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Curcumin: Its Bioavailability and Nanoparticle Formulation: A Review

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ABSTRACT

Curcumin is used as traditional Indian and Chinese medicine in order to treat various diseases as well as used as a wound healing agent. Two to five percent in turmeric is curcumin; turmeric is available in yellow colour mainly obtained from polyphenolic pigment and fat-soluble substance called as curcuminoids, mostly used in the Indian subcontinent. Various clinical trials are conducted for understanding the wide range of therapeutic uses of curcumin. According to the studies, it shows that curcumin manifests very poor oral bioavailability, and forms numerous curcumin metabolites are formed after metabolism, although the bioavailability is low but the therapeutic activity of the curcumin for the various diseases, and for treatment of the disease enhancement of bioavailability of the curcumin in the future is necessary. According to the recent study on nanocurcumin with the size less than 100 nm which is an application of polymer-based nanoparticle of curcumin. It was observed that this polymer-based nanoparticle of curcumin has similar in vitro activity as that of free curcumin in pancreatic cell lines. In in-vivo study performed with the healthy volunteers a cream containing curcuminoid loaded SLNs was topically applied over the cream containing free curcuminoid showed the improvement in efficacy. Therefore, various techniques are developing for the nanoparticulate formulations.

Keywords- Curcuminoids, bioavailability, nanoparticulate, nanocurcumin, polyphenolic.

INTRODUCTION

Curcumin is the yellow polyphenolic compound extracted from the rhizome (2) of curcuma longa belong to the ginger family of Zingiberaceae, also known as diferuloyl-methane ($C_{21}H_{20}O_6$) stems of rhizomes which are horizontally underground, turmeric is available in yellow colour mainly obtained from polyphenolic pigment and fat-soluble substance called as curcuminoids.(1), mostly used in the Indian subcontinent as spice and food colouring material (5) the mostly active compound in turmeric is curcuminoids, another type of curcuminoid are also available names as bisdemethoxycurcumin and demethoxycurcumin. Polyphenols and curcuminoids are major for forming yellow turmeric colour, enol and keto are tautomeric forms of turmeric. (3)

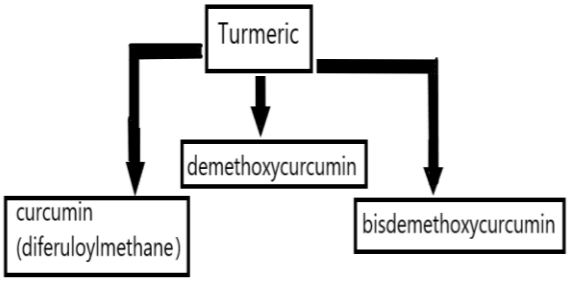
Two to five percent in turmeric is curcumin. Approximately the preparations of curcumin consist of 77% diferuloylmethane, 18% demethoxy-curcumin, and 5% bisdemethoxycurcumin. Curcumin is hydrophobic in nature and has 420 nm of absorption maxima and gets dissolved indimethylsulfoxide, acetone, ethanol, and oils. The presence of acids causes the colour of the curcumin to change from yellow to deep and this form is used in the religious ceremonies. (4)

Curcumin was isolated in 1815 from turmeric and in 1910 the structure was identified as diferuloylmethane (4) In Southeast Asia and tropical countries turmeric grows naturally and used for many purposes. Since 19,00 BCE curcuma longa has been used as a part of Indian Ayurvedic medicine use of turmeric was restrain to the Asia until the12th-13th centuries AD (7) but now a time it has been used as pigment, spice, food colouring, additive and also for medical purpose. Therefore, turmeric has reached in clinical phase I and II just in last 12-15 years. In Southeast Asia curcumin is used as alternative of medicine compound, jaundice, allergy, wounds, sprains, skin infection and many more. (2)Various clinical trials are conducted for understanding the wide range of therapeutic uses of curcumin. (6) During the last decades it was observed in the research that was taking place on antioxidant property of curcumin and the potential property of curcumin was determined. (5),(32)

When curcumin is orally administered, after that it metabolise is into curcumin glucuronide and curcuminsulfonate. However, when curcumin is administered systemically or intraperitoneally, it is metabolized into tetrahydrocurcumin, hexhyrdrocurcumin, and hexhydrocurcuminol. (4)

There are various effect of curcumin on the target cells, Curcumin can modulate numerous different transcription factors, cytokines, growth factors, kinases, and other enzymes (4),(34)

Turmeric consists of 3 curcuminoids:



Curcumin is used as traditional Indian and Chinese medicine in order to treat various diseases as well as used as a wound healing agent. Currently, numerous researches on curcumin proved that this agent can prevent the proliferation of cancer cells and acts as a cell death inducer by inducing many signalling pathways. Therefore, as an inducer of cell death curcumin has become a chemopreventive and anti-cancer agent. This can be proved by performing various in vitro experiments and preclinical studies on the animal models. (14)

Properties and medicinal use of curcumin:

- Curcumin has antioxidant, anti-inflammatory, antiviral and antifungal actions. (7)
- Curcumin have anti-inflammatory activity by inhibition the molecules, which play an important role in case of inflammation. (2)
- Turmeric is effective in reducing post-surgical inflammation. (3)
- Curcumin is also responsible for reducing LDL and increasing HDL, inhibiting platelet aggregation and inflammatory response that reduce the occurrence of myocardial infarction and cardiovascular diseases. (8)
- Curcumin having antifungal, antiviral, anti-inflammatory, antioxidant, neuroprotective, anti-rheumatoid arthritis, anti-osteoarthritis activity.
- Curcumin shows activity against inflammatory bowel disease, arthritis, colitis, gastritis and fever by suppressing the inflammatory markers. (4)
- Turmeric prevent the Growth of H.pylori, which is the main reason for gastric ulcer and linked with cancer of gastric.
- Curcumin acts as a hepatoprotective agent preventing liver fibrosis, it is also considered as an antifibrotic compound. (8)

- Curcumin leads to development of resistance to insulin in patients with diabetes mellitus II. (4)
- Toxicity of heavy metal can be prevented by binding of lead and cadmium with curcumin, it is having protective action towards brain.
- By topical administration of curcumin, anti-psoriatic activity can be observed(8)
- Curcuma longa act as inhibitor of glutathione S-transferase, cyclo-oxygenase and 5-lipoxygenase.
- It is also responsible for improving digestion by increasing the amount of bile from the gall bladder. (8)

Various properties of curcumin can be classified as

Chemical properties:	
Solubility	Soluble in acetone, ethanol, dimethylsulphoxide and is insoluble in water. (3)
Melting point	183^{o}c (3)
Molecular weight	368.37
pH	At pH 3-7 Curcumin acts as H- atom donor Above pH 7 Curcumin's hue is red Above pH 8 Curcumin acts as electron donor (3)

In curcumin the pharmacokinetics property is usually studied in animals, then in humans, that are reviewed. According to the studies, it shows that curcumin manifests very poor oral bioavailability, and forms numerous curcumin metabolites are formed after metabolism like- curcumin glucuronide, curcumin sulfate, hexahydro-curcumin, tetrahydrocurcumin, and dihydrocurcumin. In recent years, several derivatives, analogs and drug vehicle combinations of curcumin were developed by various experimental studies, these experimental outcomes helped in improving absorption and enhancing the systemic bioavailability than the parent drug curcumin. (29)

Pharmacokinetic properties	
Pre- clinical pharmacokinetics	
Oral bioavailability	Low
Administration	Orally, intravenous, intraperitoneal.
Metabolism	Intestine; rapid first pass metabolism
Excretion	In bile (3)
Clinical pharmacokinetics	
Bioavailability	Low
Distribution	Low distribution in hepatic tissue and in other tissues
Metabolism	Efficient first pass metabolism; Intestinal

According to some of experiments the effect of pharmacokinetic parameters of curcumin of a mixture of curcumin with phosphatidylcholine (CU-PC). By using the intestine sac technique in the ex vivo studies indicated that the mixture of CU-PC showed more absorption than using curcumin only.

By using isolated hepatocytes of rats in, In vivo studies and in vitro studies in rats manifests that utilizing CU-PC leads to improvement bioavailability and pharmacokinetics, this enhance the hepatoprotective activity as compared to curcumin alone. (29)

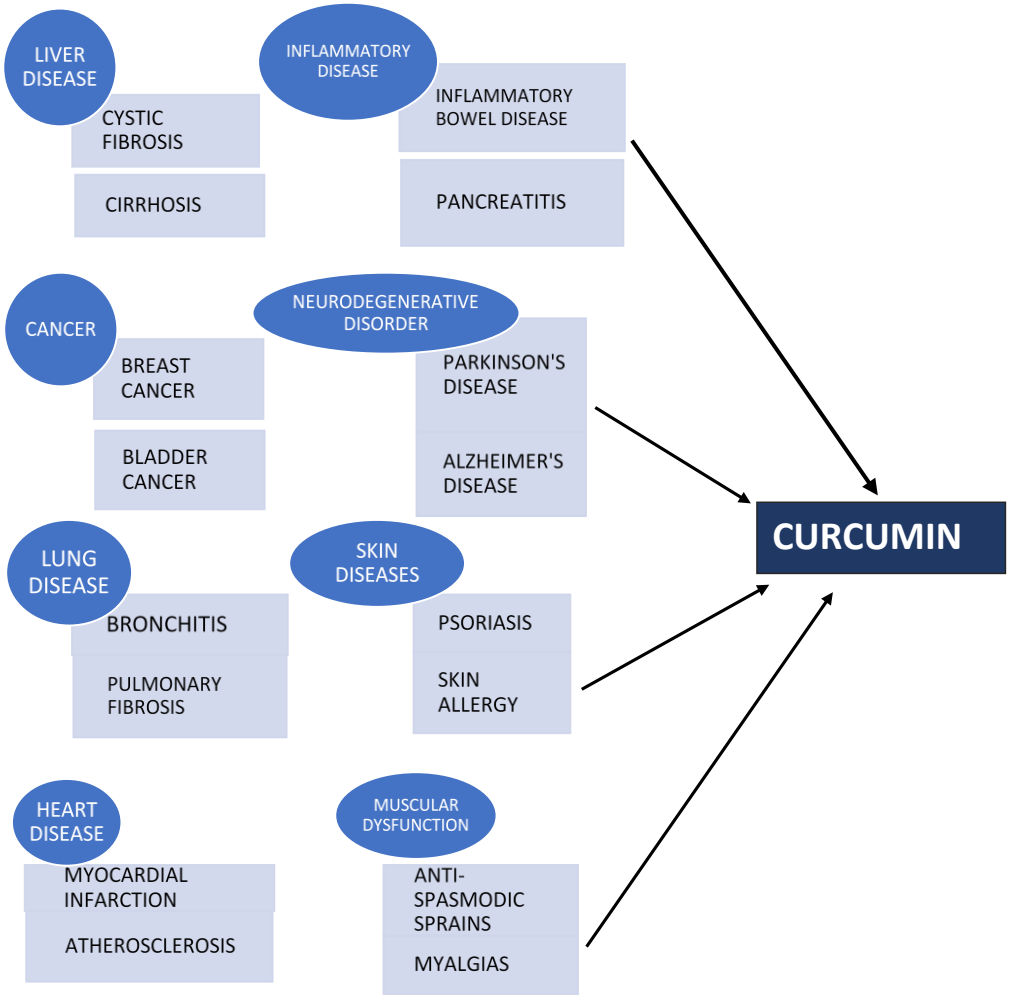


Figure 1: Uses of curcumin in various diseases

As the previous study provides curcumin having low bioavailability, various approaches are used to enhance the bioavailability, by using curcumin nanoparticles, liposomal curcumin and piperine is used as adjuvant. Bioavailability enhanced of curcumin is effective against arthritis, Crohn's disease, diabetes, neurological disease and cancer.

Problems of Curcumin Bioavailability:

There are several factors which affect the bioavailability of any agent like high rate of absorption, low intrinsic activity clearance and fast elimination from the body, low serum level, short half- life, apparent rapid metabolism, and limited tissue distribution.

According to the study which was conducted on the cancer patients mainly on pharmacokinetics, metabolites, and systemic bioavailability of curcumin. A phase I clinical trial was conducted on 25 patients, these patients have several precancerous lesions, oral doses of 4g, 6g and 8g of curcumin was daily administered for three months identification of concentrations of serum curcumin shows that absorption of curcumin is low and system in bioavailability of curcumin is limited. After the dose of curcumin levels in serum increases in 1 to 2 hrs but then decreases rapidly. Although metabolites of curcumin and excretion of curcumin was not identified in the study. (6)

In the phase I of clinical trials, high dose of curcumin that is 12g/day is proven safe for use in humans but the bioavailability that is exhibited is poor. Due to poor absorption, rapid systemic elimination and rapid metabolism the

plasma level and tissue levels of the curcumin is low.

Various approaches have been taken place for the improvement in the bioavailability of curcumin. These approaches include:

- Use of adjuvant like piperine that interferes with glucuronidation
- Use of liposomal curcumin
- Curcumin nanoparticles
- Use of curcumin phospholipid complex
- Use of structural analogues of curcumin (e.g., EF-24).

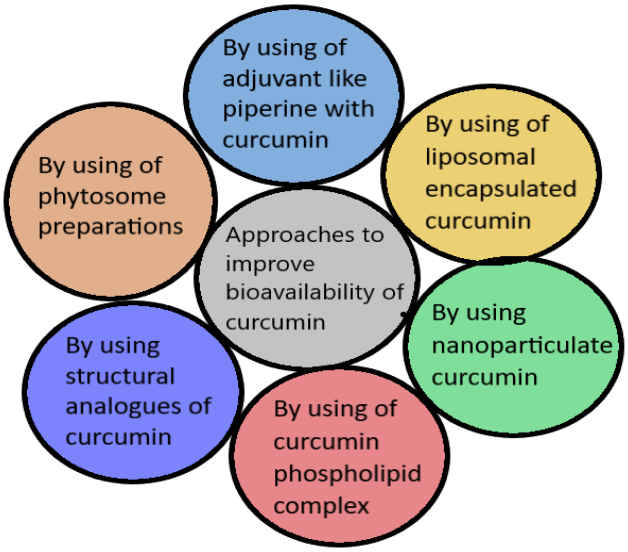


Figure 2: Various approaches to improve bioavailability.

Due to the approaches it has been reported to have rapid absorption with a peak plasma half-life. Although the bioavailability is low but the therapeutic activity of the curcumin for the various diseases, like cancer, cardiovascular diseases, diabetes, arthritis, neurological diseases and Crohn's disease etc. And for treatment of the disease enhancement of bioavailability of the curcumin in the future is necessary. (11)

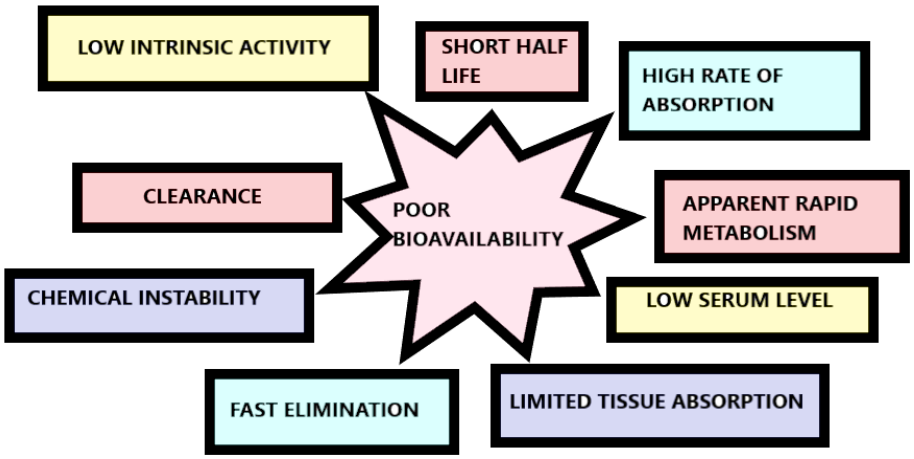


Figure 3: Factors responsible for the poor bioavailability of curcumin

Improvement of bioavailability of curcumin

1. To improve water solubility and bioavailability,

Encapsulation of curcumin was done by liposomes and then they were further coated with thiolated chitosan and formation of liposomal hydrogels takes place. These

hydrogels are liquid in room temperature and can be injected in-situ.

Evaluation: By performing the cytotoxicity test specifies that the cytocompatibility of the liposomal hydrogels is good, but after 72 hrs the MCF-7 cells were suppressed and killed after the encapsulation of curcumin with liposomes. The in vivo breast cancer recurrence experiment showed that the curcumin-liposome gel inhibited breast cancer recurrence after tumors were resected, and the tissue of defect in the CSSH/Cur-Lip gel group was repaired.

Results: According to the above study which proves that the drug-loaded liposomal hydrogels can deliver curcumin continuously and exerted an excellent tumoricidal effect in vitro and in vivo. The injectable, in situ-formable, and thermosensitive CSSH/Cur-Lip gel can be designed as a promising novel drug delivery vehicle to be used as carriers for local accurate and sustained drug delivery to minimize burst release and as tissue engineering scaffolds for tissue regeneration after tumor resection. (12)

2. According to the test performed in the rats with both the preparations phytosome and non-phytosome curcumin extract the bioavailability of the curcumin is determined.

Study:

For overnight the rats were kept on fasting, then the rats administer by mouth the phytosomal or the non-phytosomal preparation. Then after oral gavage,the blood samples were collected at particular interval of time 15, 30, 60, or 120 minutes. By oral gavage at 360 mg/kg body weight curcumin complex was administered, in either phytosome or non-phytosome preparation. (16)

Phytosome preparation	**Non –phytosomal preparation**
Result: According to the study, in the collected blood samples of rats, Curcumin I along with its metabolite's curcumin glucuronide, curcumin sulfate, tetrahydrocurcumin, and hexahydrocurcumin was identified. In this study the plasma absorption of curcumin of the phytosome preparation showed superior from the first 30 minutes for the period 0-120 minutes andfor the curcumin phytosome the AUC values were 5.6 times better. Curcumin I was accumulated in the liver in the phytosome preparation. (16)	Result: According to the study in non-phytosomal preparations, the plasma absorption was low as compared to the phytosomal preparation. Accumulation of curcumin in liver was lower in this preparation. (16)

3. The study of assessing of bioavailability of modulated curcumin in the liver and small intestine.

Study: A total of ten healthy volunteers were orally administered curcumin of 2000 mg with 20 mg of piperine and without 20 mg of piperine randomly in controlled manner to the volunteers. (13)

Dose of curcumin with piperine	**Dose of curcumin without piperine**
Result: When curcumin is administered with piperine in combination, the bioavailability increases to 2000%.	Result: When only curcumin is administered to the volunteers the increase in the bioavailability is much lower as compared with the combination of curcumin and piperine.

4. Study:

Turmeric is a natural product extracted from plants play a major role in healthcare services and in many cultures, both ancient and modern. Chemical constituent of turmeric -curcumin with anti-cancer activity but with poor solubility of water that limits the clinical activity.

Methods: A total of five series of poly (caprolactone)-poly (ethylene glycol)- poly (caprolactone) (PCL-PEG-PCL) triblock copolymers were synthesised. By using solvent evaporation method, the nanoparticles (NPs) were prepared. On the encapsulation of hydrophobic curcumin effect was assigned to the length of the copolymers' hydrophilic and hydrophobic chains to achieve the best delivery system.

Evaluation: By the HNMR, FT-IR, DSC, and GPC techniques the structure of the copolymers was characterized, entrapment efficiency and drug loading assignments was performed and the evaluation of the distribution of particle and by using the

direct dispersion method in-vitro release was evaluated.

Results: In NP_4 has 71% and in NP_5has 83% of efficiency in biodegradable nanoparticulate formulations in which curcumin was encapsulated. The particle diameter in NP4 is 112nm and in NP5 is 110nm measured by the Dynamic laser light scattering (DLS). According to the in vitro release experiments NP5 showed the effective controlled the release of curcumin, in 120 hours only 51% of curcumin was released and these leads to the enhancement of the bioavailability and water solubility of curcumin.

Conclusions: According to the results which indicate that the formulation of curcumin-loaded PCL-PEG-PCL nanoparticles were successful in the improvement of water solubility of curcumin, which shows that it has potential application in cancer treatment. (33)

The main purpose of choosing nanoparticles as drug delivery system so that the surface properties, size of particles and the release of pharmacologically active agents can be managed to attain the site-specific action of the drug at optimal therapeutic rate and dosage regimen. In curcumin which is having low aqueous solubility like in hydrophobic agents, nanoparticle-based delivery systems are used.

According to the recent study on nanocurcumin with the size less than 100 nm which is an application of polymer-based nanoparticle of curcumin. It was observed that this polymer-based nanoparticle of curcumin has similar in vitro activity as that of free curcumin in pancreatic cell lines.

In in-vivo study performed with the healthy volunteers a cream containing curcuminoid loaded SLNs was topically applied over the cream containing free curcuminoid showed the improvement in efficacy. Therefore, various techniques are developing for the nanoparticulate formulations.(22)

Strategies of nanoparticle formulation of curcumin

Formulation	Preparation	Evaluation
1.A novel curcumin nanoparticle system (CURN)	By nanoprecipitation method Curcumin of 50 mg was solubilized in 25 mL of ethanol. The solutions in organic phase were quickly injected into 75 mL of an aqueous solution that containing 300 mg of PVP. During the injection process, at 22000 rpm for 25 min homogenization of the mixed solution takes place. By rotary vacuum evaporation at 40o c in a water bath excessive amount of ethanol is removed from the mixed solution. Approximately, 70 mL left over fraction, comprising of the nanoparticle solution, was the used for the further particle size analysis and stored in a moisture proof instrument for successive characterizations (7)	1.By photon correlation spectroscopy (PCS) 2.Yield and encapsulation efficiency 3.Transmission electron microscopy (TEM) 4.Powder X-ray diffraction (XRD) 5.Fourier transform infrared spectroscopy (FT-IR) 6.Dissolution study (7)
Result: The use of nanoparticle helped in Cell proliferation assay, clonogenic assay, flow cytometry analysis etc. (7)		

Formulation	Preparation	Evaluation
2.NanoCurcTM -The predistilled monomers of NIPAAM, VP and AA are mixed together in a molar ratio of 60:20:20, respectively.	Polymerization was performed for 24 hours at 30°C under an inert gas nitrogen atmosphere, using APS and FeSO4 as initiator and activator, respectively. After complete polymerization, the total aqueous solution of polymer was purified using dialysis, and then lyophilized for post loading of curcumin, Then a stock solution of 10 ml and polymeric nanoparticles of 100 mg was mixed slowly with 150 µl of curcumin solution in chloroform 10 mg/ml, and for 15–20 minutes firmly stirred on low heating, in order to evaporate chloroform and load curcumin simultaneously. The resulting solution, of 1.5% (w/w) loaded with the curcumin in nanoparticles, was then lyophilized and frozen on a dry ice or acetone bath. The nanocurcumin powder which is lyophilized is stored at 4°C until further use. (1)	1.By Cell proliferation assay 2.Apoptosis assay 3.Cell lines and cultures 4.Cell cycle analysis 5.Protein analysis 6.Clonogenic assay 7.Flow cytometry analysis Quantitative PCR analysis (1)
Result: The use of nanocurcumin in pre-clinical in - vivo models of various diseases is beneficial. (1)		

Formulation	Preparation	Evaluation
3.Load CUR into the functionalized surface of the pores of nanocarrier	Dropwise addition of the curcumin solution in acetone to a 5 mg of guanidine functionalized pegylated KIT-6 which was kept for 24 h under inert atmosphere. At 15,000 rpm, the Solid sample was centrifuged for 5 min. The collected solid sample was then washed with 30 ml of ethyl alcohol so that extra curcumin is rinsed away. This is then dried under vacuum to get the loaded curcumin.	To evaluate the CUR-loading efficiency, the supernatant and washed solutions were collected and the residual CUR content was measured by using UVevis measurement(9)
Result: These XRD diffractograms generally confirmed that [Gu@PEGylated KIT-6] were successfully prepared for the desirable potential applications. To quantify the porous nature of the particles, the N2 adsorptionedesorption isotherm experiment was carried out. It has revealed a high pore volume and surface area in the synthesized KIT-6. (9)		

Formulation	Preparation	Evaluation
4.To evaluate the anticancer potential of curcumin within βCD-C complexes and liposomes, cell proliferation assays were performed using lung and colon cancer cell lines	At 37^{o} c temperature in 5% of CO2 10,000 cells per well are grown and seeded in 96-well plates. For 24 hrs the cells were attached before removing from the media the cells were then ready for the formulations. The samples were then added that were curcumin entrapped liposomes, βCD-C complex-entrapped liposomes, curcumin, βCD-C complexes, PBS, 0.25% DMSO and βCD, all this was prepared in PBS (except the curcumin dissolved in 0.25% DMSO) For 48 hrs the cells were incubated and a MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5diphenyltetrazolium bromide) cell viability assay was performed. Amount of PBS, DMSO and βCD were used as controls. As a percentage of cell growth, the calculation of the antiproliferative activity was done. And lastly, values of EC50 of each formulation was estimated by interpolating from the graph. (10)	1.Cell viability assay
Result: The median effective dose (EC50) of the formulations on colon cancer cells were calculated to be 0.96 μM for curcumin-entrapped liposomes, 1.9 μM for curcumin, 2.95 μM for βCD-C complexes and 3.25 μM for liposomes containing βCD-C. The EC50 of the formulations on lung cancer cells followed the same pattern, being 0.90 μM for curcumin-entrapped liposomes, 1.5 μM for curcumin, 2.4 μM for βCD-C and 2.9 μM for liposomes containing βCD-C. liposomal formulations containing native curcumin the most effective in preventing cell proliferation. However, all curcumin-containing formulations appeared to be effective in inhibiting cell proliferation. (10)		

Formulation	Preparation	Evaluation
5. Guanidine functionalized PEGylated mesoporous silica nanoparticles as a novel and efficient drug delivery system (DDS).	The particle size of Guanidine functionalized PEGylated mesoporous silica nanoparticles and curcumin loaded with Guanidine functionalized PEGylated mesoporous silica nanoparticles were about 60 and 70nm respectively. These type of nanoparticles shows high capacity of drug loading, has high and long-term anticancer efficiency in human cancer cell lines, profile of sustained drug release	Different techniques are used to characterize the modified mesoporous silica nanoparticles (MSNs)such as 1. Transmission and scanning electron microscopy (TEM & SEM) 2. N_2 adsorption-desorption measurement 3. Thermal gravimetric analysis (TGA) 4. X-ray powder diffraction (XRD) 5. Dynamic light scattering (DLS).
Result: This study showed that the use of nanoparticles only showed no cytotoxicity affect against breast cancer cells in mouse, breast adenocarcinoma cells in humans and mammary epithelial cells in humans, and it shows increased release of curcumin that leads to in vitro breast cancer therapy. (9)		

Studies of the evaluation of in- vitro characteristics and in-vivo characteristics of curcumin nanoparticulate formulation.

1. Study: To fabricate biodegradable nanoparticle formulation of bis-demethoxycurcumin analogue (BDMCA), a novel curcumin analogue, and evaluate its in vitro and in vivo characteristics.

Methods: Nanoparticle formulations were fabricated by a double emulsion solvent evaporation technique using polycaprolactone as the polymer. The nanoparticles were characterised for drug content, particles size, in vitro drug release and the drug-polymer interaction. The in vivo properties of the formulations in male Wistar rats were evaluated from the pharmacokinetics and pharmacodynamics of BDMCA following i.v. administration of the nanoparticles. BDMCA solution was administered i.v. as a reference, hepatoprotectivity of the formulation was determined in a CCl4-treated rat model.

Results: The BDMCA nanoparticles were successfully prepared using double emulsion solvent evaporation technique. The nanoparticle formulations effectively sustained the release of the drug for more than 10 days both in vitro and in vivo. They also offered better pharmacokinetic

properties to the drug than that afforded by the free drug itself. Intravenous nanoparticular administration reversed serum liver enzyme levels by 90%, compared to 52 % for repeated i.v. administration of the solution form.

Conclusion: BDMCA particle demonstrated good pharmacokinetic and pharmacodynamic properties following i.v. administration. (21)

2. Study: In Vivo Kinetic Study of the TPGS-Stabilized Curcumin Nanoparticle after Oral Administration.

Method: Male Wistar rats of 200g weight with an age of 2 months were used in this study. The animals were fasted for 12 h prior to the experiment but given free access for water ad libitum. Animals were divided into two groups of six rats each, and given TPGS-curcumin suspension or TPGS-stabilized curcumin nanosuspension orally with the same dose of 10 mg/kg BW. Blood sampling of 500 µL was performed through the tail vein at the interval times: 0; 0.25; 0.5; 1; 2; 4; 8; 12, and 24 h after oral administration. The blood samples were placed into heparinized tubes.

Evaluation: To obtain plasma, the heparinized blood samples were centrifuged at 12,500 rpm for 5 min. Curcumin in plasma samples were determined by the HPLC method. Prior to HPLC analysis, 200 µL of plasma was added with 80 µL aquabidest, vortexed for 20 s. Ethyl acetate of 480 µL was further added to the plasma-aquabidest mixture, and againvortexedfor30s. Subsequently, the mixture was centrifuged at 13,000 rpm. The organic phase of 450 µL was taken and vacuum-dried. Theresiduewasre-dissolvedin100 µL of mobile phase, vortexed for 30 s, and was then ready for HPLC analysis.

In vivo parameters of curcumin were calculated using computer software multifit (26)

CONCLUSION

Curcumin is the yellow polyphenolic compound extracted from the rhizome of curcuma longa belong to the ginger family of Zingiberaceae, turmeric is available in yellow colour mainly obtained from polyphenolic pigment and fat-soluble substance called as curcuminoids. There are several factors which effect the bioavailability of curcumin, therefore various approaches have been taken place for the improvement in the bioavailability of curcumin that are- byencapsulating of curcumin by liposomes, by using solvent evaporation method, preparation of the nanoparticles, preparations phytosome and non-phytosome curcumin etc. Nanoparticles are selected as drug delivery system and various formulations are developed as in-vivo study performed with the healthy volunteers a cream containing curcuminoid loaded SLNs was topically applied over the cream containing free curcuminoid showed the improvement in efficacy. Various formulations are a novel curcumin nanoparticle system (CURN), Guanidine functionalized PEGylated mesoporous silica nanoparticles as a novel and efficient drug delivery system (DDS), Load CUR into the functionalized surface of the pores of nanocarrier, nanoCurcTM -The predistilled monomers of NIPAAM, VP and AA are prepared and evaluated which are beneficial in various purposes. Evaluation of in-vitro and in-vivo characteristics of curcumin nanoparticle formulation includes - Biodegradable nanoparticle formulation of bis-demethoxycurcumin analogue and TPGS-Stabilized Curcumin Nanoparticle strategies which demonstrates good pharmacokinetic and pharmacodynamic properties following i.v. administration.

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