 1.67- and a 1.07-fold increase in absorption of curcumin compared with Cur-PSs and Cur-CMs. The half-life of curcumin orally administration of Cur-PS-CMs (3.16 h) was longer when compared with the other two .It enhanced the bioavailability as well as the retention time of curcumin [52].

Ethosomes loaded with curcumin and coated with silica prepared by alcohol injection method and by precipitation of silica by sol-gel process are potentially active when taken orally. By the in vitro studies it is proved that CU-SEs had good release properties when compared with curcumin-loaded ethosomes (CU-ETs) without silica-coatings and the bioavailability of CU-SEs was 2.26 times higher than that of CU-ETs. The stability of the ethosomes is promoted by the silica coating [53].

Curcumin albumin nanosuspension is a potential novel drug delivery system .In vitro studies showed 96% of the release. The mean size before lyophilization and after reconstitution was checked and found to be 245.2 nm and 240.3 nm respectively [54]. Curcumin implants reduces the biopharmaceutical problems .These implants where tested on female ACI rats for 3 months and the concentration of curcumin was measured. There was 2 fold increase in the release pattern of *in vitro* when compared to *in vivo*. Curcumin implants provides much higher plasma and tissue concentrations and are a viable alternative for delivery of curcumin.

When compared to the oral administration the polymeric implants enhance the tissue and the plasma curcumin levels [55]. Implants prepared by melt-extrusion method have a release pattern which is proportional to the surface area. There was no change in the drug release by the addition of water soluble additives too. The implant was tested and it was found that the *in vivo* drug release ~1.8 times higher than *in vitro* release. These implants release curcumin for a longer duration with better efficacy[56].

Topical route

To overcome the inflammation and irritation caused by curcumin it may be applied topically. However, care must be taken to prevent staining of cloths from the yellow pigment [57].The major problem associated with the use of curcumin as a drug is its low bioavailability. In order to enhance the bioavailability curcumin was complexed with phosphatidyl choline [58]. When administered in equimolar doses it showed increased absorption compared with curcumin. The complex also showed enhanced bioavailability, improved pharmacokinetics, and increased hepatoprotective activity [59]. The enhanced bioavailability of the complex is due to its amphiphilic nature. Another area of interest is enhancing the topical delivery of curcumin [60-63]. This approach is intended to increase the absorption of curcumin through skin. Hegge solubilized curcumin in aqueous solution along with cyclodextrins and alginates which is intended for topical delivery. The study concluded that a combination of hydroxypropyl-β-cyclodextrin and propylene glycol alginate enhances curcumin release from the vehicle [64-66]. These studies have demonstrated the importance of optimizing the solvent systems when utilizing cyclodextrins as drug carriers for topical treatments [67]. When compared to the conventional drug delivery system , transdermal drug delivery system (TDDS) can deliver certain medication to systemic circulation in a more convenient and effective way. The release pattern of the drug is shown in the **Figure 2**. Since previous pharmacokinetic studies of curcumin have reported low absorption from GIT and its rapid metabolism, it was thought worthwhile to formulate a transdermal system of curcumin.

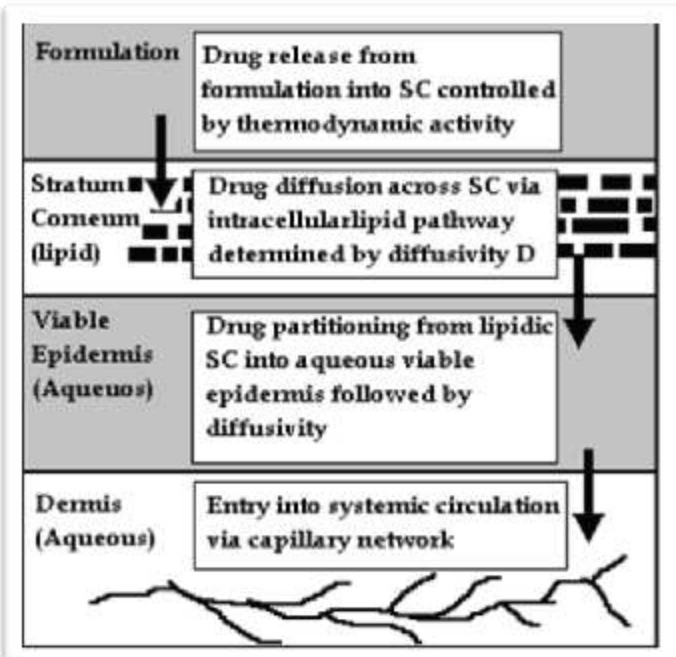

Figure 2: Release pattern of transdermal drug release

By using different polymer blends the amount of drug in the body may increase and increase the anti-inflammatory activity. Matrix-type transdermal patches with different ratios of PVP and EC containing curcumin were prepared .Since the drug is lipophilic it is suitable for transdermal drug delivery .A right combination of hydrophilic and hydrophobic polymers is compulsory for better results. Use of curcumin in TDDS can be also considered as a new version of technically improved method of ayurvedic turmeric poultice or lepa. It is well tolerated in as high a dose as 2 gm/kg (p.o) in mice [68]. It inhibits both lipoxygenase and cyclooxygenase and a potent scavenger of oxygen free radicals. Due to its extensive first pass metabolism it is a suitable candidate for transdermal patch formulation [69]. Hence, when compared to the conventional system, transdermal drug delivery system is useful in delivering medication to the systemic circulation in a more effective way [70-72].

Carbopol 934P (CRB) and hydroxypropylcellulose (HPC) were used for the preparation of gels. The enhancement of the penetration of menthol was checked by using the gel on the epidermis of the rat. The anti-inflammatory studies were done with wistar albino rats by carrageenan induced rat paw oedema method. The anti-inflammatory effect of CRB, HPC and standard diclofenac gel formulations were compared CRB gel showed better % inhibition of inflammation as compared to HPC gel [73-75].

A nano-carrier transdermal gel (NCTG) containing 97.57% of curcumin is prepared in replacement of diclofenac diethylamine (DDEA). It is found to be safe and has greater extent of absorption significant inhibition (%) of carrageenan induced paw edema. As a nano carrier it increases its biological activity due to superior skin penetration potential [76, 77].

Nano-transfersomes of Diclofenac diethylamine (DDEA) and Curcumin (CRM) were prepared. The ratio of lipid to surfactant, weight of lipid to surfactant and sonication time (independent variables) and dependent variables such as entrapment efficiency of DDEA and CRM, effect on particle size, flux of DDEA and CRM were compared. The compositions of the formulation was determined by the 2-D and 3-D plots The design established the role of the derived polynomial equation, 2-D and 3-D plots in predicting the values of dependent variables for the optimization of nano-transfersomes for transdermal drug release [78, 79].

Proniosomes are a potential drug delivery via the transdermal route. A study was performed by preparing different proniosomal gel bases by the ether injection method, using Span 60 and Span 80, Tween 20, cholesterol, and formulation PA2. They were characterized by scanning electron microscopy, revealing vesicular structures, and using rat skin they were assessed for stability and effect on *in vitro* skin permeation. Anti-inflammatory and anti-arthritic effects of formulation PA2 and PB1 were compared with a standard market product containing indomethacin. The effect of formulation PA2 and PB1 was evaluated for acute inflammation in carrageenan induced rat paw oedema and for chronic inflammation in complete Freud's adjuvant (CFA) induced arthritis in rats. The curcumin loaded proniosomal formula was proved to be non-irritant and non-toxic, but had lower anti-inflammatory and anti-arthritic effects than the marketed indomethacin products [80].

Parenteral

After i.v. administration there will be presence of blood for a short period and it fades away quickly in the blood. Curcumin, a lipophilic compound requires formulation when intended for parenteral administration .The compound are susceptible to physical degradation in high temperatures, enzymatic degradation, alkaline conditions, metabolism, and exhibits rapid physiologic clearance [81]. The free curcumin found in the blood may in reality be the glucuronide or sulfated conjugated metabolites with limited biological activity or distribution with circulating lipids. Liposomes are usually used for parenteral administration, and some pharmacokinetic profiles after intravenous injection of curcumin liposomes have been reported and found to be more effective [82].

CONCLUSION

Curcumin is undoubtedly, the nature's gift to humanity since it cures many diseases. This article highlights the role of curcumin in the treatment of rheumatoid arthritis. It shows better safety profiles when compared to the synthetic drugs but due its low bioavailability its clinical use is limited. In order to enhance the bioavailability novel drug delivery systems were introduced. Obviously, more studies are needed to fully evaluate the efficacy and the safety of reformulated curcumin, the structural analogues of curcumin as well as the combination of curcumin with existing therapies. There is also a need for greater research and emphasis for better utilization of this plant. Nevertheless, the low cost, pharmacological safety, proven therapeutic efficacy and multiple targeting potential make curcumin a promising agent for prevention and treatment of various human diseases. Meanwhile, for enhanced bioavailability, reformulations of curcumin also hold great promise in the future.

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REFERENCES

1. Raut, A.A., Joshi, A.D., Antarkar, D.S., Joshi, V.R., Vaidya, A.B., Antirheumatic formulation from Ayurveda. Ancient Science of Life XI: 66-69, (1991).
2. Rang, H.P., Dale, M.M., and Ritter, Pharmacology: 293-295, (1999).
3. The World Health Organization Home Page. (Accessed on 20 March 2012). Available online: http://www.who.int/en/ .
4. Aggarwal BB., Prasad S., Reuter S., Kannappan R., Yadev VR., Identification of novel anti-inflammatory agents from Ayurvedic medicine for prevention of chronic diseases: "reverse pharmacology" and "bedside to bench" approach. Curr Drug Targets. 12:1595-1653, (2011).

5. Garodia P., Ichikawa H., Malani N., Sethi G., Aggarwal BB.,From ancient medicine to modern medicine: Ayurvedic concepts of health and their role in inflammation and cancer. J Soc Integr Oncol ., 5:25-37,(2007)
6. Prasad S., Aggarwal BB.,Turmeric, the Golden Spice: From Traditional Medicine to Modern Medicine. In Herbal Medicine. Bimolecular and Clinical Aspects. 2: 25-37., (2011).
7. Shinde CG., Venkatesh MP., Kumar TP., Shivakumar HG., Methotrexate: A Gold Standard for Treatment of Rheumatoid Arthritis. Journal of Pain & Palliative Care Pharmacotherapy, 28(4):351-8 (2014).
8. Shishodia S., Sethi G and Aggarwal BB., Curcumin: getting back to the roots. Ann N Y Acad Sci ., 206-217,(2005)
9. Chattopadhyay I., Biswas K., Bandyopadhyay U., Banerjee RK. Turmeric and curcumin Biological actions and medicinal applications. Curr Sci., 87:44-50, (2004).
10. Maheshwari RK., Singh AK., Gaddipati J., Srimal RC., Multiple biological activities of curcumin: a short review. Life Sci., 78: 2081-2087., (2006).
11. Chattopadhyay I., Biswas K., Bandyopadhyay U., Banerjee RK., Turmeric and curcumin: biological actions and medicinal applications. Curr Sci., 87(1):44–53., (2004).
12. Negi PS., Jayaprakasha GK., Jagan Mohan Rao L., Sakariah KK., Antibacterial activity of turmeric oil: a byproduct from curcumin manufacture. J Agric Food Chem., 47:4297–300.,(1999).
13. Kawamori T., Lubet R., Steele VE., Chemo preventative effect of curcumin, a naturally occurring anti-inflammatory agent, during the promotion/progression stages of colon cancer. Cancer Res., 59:597–601., (1999).
14. Summary of Evaluations Performed by the Joint FAO/WHO Expert Committee on Food Additive. Geneva: WHO., (2005).
15. Araujo CAC., Leon LL., Biological activities of Curcuma longa L Mem Inst Oswaldo Cruz., 96(5):723–8.,(2001).
16. Goel A., Kumar A., Kunnumakkara B., Aggarwal BB., Curcumin as ‘‘Curecumin’’: from kitchen to clinic. Biochem Pharmacol., 75: 787–809., (2008).
17. Chattopadhyay I., Biswas K., Bandyopadhyay U., Banerjee RK., Turmeric and curcumin: biological actions and medicinal applications. Curr Sci., 87(1):44–53., (2004).
18. Kolev TM., Velcheva EA., Stemboliyska BA., Spiteller M., DFT and experimental studies of the structure and vibrational spectra of curcumin .Int J Qua Chem., 102:1069–79.,(2005).

19. Balasubramanian K., Molecular orbital basis for yellow curry spice curcumin's prevention of Alzheimer's disease. J Agric Food Chem., 54(10):3512–20., (2006).
20. Julie S. Jurenka., Altern Med Rev., 14(2):141-153., (2009).
21. National Toxicology Program. NTP toxicology and carcinogenesis studies of turmeric oleoresin (CAS No. 8024-37-1) (major component 79%-85% curcurmin, CAS No. 458-37-7) in F344/N rats and B6C3F1 mice (feed studies). Natl Toxicol Program Tech Rep Ser., 427:1-275., (1993).
22. Aggarwal B B ., Kumar A., Bharti AC., Anticancer potential of curcumin: preclinical and clinical studies. Anticancer Res., 23:363-398., (2003).
23. Ahmad, W., A. Hassan., A. Ansari and T. Tarannum., Curcuma longa L. -A Review. Hippocratic J. Unani Med., 5: 179-190.,(2010).
24. Lal J., Turmeric, Curcumin and Our Life? A Review. Bull Environ Pharmacol. Life Sci., 1: 11-17., (2012).
25. Wang YJ., Pan MH., Cheng AL., Stability of curcumin in buffer solutions and characterization of its degradation products. J Pharm Biomed Anal., 15:1867-1876., (1997).
26. Smolen JS., Steiner G., Therapeutic strategies for rheumatoid arthritis. Nat Rev Drug Discov., 2:473-88., (2003).
27. Sudanshu Agarwal., Curcumin and its protective and therapeutic uses .National Journal of Physiology, Pharmacy and Pharmacology. 6(1)., (2016).
28. Sharma RA., Mc Lelland HR., Hill KA., Ireson CR., Euden SA., Manson MM., Pharmacodynamic and pharmacokinetic study of oral curcuma extract in patients with colorectal cancer. Clin Cancer Res., 7:1894–900., (2001).
29. Antony B., Merina B., Iyer VS., Judy N., Lennertz K., Joyal S.,A pilot cross-over study to evaluate human oral bioavailability of BCM- 95s CG (BiocurcumaxTM), a novel bioenhanced preparation of curcumin. Indian J Pharm Sci., 70(4):445–9., (2008).
30. Shoba G., Joy D., Joseph T., Majeed M., Rajendran R., Srinivas PS., Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. Planta Med., 64(4):353–6., (1998).
31. ChengAL ., HsuCH., LinJK ., HsuMM ., HoYF ., ShenTS., Phase I clinical trial of curcumin, a chemo preventive agent, in patients with high-risk or pre-malignant lesions. Anticancer Res., 21(4B):2895–900., (2001).
32. Lao CD., Ruffin MT., Normolle D., Heath DD., Murray SI., Bailey JM., Dose escalation of a curcuminoid formulation. BMC Complement Altern Med., 6:10., (2006).

33. Summary of Evaluations Performed by the Joint FAO/WHO Expert Committee on Food Additive. Geneva: WHO. 2005.
34. Khamora P., Development and Evaluation of Transdermal Patch of Curcumin for Rheumatoid Arthritis. Pan J Pharm and Pharmaceu Sci., 2(3); 6-12., (2014).
35. Shinde CG., Venkatesh MP., Rajesh KS., Srivastava A., Osmani RA., Sonawane YH., Intra-articular delivery of a methotrexate loaded nanostructured lipid carrier based smart gel for effective treatment of rheumatic diseases. RSC Advances. 6(16):12913-24 (2016).
36. Onoue S., Takahashi H., Kawabata Y., Seto Y., Hatanaka J., Timmermann B., Yamada S., Formulation design and photochemical studies on nanocrystal solid dispersion of curcumin with improved oral bioavailability. J Pharm Sci., 99(4): 1871-1881., (2010).
37. Seo SW., Han HK., Chun MK., Choi HK., Preparation and pharmacokinetic evaluation of curcumin solid dispersion using Solutol® HS15 as a carrier. Int J Pharm, 424(1-2): 18- 25, (2012).
38. Osmani RAM., Bhosale RR., Hani U., Vaghela R., Kulkarni PK., Cyclodextrin based nanosponges: Impending carters in drug delivery and nanotherapeutics. Curr Drug Ther., 10(1):3-19 (2015).
39. Osmani RA., Kulkarni PK., Shanmuganathan S., Srivastava A., Prerana M., Shinde CG., Bhosale RR., 3^2 Full Factorial Design for Development and Characterization of Nanosponges Based Intravaginal In situ Gelling System for Vulvovaginal Candidiasis. RSC Advances, E-pub ahead of print, (2016).
40. Osmani RA., Aloorkar NH., Kulkarni AS., Harkare BR., Bhosale RR., A new cornucopia in topical drug delivery: microsponge technology. Asian J Pharm Sci Technol., 4:48-60 (2014).
41. Ouyang HZ., Fang L., Zhu L., Zhang L., Ren XL., He J ., Qi AD., Effect of external factors on the curcumin/2-hydroxypropyl-b- cyclodextrin: In vitro and in vivo study. J Incl Phenom Macrocycl Chem., 73: 423-433., (2012).
42. Muller RH., Mader K., Gohla S., Solid lipid nanoparticles (SLN) for controlled drug delivery – a review of the state of the art. Eur J Pharm Biopharm., 50(1): 161-177., (2000).
43. Kakkar V., Singh S., Singla D., Kaur IP., Exploring solid lipid nanoparticles to enhance the oral bioavailability of curcumin. Mol Nutr Food Res., 55(3): 495-503., (2011).
44. Fang M., Jin Y., Bao W., Gao H., Xu M., Wang D., Wang X., Yao P., Liu L., In vitro characterization and in vivo evaluation of nanostructured lipid curcumin carriers for intragastric administration. Int J Nanomed., 7: 5395-5404., (2012).

45. Takahashi M., Uechi S., Takara K., Asikin Y., Wada., Evaluation of an oral carrier system in rats: Bioavailability and antioxidant properties of liposome-encapsulated curcumin. J Agric Food Chem., 57(19): 9141-9146., (2009).
46. Li C., Zhang Y., Su T., Feng L., Long Y., Chen .,Silica-coated flexible liposomes as a nanohybrid delivery system for enhanced oral bioavailability of curcumin. Int J Nanomed., 7: 5995-6002., (2012).
47. Hu L., Jia Y., Niu F., Jia Z., Yang X .,Jiao K., Preparation and enhancement of oral bioavailability of curcumin using micro- emulsions vehicle. J Agric Food Chem., 60(29): 7137-7141., (2012).
48. Yu H and Huang., Improving the oral bioavailability of curcumin using novel organogel-based Nano emulsions. J Agric Food Chem., 60(21): 5373-5379., (2012).
49. Zhongfa L., Chiu M., Wang J., Chen W., Yen W., Fan-Havard P., Yee LD., Chan KK., Enhancement of curcumin oral absorption and pharmacokinetics of Curcuminoids and curcumin metabolites in mice. Cancer Chemother Pharmacol., 69(3): 679-689., (2012).
50. Bhupinder Kapoor., Application of Liposomes in Treatment of Rheumatoid Arthritis: Quo Vadis; The Sci World J.
51. Anand P., Kunnumakkara A B., Newman R A., Aggarwal B B., Bioavailability of curcumin: problems and promises. Mol pharm., 4:807-818., (2007).
52. Zheng Z., Sun Y., Liu Z., Zhang M., Li C., Cai H., The effect of curcumin and its nano formulation on adjuvant-induced arthritis in rats. . Drug Des Devel Ther., 27; 9:4931-42., (2015).
53. Zhang J., Tang Q., Xu X., Li N., Development and evaluation of a novel phytosome-loaded chitosan microsphere system for curcumin delivery. Int J Pharm., 448(1):168-74., (2013).
54. Li C., Deng L., Zhang Y., Su TT., Jiang Y., Chen ZB., Silica-coated ethosome as a novel oral delivery system for enhanced oral bioavailability of curcumin. Yao Xue Xue Bao., 47(11):1541-7., (2012).
55. Shyam S. Bansal ., Hina Kausar.,Manicka V.Vadhanam.,Srivani Ravoori.,Ramesh C. Gupta.,Controlled systemic delivery by polymeric implants enhances tissue and plasma curcumin levels compared with oral administration .,European J Pharmaceutics and Biopharmaceutics.,80: 571–577.,(2012).
56. Shyam S. Bansal., Manicka V. Vadhanam .,Ramesh C. Gupta.,Development and *In Vitro-In Vivo* Evaluation of Polymeric Implants for Continuous Systemic Delivery of Curcumin**.**Pharmaceutical Research., 28(5):1121-1130., (2011).

57. Zhang H., Zhang L., Yuan P., Wang C., Preparation and in vitro release characteristics of curcumin in nanosuspensions. Zhongguo Zhong Yao Za Zhi., 36(2):132-5., (2011).
58. Gupta, N.K., Dixit, V.K. ., Bioavailability enhancement of curcumin by complexation with phosphatidyl choline. J. Pharm. Sci., 100: 1987–1995., (2011).
59. Hegge, A.B., Masson, M., Kristensen, S., Tonnesen, H.H., Investigation of curcumin-cyclodextrin inclusion complexation in aqueous solutions containing various alcoholic co-solvents and alginates using an UV-VIS titration method. Pharmaze. 64: 382–389., (2009).
60. Hegge, A.B., Schuller., R.B. Kristensen., S. Tonnesen. H.H., In vitro release of curcumin from vehicles containing alginate and cyclodextrin. Pharmaze. 6:585–592., (2008).
61. Srivastava A., Gowda DV., Kumar TM., Rajasree PH., Shinde CG., Transdermal Drug Delivery of Glibenclamide Using Binary Polymeric Combination: In Vitro and Preclinical Studies. Journal of Biomaterials and Tissue Engineering, 4(7), 555-561 (2014).
62. Sowmya J., Gowda DV., Srivastava A., Topical Gels: A Recent Approach for Novel Drug Delivery System. International Journal of Health Sciences and Research, 5(10):302-312 (2015).
63. Begur M, Pai VK., Gowda DV., Srivastava A., Raghundan HV., Shinde CG., Manusri N., Enhanced permeability of Cyclosporine from a transdermally applied nanoemulgel. Der Pharmacia Sinica, 6(2):69-79 (2015).
64. Smolen JS., Aletaha D., Koeller M., Weisman MH., Emery P., New therapies for treatment of rheumatoid arthritis. Lancet. 370:1861-74., (2007).
65. Osmani RAM., Aloorkar NH., Kulkarni AS., Kulkarni PK., Hani U., Thirumaleshwar S., Bhosale RR., Novel cream containing microsponges of anti-acne agent: formulation development and evaluation. Curr Drug Deliv., 12(5):504-16 (2015).
66. Osmani RAM., Thirumaleshwar S., Bhosale RR., Kulkarni PK., Nanosponges: The spanking accession in drug delivery- An updated comprehensive review. Der Pharmacia Sinica, 5(6):7-21 (2014).
67. Mukhopadhyay A., Basu N., Ghatak N., Anti-inflammatory and irritant activities of curcumin analogues in rats. Agents Actions, 12: 508-515., (1982).
68. Khamora P., Review on: Development of Novel Herbal System for Rheumatoid Arthritis .Panacea J Pharm and Pharm Sci.,2(3):1-5.,(2014).
69. Anto, R.J., Kuttan, G., Babu, K.V.D., Rajasekharan, K.N., Kuttan, R., Anti- inflammatory Activity of Natural and Synthetic Curcuminoids. Pharm. Pharmacol. Commun. 4: 103-106., (1998).

70. Kulkarni, R.R., and Patki, V.P., Treatment of Osteoarthritis with Herbomineral Formulation: A Double - Blind, Placebo - Controlled, Cross Over Study. Journal of Ethnopharmacology., 33:91-95., (1991).
71. Osmani RA., Aloorkar NH., Ingale DJ., Kulkarni PK., Hani U., Bhosale RR., Dev DJ., Microsponges based novel drug delivery system for augmented arthritis therapy. Saudi Pharmaceutical Journal, 23(5):562-72 (2015).
72. Osmani RA., Aloorkar NH., Thaware BU., Kulkarni PK., Moin A., Hani U., Srivastava A., Bhosale RR., Microsponge based drug delivery system for augmented gastroparesis therapy: Formulation development and evaluation. Asian Journal of Pharmaceutical Sciences, 10(5):442-51 (2015).
73. Chaudhary H ., Kohli K., Kumar V., A novel nano-carrier transdermal gel against inflammation. Int J Pharm., 25; 465(1-2):175-86 (2014).
74. Hani U., Shivakumar HG., Srivastava A., Rashmi NG., G Shinde C., Influence of Diluents on Release Properties of Curcumin-Hydroxy Propyl β Cyclodextrin Bioadhesive Vaginal Tablet. Current Drug Therapy, 9(2):75-82 (2014).
75. Hani U., Shivakumar HG., Srivastava A., Mahammed N., Thirumaleshwar S., Kumar Varma NS., Vaghela R., Shinde CG., Gowrav MP., Design and Optimization of Curcumin–HPβCD Bioadhesive Vaginal Tablets by 2^3 Factorial Design: In Vitro and In Vivo Evaluation. Journal of Pharmaceutical Innovation, 10(1):21-35 (2015).
76. Chaudhary H., Kohli K., Nano-transfersomes as a novel carrier for transdermal delivery. Int J Pharm., 454(1):367-80., (2013).
77. Gowda DV., Srivastava A., Vaghela R., Design, Development and Characterization of 5-Fluorouracil Encapsulated Porous Chitosan Nanoparticles: A Comparative Study. Advanced Science Engineering and Medicine, 7(8):697-703 (2015).
78. Bhalla HL., Bhate AS., Feasibility Studies on Transdermal Films of Ephedrine. Indian Drugs. 31(7):328-332, (1994).
79. Patel NA., Patel NJ., Patel RP., Formulation and evaluation of curcumin gel for topical application. Pharm Dev Tech. 14(1):83-92, (2009).
80. Kumar, K, Proniosomal formulation of curcumin having anti-inflammatory and anti-arthritic activity in different experimental animal models, Int J Pharm Sci, 67(10): 852-857, (2012).
81. Matabudul D, Pucaj K, Bolger G, Vcelar B, Majeed M and Helson L. Tissue distribution of (Lipocurc™) liposomal curcumin and tetrahydrocurcumin following two- and eight-hour infusions in Beagle dogs. Anticancer Res. 32(10): 4359-4364 (2012).

82. Helson L, Bolger G, Majeed M, Vcelar B, Pucaj K and Matabudul D. Infusion pharmacokinetics of Lipocurc™ (liposomal curcumin) and its metabolite tetrahydrocurcumin in Beagle dogs. Anticancer Res. 32(10): 4365-4370 (2012).