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Recent trends in delivery of Natural Products

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***Abstract*— Natural products are recommended in today's scenario due to less toxicity, more nutritional value and less repetition of symptoms related to disease. Isolation of Phytomolecules opens a new era of active pharmaceutical ingredients which helps in generating novel formulation using them. In this context, curcumin, taxol, andrographalide are some unique examples which provide enhance pharmacological activity during treatment. In a general view, the large size of molecule needs less particle size to enhance the penetration and mechanism of action at a particular site. Novel Drug delivery system revolutionized both of the above factors and the formulations containing liposomes, nanoparticles, phytosomes, microsphere, emulsion, transferosomes, ethosomes, micropellates are unique examples that set a benchmark.**

Keywords*— Novel Drug delivery systems, Curcumin, andrographalide, taxol, pharmacological activity.

I. INTRODUCTION

Nature is the ultimate source of Healing, the synthetic routes itself are the copy of natural phenomenon. The Phytomolecules are Natural products which are healing, detoxifying, boosting immunity and providing Nutrition to Mankind from centuries. The crude plant drug, extract, juices and powders are in use. But due to the need of fast healing and remediation, the way of formulation requires more skilful work. Nies S. et al., (2007), reported that the Diseases require the medicine along with nutritional benefit to the body. Natural compounds are used in history along with other compounds in the form of extracts which provide the body a synergistic effect during the treatment [1].

Nishiyama N. et al., (2007) the powder of crude drugs is no doubt full of Nutritional benefits and other remedial effects for the body along with unwanted impurities that delay the pharmacological profile of herbal medicines. Wang et al., (2008), suggest that the process of removing such impurities improves the quality of herbal medicine and give its more remedial effect, this process is known as enrichment, it is a proven fact that the particle size matter for almost all the alterations in physicochemical properties of a drug. Enhancement of bioavailability leads to improvement in pharmacological activity [2,3].

II. TYPES OF NATURAL PRODUCTS BASED NOVEL DRUG DELIVERY IN NANOMEDICINES

A. LIPOSOMES BASED DRUG DELIVERY SYSTEM

Liposomes are defined as nanosized vesicular structure consisting of aqueous core surrounding with phospholipid layer as depicted from fig.1. McNeil S.E. *et al.*, (2009) reported that for the pharmacological prospects of liposomes are improved during studies. Jagtap S. et al., (2009) informed that Quercetin, curcumin are some legendry examples for the liposomal drug delivery system [4,5].

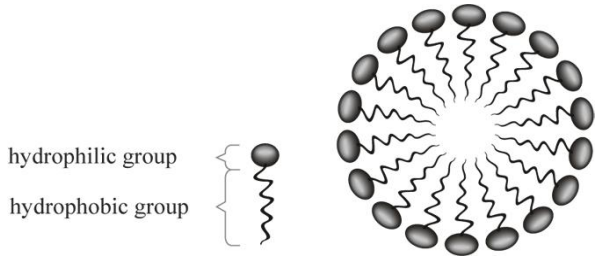


Fig.1. Structure of Liposome

B. NANO PARTICLE DRUG DELIVERY SYSTEM

Nanoparticles are the microscopic particles confined to nanoscale in all three dimensions (1-100nm). The structure is described by fig 2. Li DC. *et al.*, (2009) informed about the application of targeted drug delivery system in Chinese medicine in which they discussed the nano particle drug delivery system for the drug having short half-life and solubility problems[22].

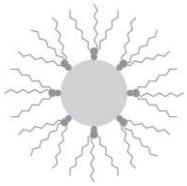


Fig 2. Structure of Nanoparticle

C. PHYTOSOMAL DRUG DELIVERY SYSTEM

Phytosome is a biocompatible and biodegradable delivery system that is formed through complexation –in a stoichiometric ratio-of a phytochemical, or a mixture of phytochemicals, with a phospholipid, mainly phosphatidylcholine or phosphatidylserine, in an aprotic solvent as shown in Fig. 3. Leonard K. *et al*., (2010) and Hou J. *et al*., (2008) reported the in situ green synthesis of biocompatible ginseng capped gold nanoparticles with remarkable stability, in their studies the phytosomal preparations of ginseng extract were observed and compared with the stability of ginseng capped gold nanoparticles [40, 41].

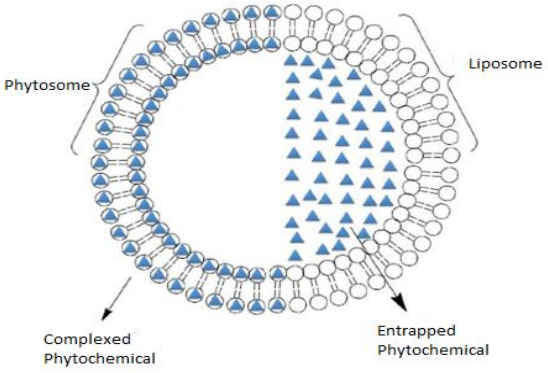
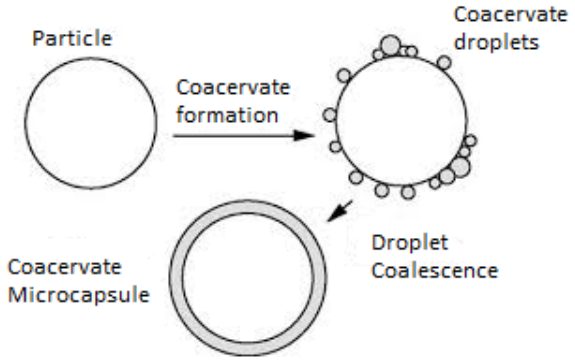


Fig 3. Structure of Phytosome

D. MICROSPHERE DRUG DELIVERY SYSTEMS

Microsphere are the spherical microparticles with diameters from 1 to 1000 µm. Fig. 4 depicted the formation of microspheres, Lertsuthiwong P. *et al*., (2008) prepared alginate capsules containing turmeric oil such formulation contains the microspherical size particles which act as shell to the oil. Chauhan H.S. et al., (2009) reported that phospholipid contain drug delivery system increases the systematic drug delivery. Verma H. et al., (2011) informed that the compounds having the antioxidant, anticancer, hepatoprotective activities get effective delivery by novel drug delivery system. Maiti K. *et al*., (2006) gave the data which relate the phospholid-curmin complex with restoration of liver glutathione system in liver. [50, 51, 52, 53].



.Fig 4 Structure of Microsphere

E. EMULSION SYSTEMS

Emulsions are the class of dispersed system consists of two immiscible liquids. Yue PF. *et al*., (2010) reported the oxymatrine-phospholipid complex was studied for the enhancement of the oral bioavailability and this study also shows that oxymatrine-phospholipid complex increase the permeability of hepatocytes. Das MK. *et al*., (2008) informed about the Morphology and release characteristics of ionic cross linking technique during which the stage of emulsion was also studied. Kanan K. *et al*., (2009) gave the evaluation of sustained release microspheres of acetazolamide by solvent evaporation technique such technique include the stage where initially the emusion stage occurs [59, 60, 61] .

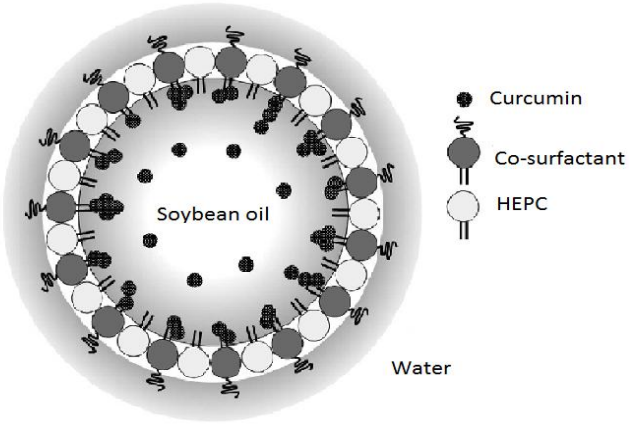


Fig.5 Structure of Emulsion system for curcumin

F. TRANSFEROSOMAL DRUG DELIVERY SYSTEM

Gangwar S. *et al*., (2010) reviewed that the Ethosomes are the novel tool for drug delivery system through the skin. For transdermal delivery of drug the ethosomes are the ethanolic phospholipids vesicles which increase the permeation by increasing the cell membrane fluidity. The deliver the drug by increase the permeation inside the skin and fuse with cell membrane [68] .

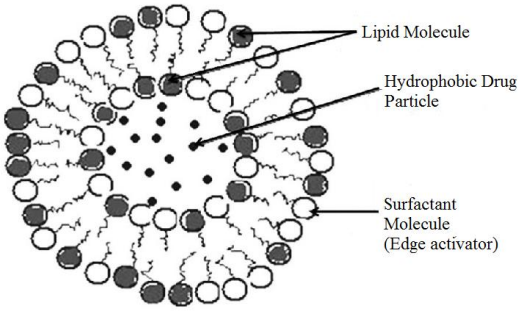


Fig.6 Structure of Transferosomes

G. ETHOSOMAL DRUG DELIVERY SYSTEM

Ethosomes are noninvasive delivery carriers that enable drugs to reach the deep skin layers and/or the systemic circulation. Yun Z. *et al*., (2010) prepared the Ethosomal total alkaloids of alopecuroides and performed their evaluation by transmembrane pH- gradient method [71].

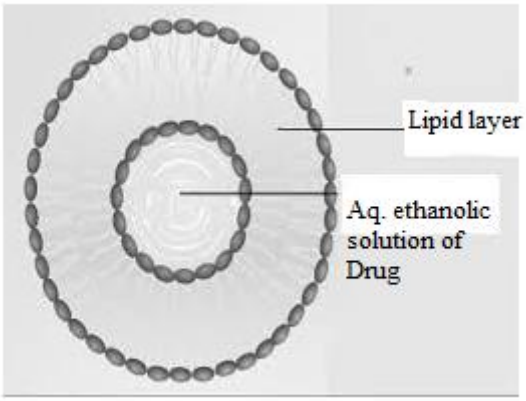


Fig.7 Structure of Ethosomes

H. MICROPELLATIZATION DRUG DELIVERY SYSTEM

Prabhakaran L. *et al*., (2007) gave an overview of the pharmaceutical micropellets and discussed that the pellets of size 1-1000 µm are suitable for dosage form design and also increase the efficacy of the bioactive agents. Shariff et al., (2007) formulate the andrographalide in cross linked alginate pellets evaluate the associated release kinetics. Kumar RS. *et al*., (2009) formulate and evaluate the curcumin pellets for colon delivery of pectin hydroxyl methylcellulose coating. Fig.8 depicted the process of micropellets formation [75, 76, 77].

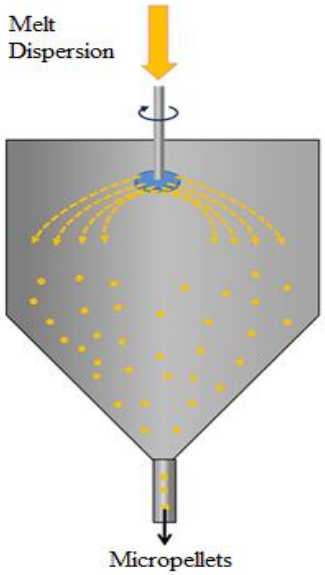


Fig.8 Preparation of Micropellets

III. CURRENT CHALLENGES AND POTENTIAL OPPORTUNITIES

A. Quality of source of Plant material and evaluation of its constituents

Devi VK. *et al*., (2010) reported that the modern phytopharmaceutical research can solve the scientific need of herbal medicine to be incorporated in novel drug delivery system. Quality of plant material depends on the authenticity of seeds requires for sowing, the quantity of excess fertilizer, pesticides given during the cultivation and the ripening, contaminating conditions during storage. The systematic approaches in cultivation, postharvest management will improve the quality of medicinal plants [80].

B. Innovation in the evaluation of the pharmacological profile of Herbal medicines

Pinto JF (2009) gives evaluation of the pharmacological profile of the Drugs includes the studies with respect to a single molecule. In case of herbal medicine, the pharmacological profile the synergistic effect of the number of molecules present in the extract. The evaluation of this synergistic effect requires the development of the efficient pharmacological model which can differentiate the specific and general effect of the herbal medicine. Further he studied the site specific drug delivery system [81].

C. The Interface with Regulatory Science

Singh H., (2011) suggested that traditional medicine the use of Natural products is an integral part. The International organization such as WHO is working to classify the Natural products in context to the International classification of Diseases. The International Standardization organization is trying to develop the international standards for a group of products. The export-import of Natural medicines requires proper controls. “Dreadful ducklings” is a term general use by medicinal chemist for Natural products as they contain structural complexity, multiple hydroxyl moieties and chiral centers. To overcome this problem, combinatorial chemistry is emerge as new area for chemical diversities. It is proven in case of HIV protease inhibitors as drug discovery [82].

IV. RECENT ADVANCES

Nanotechnology is an emerging field in drug delivery systems. The definition of Nanoparticles, however, debated and many sources define them as the particles having the size of range 1nm to 100 nm. Bhatta RS. et al., (2012) concluded that at nanoscale structure the properties and interactions are unique which improves the pharmacological action. Polymer Nanoparticles, solid lipid nanoparticles (SLNs), liposomes, crystal nanoparticles, dendrimers and micelles are the types of Nanoparticles havine potential applications in Pharmaceutical sciences [83].

Natural products have been tested mostly with polymeric nanoparticles. Poly (lactic-co-glycolic acid) (PLGA), polyethylene glycol (PEG), polyvinyl alcohol(PVP), polycaprolactone (PCL), chitosan and poly-1-lactic acid (PLA) are the commonly used polymers which are used to the properties of biodegradability, biocompatibility and funtionalizability. Li Y. *et al*., (2013) reported that Biopharmaceutical classification system (BCS IV) flavonoid

glycosides have poor membrane permeability and permeation this problem is resolved by developing bioactive lipophilic aglycone icaritin into nanocystals by anti-solvent precipitation method. Natural polymer, chitaosan, is currently proves its applications in natural product delivery. Nanocaplsules and nanospheres are two polymeric types of nanoparticles. Nanocapsules are drug delivery systems which contain a core part of drug-filled at center and polymer membrane is surrounding it. The nanospheres are porous in nature and the drug in distributed uniformly at pores. Phospholipids are composed of liposomes and micelles [84].

Solid lipid nanoparticles are choice of drug delivery system for hydrophobic drugs. These are more stable than liposomes and less toxic than polymeric nanoparticles. Tran TH. *et al.*, (2014) reported that quercetin-containing self nanoemulsifying drug delivery system improves the oral bioavailability. Further, liquid lipid has introduced into the solid structure which forms nano structured lipid carriers. Such systems are divided into imperfect type, an amorphous type and multiple type. The drug loading capacity is enhanced by imperfect type of system. In amorphous type system, the solid lipids are mixed with special lipids, e.g. medium-chain triglycerides which prevent crystallization and drug expulsion during storage. The solubility of drugs enhance due to multiple-type system [85].

Cancer and other chronic human diseases needs the nanotechnology based delivery system especially in case of natural products. Such system improves the bioavailability, targeting and controlled release profiles of Herbal medicines.

V. BENEFITS OF NANOTECHNOLOGY

A. *Bioavailability*

Both the prevention and treatment of disease can improve by using natural compounds as Nanaoparticles due to increase in their bioavailability. Siddiqui IA. *et al*., 2010 studied the efficacy of well identified chemopreventive agent epigallocatechin-3-gallate encapsulated in polylactic acid and polyethylene glycol nanoparticles. Highly lipohilic drugs like curcumin, resveratrol are not ideal for drug delivery due to their dissolution problem in bloodstream. For the desired therapeutic effect their large quantity is required due to less bioavailability.

But the large dose of these compounds leads to acute toxicity and low patient compliance. Their solubility and efficiency can be improved by encapsulation. Singh M. *et al*., (2011) found that when the bergamot essential oil is encapsulated in liposomes, the solubility of drug increases and increase in anticancer properties has observed by increase cell death in vitro [86,87].

Same is the case of nanoemulsified berberine. Golukumar M. *et al*., (2014) reported that silybin loaded nanoparticles enhanced cytotoxicity and apoptosis induced anticancer effect. When nanoberberine was added to a phosphate buffer, 85% of the compound was dissolved in 45 minutes, as compared to the 60% of the free berberine with same time interval. Tannins and terpenoids are highly hydrophilic and have low bioavailability. Nanoparticle drug delivery system increases the bioavailability and lowers the therapeutic dose [88].

Majumdar D. *et al*., (2014), studied the invitro and invivo anticancer activity of luteolin nanoparticles in chemoprevention. Admininstered orally liposome-encapsulated curcumin (LEC) nanoparticles to Sprague Dawley rats and measured their plasma curcumin levels. The area under the curve values for the LEC was 4.96 times greater than those for curcumin [89].

Bhardwaj RK. *et al*., (2002) studied that piperine inhibits human P-glycoprotein and CYP3A4. Biopotentiation is a term used by ayurvedic peoples also known as “Yogvahi” that meant to use herbs to increase plasma concentration of drug. Piperine form black pepper is the first in the series of biopotentiation. Study reveals that biopotentiator show enhancement of bioavailability of active pharmaceutical ingredient at lower dose. Naringin, quercetin, glycyrrhizin, genistein, sinomenine, cow urine distillate, nitrile glycoside have proven to be biopotentiator. The effect of biopotentiation redues dose, toxicity and adverse effects of Drug. As a result, the time and cost of treatment is also reduced. Many novel drug delivery formulations such as liposomes, transferosomes, ethosomes are recently incorporated with bioenhancer. Other drugs like antibiotics, antitubercular, anticancer and cardiovascular were used with this concept [90]. Bioenhancer shoud have following properties-

1. They should be nontoxic, non-allergenic and non-irritating.
2. They should not produce own pharmacological effects.
3. They should be rapid-acting with predictable and reproducible activity.
4. They should be unidirectional in action.
5. They should be compatible with other active pharmaceutical ingredients.
6. They should be stable with time and environment.
7. They should be easily formulated into a various dosage form.

They should be easily available and cost effective.

B. *Targeting*

Nanoparticle drug delivery of natural compounds increases the ability to target specific tissues or organs. Following are the reasons which describe the beneficial effects of targeting-

1. Improvement in the amount of fractions of drug reaches the tissue of interest.
2. Targeted drug delivery is released in a localized area of the body which reduces the toxic side effects of the drug.

Al shawi. *et al*., (2005) described the multidrug transporter role of P-glycoprotein. They targeting approaches depends upon the different types of nanoparticles. In first case, the ligand is attached to the surface of nanoparticle and it is known as active targeting. In second type, the nanoparticle reaches the targeted area without specific chemical interaction due to the properties of size, shape and surface charge [91].

When nanoparticles are functionalizing with protein, peptide, antibody, or other small molecule, then only the active targeting is generally possible. Gupta V. *et al*., (2009) reported about the fabrication and characterization of silk fibroin derived curcumin nanoparticles for cancer chemotherapy. As a result of this functionalization the particles are allowed to localized and internalized by specific tissues. When nanoparticles are conjugated with monoclonal antibodies, even the blood brain barrier can be targeted. In case of Natural products this conjunction has not been used. In case of Natural product this conjunction has not been used. In the treatment of cancer cells the conjugation of nanoparticles with folic acid (FA) has shown promising effect. Many types of cancers overexpress FA receptors on the cell surface, this induces the targeting of cancer cell with the conjugation of FA to nanoparticle. This method is used for encapsulation of quercetin in PLGA nanoparticles which are stabilized by PEG. As a result, the biocompatibility and the circulation lifetime increases. Some targeting techniques are given in following table 9 [92].

C. *Controlled release*

The release of the drug can also be achieved by using the nanoparticles for the delivery of natural compounds. Min KH. *et al*.,(2008) that tumor targeting in cancer therapy enhanced by formulating the hydrophobically modified glycol chitosan nanoparticles of camptothecin. reported the prevention of neuroinflammation by quercetin nanoparticles. Particle type, size, amount of drug encapsulated, natural compound used are the factors on which the rate and amount of drug released depends. The drug release profile of the drug depends on the type of nanoparticle. Some natural-based nano particles for controlled release are summarized in table 10 [97].

VI. NATURAL PRODUCT BASED NOVEL DRUG DELIVERY FORMULATIONS AVAILABLE IN MARKET

A. *New Formulations*

Biological sciences, engineering, chemistry and medicine are the major field in which nanotechnology is emerging as a modern tool technique. Italia JL. *et al*., (2008) informed that nanoparticles enhance oral bioavailability. Nanoscale herbal decoction attenuate hepatic stellate cell activity and chloroform induced liver damage in rats. Nanotechnology deals with the control of matter on a molecular scale usually ranging in 10^{-9} m and use to develop devices on same scale. The principle behind the nanotechnology is the novel properties of optical, electronic, magnetic and structural behaviour of nanoparticles of polymeric, semiconductor and metals. Individual molecules and bulk solids lack such properties. Cancer management and therapeutics is the emerging area where nanotechnology plays a major role in diagnosis and treatment [102].

Epigallocatechin-3-gallate (EGCG)

Dube A. et al., (2010) reported than Green tea contain a polyphenol epigallocatechin-3-gallate (EGCG) is formulated as sustained release nanoparticle system using nanotechnology. Han D.W., (2009) reported the In vitro and in vivo efficacy of EGCG was assessed by encapsulating EGCG in poly (L-lactide)-poly (ethylene glycol), (PLA-PEG). Italia JL. *et al*., (2008) concluded that 10-fold dose advantage for exerting efficacy of drug was observed. The following method was employed [100, 101,102].

Curcumin

Yadav V.R., et al., (2011) reported that curcumin is a golden spice that target multiple angiogenic pathways. It is the most extensively studied molecules in nanotechnology. Curcumin is the principal curcuminoid of the Indian spice turmeric (Curcuma longa). Ghoneum M. et al., (2011) concluded the synergistic apoptotic effect of rice bran oil and curcumin on human multiple myeloma cell lines U266. the capacity to exert apoptosis in cancer cells which show its anticancer potential. The major issues reported are its low solubility, bioavailability, unstability in the gut and rapid degradation in GI tract. Nanotechnology solves these issues, Bisht *et al.*, (2007), reported the incorporation of N-isopropylacrylamide (NIPAAM) with N-vinyl-2-pyrrolidone (VP) and poly (ethylene glycol) monoacrylate (PEG-A) nanoparticles. In another study, following method was employed [103, 104].

Taxol

George J., (2009) reported that a combination of taxol and Bcl-2 siRNA induces apoptosis in human glioblastoma cells and inhibit invasion, angiogenesis and tumour growth. Taxol is the first FDA-approved chemotherapy drug that originated from natural sources, its band name is Paclitaxel. Feng S.S. et al., (2004) informed that the nanoparticle with biodegradable polymer for clinical administration of Paclitaxel. The problem associated with Taxol is its water insolubility. For solubilisation, ethanol or cremophor EL are used but their own side effects is another problem. For improving therapeutic index, the polymeric drug delivery system was developed which also reduces the adverse effects of cremophor EL. Feng *et al.*, (2015) reported that modified solvent extraction/evaporation techniques for paclitaxed in PLGA nanoparticles. It was also observed that natural emulsifiers are more effective in this case. Almost 100% drug encapsulation efficiency was observed [108, 109].

Camptothecin

Wall and Wani in 1966 had discoverd Camptothecin which a cytotoxic alkaloid. The major problem was the extrame

lypophilicity and instability of the lactone ring. Onishi *et al*., (2003), used the incorporation of irinotecan with PLGA nanoparticles. Ebrahimnejad P et al., (2008) studied the antibody targeting of camptothecin loaded PLGA loaded particles to tumour cell. Min K.H. *et al*., (2008) studied the hydrophobically modified glycol chitosan nanoparticles encapsulated camptothecin enhanced the drug stability and tumour targeting in cancer therapy. It was observed that drug residence time was improved with better suppresiong of the tumor [95,97].

VII. Marketed herbal novel drug delivery formulations

Li Z. et al., (2011) studied the fabrication of nanoparticles using partially purified pomegranate ellagitannins and gelatin for their apoptotic effect. Nanotechnology is emerging as a potential tool for cancer diagnosis and treatment because the biological processes like cancer-related take place on a nanometer scale, thus this field is also known as 'cancer nanotechnology'. These novel therapies enable the drug to increase its solubility, bioavailability and designed them to target tumors. National cancer institute consider cancer nanotechnology as an extraordinary, paradigm-shifting advances in treatment of Cancer. Here are some examples of drug where nanotechnology plays a key role to enhance their potential. Following is the list of phytosomes available in market manufactured by Indena international ltd. Italy [110].

VIII. Issues

Novel drug delivery systems works on very small particle size due to which potential toxicity is the major problem. Narayanan S. *et al*., (2010) reported folate targeted polymeric 'green' nanotherapy for cancer. Very small particle size enables the drug to cross blood brain barrier and can be phagocytocised. The systemic toxicity may occur because nanoparticles can undergoes endocytosis. Zhang L. *et al*., (2008) informed about the therapeutic application and development of nanoparticles in medicine. The biocompatible polymers, phospholipids are safe to healthy cells and hence, their incorporation with nanoparticles is safe. In another case, nanoparticles undergoes changes in the body. Kawasaki E.S. *et al*., (2005) reported the effective therapies for cancer using nanomedicine. The shape and surface charge of the particles changes due to the movement of these particles through different membranes, tissues, and organs in the body. Such changes affects the bioavailabiliy, targeting and release kinetics of the drug. The immune macrophage system in the liver and spleen shortened the half-life of nanoparticles. PEGylation and adjustment of size and charge are some techniques that lowers the detection of nanoparticles by macrophages [111,112,113].

IX. Conclusion

Novel drug delivery system changes the era of herbal medicine and open a new stream of technology to introduce herbal medicine in market. The efficacy of herbal medicines enhance by other novel drug delivery systems. First pass metabolism is the major problem associated with herbal drugs which is solved by using novel drug delivery system such as sublingual tablets. Enhancement in bioavailability is absorbed due to the increment of absorption of drug molecule which can be used as unit dosage form under mucoadhesive drug delivery system.

The drugs which are having the properties of absorption in upper GI tract, then for such systems Floating drug delivery system can be used.

Acknowledgment

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