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A REVIEW ARTICLES ON CURCUMIN IS A NOVEL DRUG AND ITS ANTICANCER ACTIVITY

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ABSTACT
Curcumin is a potential drug for various diseases including cancer. Prime limitations associated with curcumin are low water solubility, rapid hydrolytic degradation and poor bioavailability. Numerous studies have demonstrated that curcumin possesses anti-oxidant, anti-inflammatory and anticancerous properties. The purpose of this review is to focus on the anti-tumor effects of curcumin. More recently curcumin has been found to possess anti-cancer activities via its effect on a variety of biological pathways involved in mutagenesis, oncogene expression, cell cycle regulation, apoptosis, tumorigenesis and metastasis. Curcumin has been studied in multiple human carcinomas including melanoma, head and neck, breast, colon, pancreatic, prostate and ovarian cancers. Curcumin has the activity to inhibit cell proliferation, cytochrome P450 isoenzymes. It suppress certain oncogenes. It inhibits cell-cycle-related proteins, tumor implantation. Curcumin has been used extensively in Ayurvedic medicine for centuries, as it is nontoxic and has a variety of therapeutic properties including anti-oxidant, analgesic, anti-inflammatory and antiseptic activity. This novel curcumin has an opportunity to treat cancer with SLN making formulation, nanospheres, liposomes, in a better manner with lower dose by Homogenous SLN which obtain by Homogenization –ultrasonication method. Curcumin is one such potential candidate. The study postulates the drug form has the potential to be used as an anticancer agent in affected human subjects.

KEYWORDS: Curcumin, Anticancer drug, Bioavaiability, Solid lipid nanoparticles, Homogenisation.

INTRODUCTION

Despite progress in the development of strategies for cancer prevention and diagnosis, the disease continues to remain the leading cause of death worldwide. Although chemotherapy is a widely practiced treatment modality, this method has several limitations. Most of the currently used chemotherapeutics suppress the immune system, predisposing cancer patients to secondary infections.[1]

Turmeric is a spice derived from the rhizomes of *Curcuma longa*, which is a member of the ginger family (*Zingiberaceae*). Rhizomes are horizontal underground stems that send out shoots as well as roots {(Fig.1) A. Turmeric plant with root, B.Turmeric buds}. The bright yellow color of turmeric comes mainly from fat-soluble, polyphenolic pigments known as curcuminoids). Curcumin, the principal curcuminoid found in turmeric, is generally considered its most active constituent. Other curcuminoids found in turmeric include demethoxycurcumin and bisdemethoxycurcumin. In addition to its use as a spice and pigment, turmeric has been used in India for medicinal purposes for centuries. More recently, evidence that curcumin may have anti-inflammatory and anticancer activities has renewed scientific interest in its potential to prevent and treat disease.

Fig. 1: A.Turmeric Plant with Root B. Turmeric buds.

Tumeric is the dried ground rhizome of *Curcuma longa* Linn.[2] It is used as a spice in Indian, Southeast Asian, and Middle Eastern cuisines. Curcuminoids comprise about 2-9% of turmeric.[3] Curcumin is the most abundant curcuminoid in turmeric, providing about 75% of the total curcuminoids, while demethoxycurcumin provides 10-20% and bisdemethoxycurcumin generally provides <5%. Curry powder contains turmeric along with other spices, but the amount of curcumin in curry powders is variable and often relatively low.[4] Curcumin extracts are also used as food coloring agents.[5] Although curcumin has shown a wide range of pharmacological activities, its anticancer activity have attracted a great interest.

Properties of Curcumin

Curcumin is insoluble in water under acidic or neutral conditions (0.1 mg/ml) but dissolves in alkaline environment (3 mg/ml). Curcumin is hydrophobic in nature and frequently soluble (1 mg/ml) in acetone (20 mg/ml), ethanol, dimethylsulfoxide, dimethyl formamide and oils. Curcumin is highly unstable undergoing rapid hydrolytic degradation in neutral or alkaline conditions to feruloyl methane and ferulic acid. It is reported to be stable below pH 6.0. Thus, the use of curcumin is limited by its poor aqueous solubility in acidic or neutral conditions and instability in alkaline pH. This leads to slow dissolution and reduced bioavailability to incomplete oral absorption 60%, such that therapeutic effects are essentially limited to the tubular lower GI tract (i.e., colorectum).

Phase I clinical trials have shown that curcumin is safe even at high doses (12 g/day) in humans but exhibits poor bioavailability. The development of a delivery system that can enable parenteral administration of curcumin in an aqueous phase medium will significantly harness the potential of this promising anti-cancer agent in the clinical area. Several approaches to enhance the solubility of Curcumin in such as chemical derivatisation, complexation or interaction with macromolecules e.g. gelatin, polysaccharides, protein, and cyclodextrin have been reported but not successful yet in practical utility.

Curcumin as a food additive

Turmeric is an ingredient of spice blends, mainly curry powder, which generally consists of turmeric, clove, paprika, ginger, cardamom, coriander, cumin, mace, pepper and cinnamon. Turmeric is commonly used as natural pigment (yellow 3) in the cosmetic and textileproduction but it is widely used in food industry. Indeed, turmeric isclassified as an additive in E100 category and is used as food color additive in mustard, pastries, daily products and canned fish.[6] Furthermore, according to the Joint FAO/WHO Expert Committee on Food Additives (JECFA) the admissible daily intake (ADI) is 0–3 mg/kg body weight and it was established at the 61st JECFA in 2003.[7]

Curcumin: traditional uses in folk medicine and biological properties

Curcuminoids have been consumed as therapeutic infusions over the centuries worldwide. In Ayurvedic medicine, curcumin isa well-documented treatment for various respiratory conditions such as, asthma, bronchial hyperactivity and allergy, as well as forliver disorders, anorexia, rheumatism, diabetic wounds, runny nose,cough and sinusitis.[8] In traditional Chinese medicine curcumin has been used to treat diseases associated with abdominal pain.[9] In ancient Hindu medicine, it was used to treat sprains and swelling.[10] In Oriental cultures, it has traditionally been used asgood therapeutic alternative, particularly as an anti inflammatory,antioxidant, anticarcinogenic and antimicrobial reagent. In fact, ithas scientifically proven that curcumin is indeed antioxidant.[11,12,13,14] anti-inflammatory,[15,16] and antibacterial,[17] Moreover, it has also been used because of its hepatoprotective,[18] thrombosuppressive, neuroprotective,[19] cardioprotective,[20] antineoplasic,[21] antiproliferative,[22] hypoglycemic and antiarthritic effect,[23] Curcumin has also been used for the treatment of intestinal parasites and as a remedy for poisoning, snakebites and various other complaints.[24]

Chemistry and structural characterization of curcumin

CUR [(1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione or diferuloylmethane, 1] (Figure 1) belongs to a class of chemicals called flavonoids which induces turmeric's yellow color.[25] Turmeric consists of 2–5% CUR. For the first time, CUR was purified from turmeric, and the chemical formula was found as diferuloylmethane.[26] Recent study shows that CUR's samples include nearly 4% bisdemethoxycurcumin, 20% demethoxycurcumin, and 76% diferuloylmethane.[26] According to these structures, CUR has a seven carbon

linker and three major functional groups including an alpha, beta-unsaturated beta-diketone moiety and an aromatic o-methoxy phenolic group.[26] The antioxidant activity of CUR is related to the omethoxyphenol group and methylenic hydrogen and it also contributes an electron/hydrogen atom to free radicals. The alpha, beta unsaturated beta-diketone moiety strongly via Michael reaction acts with protein thiols.[26] CUR acts as a chelator of heavy metals via interaction of beta-diketo groupwith transition metals, thereby decreasing metal toxicity.[27] CUR is a hydrophobic compound and mostly dissolvable in acetone, oils, ethanol, and, dimethylsulfoxide. In acidic condition, the dye of turmeric/CUR changes from amber to dark red.[26] Among three analogs, CUR exhibits most potent activity in some systems.[28] CUR is metabolized into curcumin sulfonate and curcumin glucuronide after orally prescription and metabolized into hexahydrocurcuminol, tetrahydrocurcumin (THC), and hexahydrocurcumin after i.p. injection,[28] THC has been activated in some circumstance; however, the biological activity of CUR is not known. Fig. 2.

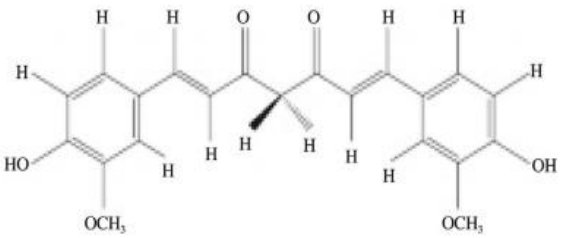

Fig. 2: Structure of Curcumin.

Biological activities of curcumin

Antioxidant Activity

Curcumin is an effective scavenger of reactive oxygen species and reactive nitrogen species in the test tube (*in vitro*),[29,30] However, it is not clear whether curcumin acts directly as an antioxidant in vivo. Due to its limited oral bioavailability in humans (see Metabolism and Bioavailability above), plasma and tissue curcumin concentrations are likely to be much lower than that of other fat-soluble antioxidants, such as alpha-tocopherol (vitaminE). However, the finding that oral curcumin supplementation (3.6g/day) for seven days decreased the number of oxidative DNA adducts in malignant colorectal tissue suggests that curcumin taken orally may reach sufficient concentrations in the gastrointestinal tract to inhibit oxidative DNA damage.[31] In addition to direct antioxidant activity, curcumin may function indirectly as an antioxidant by inhibiting the activity of inflammatory enzymes or by enhancing the synthesis of glutathione, an important intracellular antioxidant (see below).

Anti-inflammatory activity

The metabolism of arachidonic acid in cell membranes plays an important role in the inflammatory response by generating potent chemical messengers known as eicosanoids.[32] Membrane phospholipids are hydrolyzed by phospholipase A2 (PLA2), releasing arachidonic acid, which may be metabolized by cyclooxygenases (COX) to form prostaglandins and thromboxanes, or by lipoxygenases (LOX) to form leukotrienes. Curcumin has been found to inhibit PLA2, COX-2, and 5-LOX activities in cultured cells.[33] Although curcumin inhibited the catalytic activity of 5- LOX directly, it inhibited PLA2 by preventing its phosphorylation and COX-2 mainly by inhibiting its transcription. Nuclear factor-kappa B (NF-kB) is a transcription factor that binds DNA and enhances the transcription of the COX-2 gene as well as other pro inflammatory genes, such as inducible nitric oxide synthase (iNOS). In inflammatory cells, such as macrophages, iNOS catalyzes the synthesis of nitric oxide, which can react with superoxide to form peroxynitrite, a reactive nitrogen species that can damage proteins and DNA. Curcumin has been found to inhibit NF-kB-dependent gene transcription,[34] and the induction of COX-2 and iNOS in cell culture and animal studies.

Effects on biotransformation enzymes involved incarcinogen metabolism

Biotransformation enzymes play important roles in the metabolism and elimination of a variety of biologically active compounds, including drugs and carcinogens. In general, phase I biotransformation enzymes, including those of the cytochrome P450 (CYP) family, catalyze reactions that increase the reactivity of hydrophobic (fat-soluble) compounds, preparing them for reactions catalyzed by phase II biotransformation enzymes. Reactions catalyzed by phase II enzymes generally increase water solubility and promote the elimination of these compounds.[35] Although increasing biotransformation enzyme activity may enhance the elimination of potential carcinogens, some carcinogen precursors (procarcinogens) are metabolized to active carcinogens by phase I enzyme.[36] CYP1A1 is involved in the metabolic activation of several chemical carcinogens. In cell culture and animal studies, curcumin has been found to inhibit procarcinogen bioactivation or measures of CYP1A1activity.[37,38] Increasing phase II biotransformation enzyme activity is generally thought to enhance the elimination of potential carcinogens. Several studies in animals have found that dietary curcumin increased the activity of phase II enzymes, such as glutathione Stransferases (GSTs).[39,40] However, curcumin intakes ranging from 0.45-3.6g/day for up to four months did not increase leukocyte GST activity in humans.[41]

Inductions of cell cycle arrest and apoptosis

After a cell divides, it passes through a sequence of stages—collectively known as the cell cycle—before it can divide again. Following DNA damage, the cell cycle can be transiently arrested to allow for DNA repair or, if the damage cannot be repaired, for activation of pathways leading to cell death (apoptosis).[42] Defective cell-cycle regulation may result in the propagation of mutations that contribute to the development of cancer.

Curcumin has been found to induce cell-cycle arrest and apoptosis in a variety of cancer cell lines grown in culture.[43] The mechanisms by which curcumin induces apoptosis are varied but may include inhibitory effects on several cell-signaling pathways. However, not all studies have found that curcumin induces apoptosis in cancer cells. Curcumin inhibited apoptosis induced by the tumor suppressor protein p53 in cultured human colon cancer cells.[44] and one study found that curcumin inhibited apoptosis induced by several chemotherapeutic agents in cultured breast cancer cells at concentrations of 1-10 micromoles/liter.

Effects on autophagic cell death

Autophagy is a catabolic process in which cells break down their own components via engulfment in vacuoles and degradation through the lysosomal system. The hallmark of autophagy is thus the formation of these so-called "autophagosomes", double layered vacuoles which contain cytoplasmic proteins and organelles targeted for degradation upon fusion with the lysosome.[45] Autophagy is a housekeeping process by which cells may dispose of old or damaged cytoplasmic organelles and proteins, and also serves an adaptive function under conditions of nutrient stress by allowing cells to recycle endogenous biosynthetic substrates such as amino acids. In addition to promoting cell survival and function, autophagy is also a method by which cells may undergo programmed cell death.[46] Autophagy is considered Type II programmed cell death (apoptosis is type I and necrosis is type III) and, thus has come under interest as a potential process that may be exploited in the development of anti-cancer chemotherapeutics. The possible roles of autophagy in carcinogenesis as well as tumor regression in response to therapy are still being elucidated, with seemingly conflicting studies suggesting that induction of autophagy enhances cell death in certain tumor types while mediating chemotherapeutic resistance in others. On one hand, there is evidence that autophagy may be employed by cancer cells to facilitate growth under the stressful metabolic conditions commonly encountered in the tumor microenvironment (such as hypoxia and decreased availability of glucose and other nutrients due to poor vascularization).[47] In addition, the induction of autophagy as an adaptive response mediating resistance to chemotherapy has been observed in multiple tumor types including malignant gliomas, lymphoma, breast, lung and hepatocelluar carcinomas.[48,49] While autophagy appears to play a role in mediating chemoresistance in certain cancers as described above, there is also data supporting that autophagy may also induce non-apoptotic cell death in response to chemotherapy. In human (MCF-7) estrogen receptor positive breast cancer, both tamoxifen and paclitaxel were found to induce autophagic cell death in cell culture.[48] while autophagy induced by arsenic trioxide resulted in increased cell death, treatment with temolozamide and etoposide led to an increase in ATP that exerted a protective effect.[50] Likewise, there is controversy regarding the effect of autophagy induction on radiation sensitivity. Studies in breast cancer have suggested that vitamin D-dependant radiosensitization is mediated through autophagy, while autophagy has demonstrated both radiosensitizing and dampening effects in malignant gliomas.[51] Curcumin has been shown to be an inducer of autophagic cell death in chronic myelogenous leukemia, esophageal cancer and malignant glioma cells.[52] In malignant glioma cells, curcumin induced G2/M cell cycle arrest and non-apoptotic autophagic death. While the current data on autophagy and cancer is far from providing a consensus, it is evident that regulation of this process may play an important role in tumorigenesis and response to therapy thus making pharmacologic modulators of autophagy attractive candidates for further study.

Inhibition of tumor invasion and angiogenesis

Cancerous cells invade normal tissue with the aide of enzymes called matrix metalloproteinases. Curcumin has been found to inhibit the activity of several matrix metalloproteinases in cell culture studies.[53] To fuel their rapid growth, invasive tumors must also develop new blood vessels by a process known as angiogenesis. Curcumin has been found to inhibit angiogenesis in cultured vascular endothelial cells and in an animal model.[54]

Curcumin as anticancer drugs

Curcumin has been shown to suppress transformation, proliferation, and metastasis of tumours. These effects are mediated through its regulation of various transcription factors, growth factors, inflammatory cytokines, protein kinases, and other enzymes. It also inhibits proliferation of cancer cells by arresting them in various phases of the cell cycle and by inducing apoptosis. Moreover, Curcumin has the ability to inhibit carcinogen bioactivation via suppression of specific cytochrome P450 isozymes, and to induce the activity or expression of phase II carcinogen detoxifying enzymes, which may account for its cancer chemopreventive effects. Curcumin has been shown to have protective and therapeutic effects against cancers of the blood, skin, oral cavity, lung, pancreas, and intestinal tract, and to suppress angiogenesis and metastasis in rodents. Curcumin inhibits P-gp (drug efflux protein) for which, removal of cytotoxic drugs can’t happens from the cancer cells and the drug substances can exert their pharmacological effects.[55] Cancerous tumours are characterized by cell division, which is no longer controlled as it is in normal tissue. "Normal" cells stop dividing when they come into contact with like cells, a mechanism known as contact inhibition. Cancerous cells lose this ability. Cancer cells no longer have the normal checks and balances in place that control and limit cell division. The process of cell division, whether normal or cancerous cells, is through the cell cycle. The cell cycle goes from the resting phase, through active growing phases, and then to mitosis (division).

The ability of chemotherapy to kill cancer cells depends on its ability to halt cell division. Usually, the drugs work by damaging the RNA or DNA that tells the cell how to copy itself in division. If the cells are unable to divide, they die. The faster the cells are dividing, the more likely it is that chemotherapy will kill the cells, causing the tumour to shrink. They also induce cell suicide (self-death or apoptosis). Chemotherapy drugs that affect cells only when they are dividing are called cell-cycle specific. Chemotherapy drugs that affect cells when they are at rest are called cell-cycle non-specific. The scheduling of chemotherapy is set based on the type of cells, rate at which they divide, and the time at which a given drug is likely to be effective. This is why chemotherapy is typically given in cycles.

In vitro and animal studies have proven that curcumin has anti-tumor, anti-oxidant, anti-arthritic, anti-amyloid, anti-ischemic and anti-inflammatory properties. Its potential anticancer effects stem from its ability to induce apoptosis in cancer cells without cytotoxic effects on healthy cells. Curcumin can interfere with the activity of the transcription factor NF-κB, which has been linked to a number of inflammatory diseases such as cancer. Curcumin affected expression of metallothionein genes, tubulin genes, p53 and other genes involved in colon carcinogenesis. Curcumin has multiple therapeutic activities against the diseases of the cardiovascular, loss of bone and muscle, depression and neuropathic pain.[56]

Solid Lipid Nanoparticle

Nanoparticles are solid colloidal particles which are ranging from 10 to 1000 nm (1.0 μm), in which the active principles mean drug or biologically active material are dissolved, entrapped, and to which the active principle is adsorbed or attached. Significant effort has been devoted in recent years to develop nanotechnology for drug delivery, since it offers a suitable means of delivering small molecular weight drugs, as well as macromolecules such as proteins, peptides or genes to cells and tissues and prevents them against enzymatic degradation. Main advantages of nanoparticles as drug delivery systems are that they are biodegradable, non-toxic, and capable of being stored for longer periods of time as they are more stable.[57]

For poorly water soluble drugs Solid lipid nanoparticles (SLNs) are introduced as a carrier system for that type of drug. The drug delivery in nanoparticle depends on their ability to penetrate through several anatomical barriers, sustained release of the contents and their stability in the nanometer size. Due to their high cost and scarcity of safe polymers they have some limitations with regulatory approval. For overcoming this limitation lipid is used as an alternative system in polymeric nanoparticles. These nanoparticles are known as solid lipid nanoparticles (SLNs). An alternative system for polymeric nanoparticles, liposome and emulsion SLNs are developed. SLNs possess unique property like small size, large surface area, high drug loading and interaction of phase at the interphase. For intravenous application SLNs are attracting major attention in novel colloidal carrier. SLNs are the one of the new generation of submicron-sized lipid emulsions where the liquid lipid (oil) has been substituted by a solid lipid.[58]

Advantages of solid lipid nanoparticles

- SLNs possess better stability and ease of upgradability to production scale as compared to liposome.
- In case of SLNs the lipid matrix is made up of physiological lipid which decreases the chances of acute and chronic toxicity.
- Stability is very high.
- Manufacturing of SLN is easy than bipolymeric nanoparticles.
- It has better control over release kinetics of encapsulated compound.
- The bioavailability of entrapped bioactive can be enhanced by making it in the form of SLNs.
- SLN can provide better chemical protection to the labile incorporated compound.
- In case of SLNS raw material which are to be required are same as that of emulsion.
- Production in large scale is possible.
- Functional compound can be achieved in high concentration.
- Lyophilization is possible.[59]

Disadvantage of solid lipid nanoparticles

- Drug loading capacity is poor.
- Drug expulsion after polymeric transition is occur during storage.
- It contains relatively high water content of the dispersions (70-99.9%).
- SLN have low capacity to load hydrophilic drugs due to partitioning effects during the production process.[60]

Preparation of SLNs

Generally, SLNs are made up from solid lipid, emulsifier and water/solvent by using different method. The lipids which may be used are triglycerides (tri-stearin), partial glycerides (Imwitor), fatty acids (stearic acid, palmitic acid), steroids (cholesterol) and waxes (cetyl palmitate). In SLNs various emulsifiers and their combination are used to stabilize the lipid dispersion. The different combination of emulsifiers is used to prevent particle agglomeration more efficiently.

- High pressure homogenization

1. Hot homogenization
2. Cold homogenization

- Ultrasonication/high speed homogenization
- Solvent evaporation method
- Solvent emulsification-diffusion method
- Supercritical fluid method
- Microemulsion based method
- Spray drying method

- Double emulsion method
- Precipitation technique
- Film-ultrasound dispersion.[61]

High Pressure Homogenization (HPH)

HPH is the one of the reliable and powerful technique, which is mainly used for the production of SLNs. A liquid is pushed with high pressure (100–2000 bar) through a narrow gap (in the range of a few microns) in case of High pressure homogenizers. In a very short distance the fluid accelerates on to very high velocity (over 1000 Km/h). The particles are disrupting by very high shear stress and cavitation forces to the submicron range. Generally, SLN contain 5-10% of lipid but up to 40% lipid content has also been investigated. Under HPH two general approaches are there, hot homogenization and cold homogenization, which are work on the same concept of mixing the drug in bulk of lipid melt.

Hot homogenization:

At temperatures above the melting point of the lipid hot homogenization is carried out and can therefore be regarded as the homogenization of an emulsion. A pre-emulsion of the drug loaded lipid melt and by high-shear mixing device the aqueous emulsifier phase (same temperature) is obtained. At temperatures above the melting point of the lipid HPH of the pre-emulsion is carried out. In general, higher temperatures lower particle sizes are results due to the decreased viscosity of the inner phase. However, the degradation rate of the drug and the carrier increases with high temperatures. The size of the particle increases by increasing the homogenization pressure or the number of cycles often results in a due to high kinetic energy of the particles. Many SLNs have been prepared by this method for anticancer therapy: Eg: Edelfosine,[62] 5-Fluorouracil,[63] Resveratrol,[64] Retinoic acid.[65]

Cold homogenization

Cold homogenization has been developed to minimize the various problems associated with hot homogenization such as: Temperature-induced drug degradation, drug distribution into the aqueous phase during homogenization, problem associated with complexity of the crystallization step of the nanoemulsion leading to several modifications and/or super cooled melts. In this technique first cooled the drug containing lipid which are melted, then solid lipid ground to lipid microparticles and after that these lipid microparticles are dispersed in a cold surfactant solution yielding a pre-suspension. Then this pre-suspension is homogenized through homogenizer at or below room temperature, the gravitation force is strong enough to break the lipid microparticles directly to solid lipid nanoparticles**.** Many SLNs have been prepared by this method for anticancer therapy like Ketoconazole.[62]

Advantages

- It has low capital cost.
- Demonstrated at lab scale.

Disadvantages

- Energy intensive process.
- Demonstrated at lab scale Biomolecule damage.
- Polydisperse distributions.
- Unproven scalability.

Ultrasonication/High Speed Homogenization:

By an ultrasonic and high speed homogenization method SLNs were successfully prepared to improve the oral bioavailability of the poorly water-soluble drug like cryptotanshinone. The incorporation of drug in SLNs had markedly changed the metabolism behavior and absorption is enhanced significantly by employing SLN formulations. It is very simple and it can have many advantageous properties over other method like hot and cold homogenization because the equipment used in here for this technique is very common in every lab.[64] Many SLNs have been prepared by this method for anticancer therapy like: Eg: Gemcitabine Hydrochloride.[65]

Advantages

- Reduced Shear Stress

Disadvantages

- Metal contamination due to ultrasonication.
- Physical instability like particle growth upon storage.

Solvent Evaporation

SLNs can also prepared by Solvent evaporation method. Here nanoparticle is formed by dissolving the lipophilic material in solvent that does not blend with water (e.g. cyclohexane), emulsified in the water phase. The nanoparticle dispersion is created after evaporating solvent through precipitating the lipid in water phase. The diameter of the particles was found upto 25 nm. In an aqueous phase the solution was emulsified by high pressure homogenization. The emulsion is then evaporated under reduced pressure (40–60 mbar) for the removing of organic solvent.[66] Many SLNs have been prepared by this method for anticancer therapy like: Eg: Solid Lipid Nanoparticle of Docetaxel Prepared with High Melting Point Triglycerides, Paclitaxel Loaded SLN Using Glyceryl Monostearate.

Advantages

- Scalable.
- Mature technology.
- Continuous process.
- Commercially demonstrated.

Disadvantages

- Extremely energy intensive process.
- Polydisperse distributions.
- Biomolecule damage.

Solvent Emulsification-Diffusion Method

This technique is used to get the particles size with average diameters of 30-100 nm. The one most important advantage of this technique is that voidance of heat

during the preparation. The solvent which are used here must be partially miscible with water and this technique will be carried out either in aqueous phase or in oil.[67] Many SLNs have been prepared by this method for anticacer therapy like: Eg: Silibinin loaded Solid Lipid Nanoparticles, Isoniazid.

Supercritical Fluid Method:
This is one of the alternative method of preparing SLNs by particles from gas saturated solutions (PGSS-Particles from Gas-saturated Solutions/Suspensions). Here, SLN can be prepared by the rapid expansion of supercritical carbon dioxide solutions and this method is called as RESS (Rapid Expansion of Supercritical Solutions) method. Carbon dioxide with 99.99% is used here, which is one of the good solvent.

Advantages
- Use of solvents is avoided
- Instead of suspensions, in this particles are obtained as a dry powder,
- Mild pressure and temperature conditions

Microemulsion Based Method
This method is mainly based on the dilution of microemulsions. As micro-emulsions are two-phase systems in which inner and outer phase (e.g. o/w microemulsions) are there. They are mainly made by stirring an optically transparent mixture at 65-70°C, which typically composed of a low melting fatty acid (e.g. stearic acid), an emulsifier (e.g. polysorbate 20), co-emulsifiers (e.g. butanol) and water. Then under stirring hot microemulsion is dispersed in cold water (2-3°C). As granulation fluid SLN dispersion can be used for transferring in to solid product (tablets, pellets) by granulation process, but too much of water needs to be removed in case of low particle content. High-temperature promote rapid lipid crystallization and inhibit aggregation. Due to this dilution step; lipid contents are considerably lower when compared with the HPH based formulations.

Advantages
- Low mechanical energy input.
- Theoretical stability.

Disadvantages
- Extremely sensitive to change.
- Labour intensive formulation work.
- Low nanoparticle concentrations

Spray Drying Method
Spray-drying is the one-step process which converts a liquid feed to a dried particulate form. The feed which is used here generally is a solution, but it can also be a coarse or fine suspension or a colloidal dispersion (e.g., emulsions, liposomes, etc.); after this feed is first atomised through a various technique like (centrifugal, pneumatic, ultrasonic and electrostatic atomisation) to a spray form, it will then put immediately into thermal contact with a hot gas, which results in the rapid evaporation of the solvent to form dried solid particles. Then for separating dried particles from the gas is done by the means of a cyclone, an electrostatic precipitator or a bag filter.[68]

Double Emulsion Method
For the preparation of hydrophilic loaded SLN, one of the novel methods is used based on solvent emulsification-evaporation. Here the drug to be incorporated is encapsulated with a stabilizer to prevent drug partitioning to external water phase during solvent evaporation in the external water phase of w/o/w double emulsion.[69] Many SLNs have been prepared by this method for anticancer therapy.

Precipitation Method
Here the lipids (glycerides) are dissolved in an organic solvent (e.g. chloroform) and the solution is emulsified in an aqueous phase. After the evaporation of organic solvent for forming of nanoparticle the lipid will be precipitated.

Film-Ultrasound Dispersion
Before decompression, rotation and evaporation of the organic solutions, the lipid and the drug were put into suitable organic solutions for the formation of a lipid film, then the aqueous solution which includes the emulsions was added. At last by using the ultrasound with the probe to diffuser, the SLN with the little and uniform particle size is formed. Many SLNs have been prepared by this method: E.g.: Doxorubicin and Lapatinib Combination Nanomedicine for Treating Resistant Breast Cancer.

CONCLUSION
Curcumin is herbal neutraceutical that has great potential to prevent and treat a wide spectrum of diseases under which mainly comes disease like cancer. It is safe to take even at high doses (12 g/day). A regular intake of curcumin as a supplement may delay or prevent these diseases. Despite its high potential in treating various chronic diseases, it is not clinically available for regular use because of its poor oral bioavailability. As a natural product, curcumin is both non-toxic as well as diversified in its inhibitory effects on a multitude of pathways involved in carcinogenesis and tumour formation.

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