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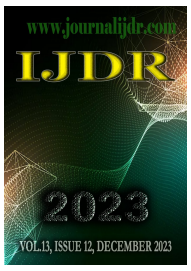

RESEARCH ARTICLE OPEN ACCESS

FORMULATION, EVALUATIONS AND APPLICATIONS OF SOLID LIPID NANOPARTICLE

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ABSTRACT

The liquid crystalline state has both the properties of liquid and solid. The liquid state is found to associate with flow property whereas the solid state has structural properties of crystallinity in aspects of orientation and position. Liquid crystalline phases represent intermediate states and are also called asmesophases. The studies were done with different formulations to ensureits controlled drugrelease and bioavailability research has progressively highlighted on clues from conventional use of herbal medicines to introduce new anticancer drugs. Aloe-emodin (AE) is a herbal drug with promising anticancer activity. Nevertheless, its clinical utility is handicapped by its low solubility. PEGylated LCNPs could serve as a promising nanocarrier for efficient delivery of AE to cancerous cells. In this review attention is focused to give the brief regarding formulation aspect, method of preparation characterization techniques, evaluation parameters and various application of the nano emulsions, several techniques are to be used for preparation of nanoemulsions like microfluidization, high pressure homogenization, low energy emulsification and solvent evaporation method and parameter that are to be used for its characterization like droplet size analysis ,viscosity determination, drug content, refractive index, pH, zeta potential, Transmission electron microscopy, thermal stability, release and in vitro skin permeation study. These are applicable in drug targeting.

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INTRODUCTION

Tablets are the most widely utilized solid oral dosage forms because of the advantages of self administration, stability, ease of handling, transportation, and good patient compliance. Overtime, extensive advances have been made in tableting technology. This review aims to provide an insight about the advances in tablet excipients, manufacturing, analytical techniques and deployment of Quality by Design (QbD). Various excipients offering novel functionalities such as solubility enhancement, super-disintegration, taste masking and drug release modifications have beendeveloped. Furthermore, co-processed multifunctional ready-to-use excipients, particularly for tablet dosage forms, have benefitted manufacturing with shorter processing times. Advances in granulation methods, includingmoist, thermaladhesion, steam, melt, freeze, foam, reversewet and pneumaticdry granulation, have been proposed to improve product and process performance. Furthermore, methods for particle engineering including hot melt extrusion, extrusion-spheronization, injection molding, spray drying/ congealing, coprecipitation and nanotechnology-based approaches have been employed to produce robust tablet formulations. Numerous advances have been introduced to improve material attributes, engineering of manufacturing equipment and development of efficient analytical techniques. Quality by design-based formulation development approaches have been applied toreduce the variability in the processes to develop robust tablet dosage forms. In addition, new raw materials have been deployed to improve manufacturability and functionality of tablet formulations. These include the modification of existing excipients with enhanced purity or physical properties (e.g., particle size) and co-processing with other materials to improve their performance in manufacturing processes. Moreover, development and use of multi-functional materials provide lean manufacturing opportunities with significant economic impact[1]. Nanotechnology is a cross-disciplinary field, which involves the ability to design and exploit the unique properties that emerge from man-made materials ranging in size from 1 to greater than 100 nm. A self- nanoemulsifying drug delivery system is a fairly similar liquid lipid dosage form designed for oral delivery which composed of oils, surfactantsand possibly cosurfact antsorcosolvents. Felodipineisa calcium channel blocker (CCB). It acts primarily on vascular smooth muscle cells by stabilizing voltage-gated L-type calcium channels in their inactive conformation. The aim of this paper was to formulate Felodipine self

nanoemulsifying system to overcome the poor aqueous solubility of Felodipine (3ug/ml) and hence improving its poor dissolution which is the main cause of its poor oral bioavailability. Evaluation, Characterization and In-Vitro release of orally Felodipine Self-nanoemulsifying Drug Delivery Systems were studied in comparison with the market product. Hypertension known as high blood pressure (HBP), is a long-term medical condition in which the blood pressure in the arteries is persistently elevated. High blood pressure usually does not cause symptoms. Long-term high blood pressure, however, is a major risk factor for coronary artery disease, stroke, heart failure, peripheral vascular disease, vision loss, and chronic kidney disease. [2] In order to achieve a desired pharmacological response, the drug must reach a reasonable significant concentration in plasma which is mainly correlated to its solubility in GIT fluids, except pinocytosis, all other drug absorption mechanisms from GIT require the presence of drug in solution form. For poorly water soluble drugs, mainly categorized as class II in BCS classification system (low solubility and high permeability), the dissolution is the rate determining step in the absorptionprocess. So after oral administration, these drugs usually suffer slow and inadequate absorption from GIT, low bioavailability and probable mucosal damage. [3]Microspheres of biodegradable polymers have been widely studied as drug delivery systems. Besides their ability to improve the delivery of drugs to the target site, they have been reported to control drugrelease, reduce drug associated adverse effects, protect the compound from inactivation before reaching its site of action, increase the intracellular penetration and enhance the pharmacological activity.A great variety of both naturaland synthetic biodegradable polymers such as chitosan, gelatin, polylactic-coglycolic acid, polyalkylcyanoacrylate, polymethylmethacrylate, polylactic acid and polycaprolactone are used forthe preparation of drug loaded microspheres. In particular, polylactic-co-glycolic acid (PLGA) has received tremendous interest for the development of controlled drug delivery systems due to its excellent biocompatibility and biodegradability. Several methods, including phase separation or coacervation. emulsification diffusion, spray-drying. and emulsion-solvent evaporation techniques have been used to obtain PLGA microspheres. [4] Additionally, coadministration with a penetration enhancer has been suggested for drugs that slowly or incompletely penetrate the oral mucosal membranes in order to reduce barrier properties of the buccal epithelium. [10]

Lyotropicliquidcrystalline structures: Based on theirinternal structures, lyotropic LCNPs are classified into three types: lamellar, cubic, and hexagonal phase (Fig. 1). Lamellar phases have the highest concentration of surfactant compared to the other phases. They have high fluidity; because of which lamellae can easily slide over oneanother. This property is useful in topical applications. Cubic (cubosomes) and hexagonal (hexosomes) phases are widely used in pharmaceuticals because they have the ability to form highly ordered structures internally, resulting in the formation of a sustained release matrix for drugs of various polarities and sizes. Moreover, they can encapsulate hydrophobic, hydrophilic, as well as amphiphilic drug molecules. Hydrophilic drugs can be encapsulated in the internal water channels, hydrophobic drugs can be encapsulated in the hydrophobic part of the nanocarrier, and the amphiphilic drugs can be loaded at the hydrophobic-hydrophilic interface. The cubic phase has a unique structure and consists of a curved bicontinuous lipid bilayer extending in three dimensions, and two aqueous channels. The cubic phase is formed in the aqueous phase spontaneously. Cubic phases contain non-intersecting water channels internally, that are not in contact with the external aqueous environment. Also, the interfacial area is larger when compared to the other phases. These unique properties impart controlled release and bioadhesive properties to cubosomes. Thus, they can beutilized fororal, buccal, nasal, pulmonary, vaginal, and rectaldrug delivery. There are two types of reversecubic phases: 3 Dreverse. Discontinuous and 3 Dreversebicontinuouscubic phases.They are termed reverse because they are formed in the organic solvent. In the reverse phase, the polar head of the amphiphile faces inwards towards the water, and the nonpolar tails migrate outside towards the organic solvent.

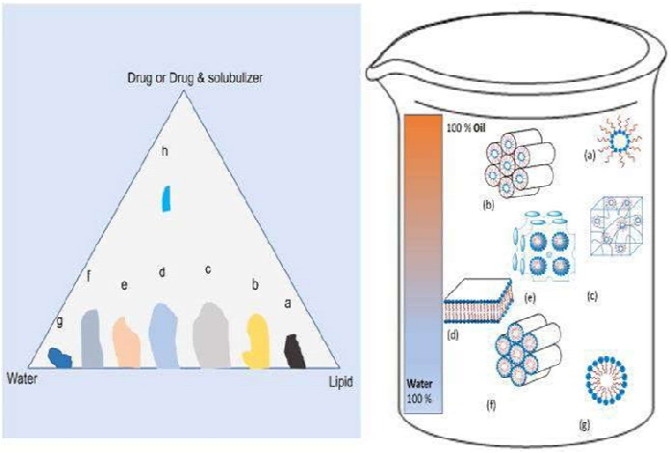

Figure 1. Different types of liquid crystal nanoparticles and ternary phase diagram illustrating differentphases.(a) Reversemicelles; (b) reversehexagonal; (c) reversebi continuouscubic; (d) lamellar; (e) normal discontinuouscubic; (f) hexagonal; (g) normalmicelles; (h) microemulsion. Reprinted from with permission from Elsevier. [5]

AE has loworal bioavailability that could be attributed to its poor aqueous solubility, erraticintestinal absorption, as well as its pre-systemic metabolism via glucuronidation and P-glycoprotein efflux process. This scanty bioavailability compromises the oral efficacy of AE. On the other hand, parenteral administration of AE for chemotherapy is disabled by its hydrophobicity and inherent crystallization tendency in aqueous solution. Therefore, a novel drug delivery system is required to overcome the poor bioavailability of AE and enable its parenteral use. Various attempts have been madeto enhancethe delivery ofAE, including β-cyclodextrin inclusion complexes, solid dispersions, liposomes, and solid lipid nanoparticles.

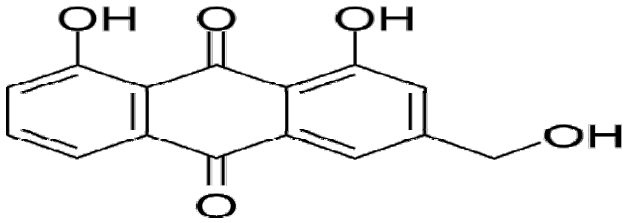

Figure 2. Chemical structure of AE

However, cyclodextrins are associated with toxicity and liposomal instability, which are the possible drawbacks. Furthermore, solid lipid nanoparticles have low drug encapsulation and sophisticated techniques are required for their preparation. Hence, other drug delivery systems are required to ameliorate these obstacles and to improve the anticancer efficacy of AE. [12]Berberine, in combination with gefitinib, is currently under phase II clinical trial for the treatment of advanced NSCLC (NCT03486496).

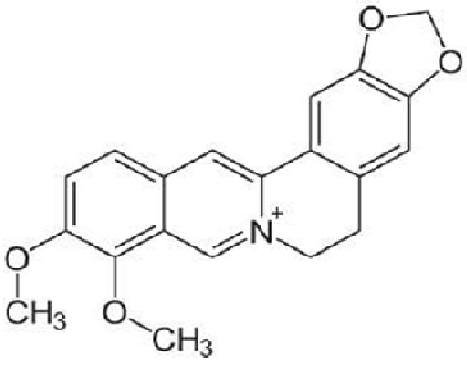

Figure 3. Chemical structure of berberine

Berberine exerts anti-cancer activity by causing cell cycle arrest and autophagy, promoting apoptosis, and inhibiting angiogenesis of tumor cells. Berberine also suppresses endothelial–mesenchymaltransition ability and downregulates the expression of megastars is related proteins such as matrix metalloproteinase and signaling path ways and tumor xenograft in mice.

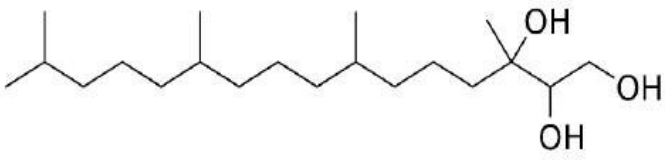

Figure 4. Structure of phytantriol

The anti-cancer drug hydroxycamptothecine (HCPT), where the results showed that a phytantriol-based cubic phase embolic gelling solution can be a promising carrier for HCPT delivery and sustained drug release by vascular embolization. Incorporating berberine into phytantriol-based LCNs could potentially rectify the solubility and stability issues of berberine. In addition, poloxamer. [19] Lipid-based liquid crystalline nanoparticles (LCNPs) have attracted growing interest as a new drug nanocarrier system for improving bioavailability for both hydrophilic and hydrophobic drugs. [20] The use of liquid crystalline nanoparticles is a novel approach in the field of controlled drug delivery. Tacrolimus, being a highly lipophilic drug, is easily incorporated in the hydrophobic core of these nanoparticles. Which are prepare by pseudo binary mixture technique by using polymers like monoolein and poloxomer 407 to extend the drug release for about 32 hours, there by improved bioavailability. [23]

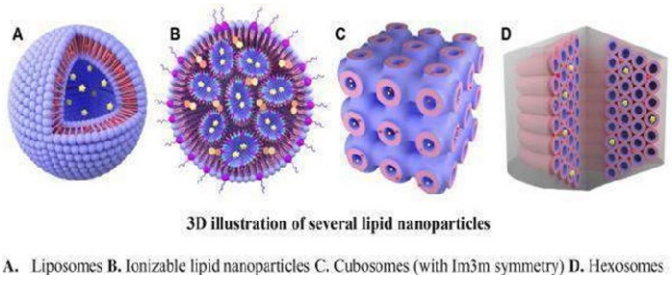

Figure 5. Recent Advances In Versatile Inverse Lyotropic Liquid Crystals

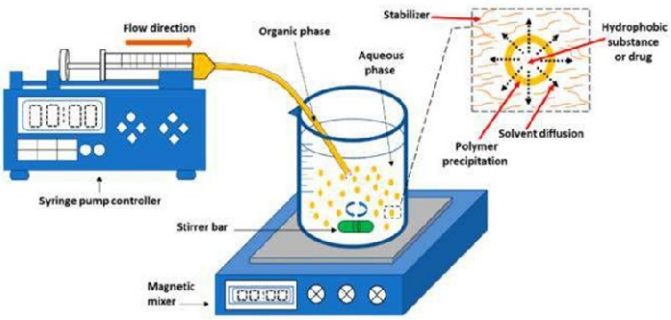

Figure 6. Different types of liquid crystal nanoparticles and ternary phase diagram illustrating different phases. (a) Reverse micelles; (b) reverse hexagonal; (c) reverse bicontinuous cubic; (d) lamellar; (e) normal discontinuous cubic; (f) hexagonal; (g) normal micelles; (h) microemulsion. Reprinted from [36] with permission from Elsevier

MATERIALS AND METHODS

Materials

Flutamide and glyceryl palmtostearate (Precirol ATO-5_) were kindly donated by MehrDaru Pharmaceutical Company (Tehran, Iran) and Gattefosse´ Company (Lyon, France), respectively. Span_ 80 was obtained from BDH Laboratory (Cambridge, England). Poloxamer_ 407 was supplied from Sigma-Aldrich Company (Darmstadt, Germany). Chloroform (Dae-Junge, Korea), methanol (Caledon, Canada) and diethyl ether (KianKaveh Pharmaceutical and Chemical Company, Tehran, Iran) were used as received. Rhodamine B was obtained from Merck Chemicals Company (Darmstadt, Germany).

Preparation of flutamide-loaded SLNs Solid lipid nanaoparticles (SLNs): were prepared by the hot melt homogenization method35. The primary goal in the first step of SLN production is to prepare a nanoemulsion from molten solid lipid. For this purpose, the easiest way is to use high pressure homogenizer. But any equipment which can be able to prepare this nanoemulsion, the easiest method is using a high pressure homogenizer such as a simple high speed homogenizer. Precirol ATO-5_ was melted at about 80 _C and Span_ 80, as an oil phase surfactant, was added to the melted lipid phase. Subsequently, Flutamide was dissolved in ethanol: water solution (70:30 v/v) and added dropwise into the oil phase under stirring at 20000 rpmbyhomogenizer (DIAX900, Heidolph, Germany). Finally, aqueous phase (Poloxamer_ 407 5% w/v) was dropped into the oil phase, keeping the temperature at 80_C and stirring rate at 20000 rpm, to preparean oil in water nanoemulsion. Flutamide-loadedSLN were obtained by allowing the hot nanoemulsion to cool down at room temperature. Flutamide was not solublein moltenlipids. Its dispersion in the moltenlipid phase affects thefinal size of SLNs and also results in the low drug encapsulation. Therefore, to maximize drug encapsulation into SLNs, the drug was dissolved in an almost aqueous phase (hydroalcoholic solution) and added into the molten lipid phase to prepare initial w/o emulsion. Finally, the external aqueous phase containing polymeric surfactant was added to increase the stability of the nanoparticles. Each formulation was prepared and characterized in triplicate. [6]

Nano precipitation method: Nano precipitation or solvent displacement method was introduced by Fessi and co-workers and has become a popular technique to prepare nanoparticles due to narrow size distribution, absence of shear stress, and absence of surfactants for amphiphilic polymers. In this method, particles are formed spontaneously by precipitation and subsequent solidification of the polymer upon rapid solvent diffusion. The polymer and drug are dissolved in a water miscible organic solvent for exampleacetone or methanol. The solution is then poured under magnetic stirring into an aqueous solution which contains surfactant. Through rapid solvent diffusion, the nanop articles are formed immediately. After that, the solvents are removed under reduced pressure. The mechanism of formation of NPs by this technique has been explained by the interfacial turbulence generated at the interface of the solvent and non-solvent. Thus, the process is often called solvent displacement or interfacial deposition.

Emulsification solvent diffusion method: In this technique, the organic solvent containing the dissolved polymer and the drug is emulsified inan aqueous surfactant solution (usually with PVA as a stabilizing agent) by using a highspeed homogenizer. Water is subsequently added under constant stirring to the O/W emulsion system, thus causing phase transformation and outward diffusion of the solvent from the internal phase, leading to the nanoprecipitation of the polymer and the formation of colloidal nanoparticles. Finally, the solvent can be eliminated by vacuum steam distillation or evaporation. The most important fabrication step is solvent diffusion, in which the organic phase diffuses from the oil phase to outer water phase and the formed particles become hardened. The selection of the surfactants in the outer water phase is also crucial for successful fabrication. [9]

Materials

Clotrimazole, Tween_80 (polyoxyethylene (20) sorbitanmonooleate), Tween_20 (polyoxyethylene (20) sorbitanmonolaurate), Pluronic_F68 (polyoxyethylene-polyoxypropylene (150:29) block copolymer) anddialysistubewerepurchasedfromSigma(USA).Chremophore_EL(polyethoxylatedcastoroil)was gift samples from BASF (Germany).

Compritol_ 888 ATO (glycerol dibehenate/ behenate), Precirol_ ATO 5 (glycerol distearate), Geleo (Glycerol monostearate), Suppocire_ NC (semi-syntheticTriglycerides of C10 to C18 saturated fatty acids) and Labrafa CC (Caprylic/Capric Triglyceride) were generous gift by Gattefossé (France). Dynasan_ 114 (glycerol trimyristate) and Dynasan_ 118 (glycerol tristearate) and Imwitor_ 900 K (glyceryl stearate) were kindly donated by Sasol (Germany). HPLCgrade acetonitrile and methanol were bought from Fisher Scientific (USA) and J.T. Baker (USA), respectively. Phosphoric acid was obtained from Kanto Chemical Co. Inc. (Japan). Purified water was collected from Millipore Q_ Gradient A10 ultra-pure water system (Millipore, France) for the study.

Preparation of LCNPs and HGC: The compositions of the LCNP formulations are described in Table 1 and the PIT method used for preparingthe formulations is as follows: first, the lipid (composed of lipids, drug, and surfactants) and aqueous portions were heated separately at ~85°C. The aqueous portion was then added to the lipid portion and stirred until the hazymixtureturned semi-transparent. The mixture was then cooled to 25°C in awater bathcontainingicefor1 minute to obtain the LCNPs. The PIT was measured with a conductivity meter (Cond 6+; Eutech Instruments Pte Ltd, Singapore), which measures the conductivity change at the emulsion inversion zone. LCNP formulations with the compositions described in Table 2 were prepared for the PK and structure analysis.

Entry (LCNP)	Composition				Results	
	PartA (wt%)			PartB (wt%)		
	Emulgade SE-PF	PEG-12 cetostearyl ether	Tetradecyl tetradecanoate	Water	PIT (°C)	Appearance
1.	10.00	0.00	10.00	80.00	–	Separated
2.	8.00	2.00	10.00	80.00	–	Macroemulsion
3.	6.00	4.00	10.00	80.00	73	Transparent
4.	5.00	5.00	10.00	80.00	83	Transparent
5.	4.00	6.00	10.00	80.00	83	Transparent
6.	2.00	8.00	10.00	80.00	93	Macroemulsion
7.	0.00	10.00	10.00	80.00	98	Macroemulsion

Note: Compositions, phase inversion temperatures, and appearances of liquidcrystalnanopar
Abbreviations: LCNPs, liquid crystal Nanoparticles; PEG-12, polyethylene glycol-12; PIT, phase inversion temperature; wt, weight.

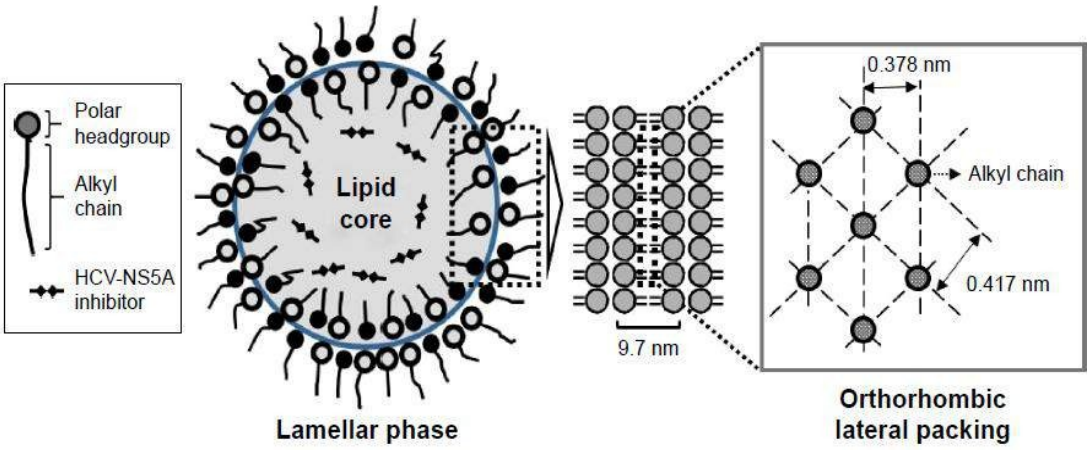

Figure 7. Illustration of the structure of the prepared liquidcrystalnanop articles (LCNPs).[18]

Formulation technique: Emulsification-ultrasonication technique was used to prepare SLNs and NLCs. Incase of SLNs, solid lipid was weighed in anamberg lass colored bottle and heated at 75°C to meltthelipid. Incase of NLCs, solid and liquid lipids were first put together in an amber colored glass bottle and then heated at 75 °C with continuous stirring to homogeneously mix the lipids. The drug was added in the melted lipid (SLNs) or lipidmixture (NLCs) and mixed well to fully dissolve the drug in lipid (s). In a separate container, surfactant was dissolved inultra-pure water and heated at 75°C. Then this hotaqueous surfactant solution (aqueous sphase) was poured in the melted lipid(s) containing drug (oil phase) and homogeneously dispersed using a homogenizer (IKA_ T-10 basic Ultra-Turrax_, Germany) at _14,000– 15000 rpm, while maintaining the temperature at 75 °C. This step produced coarse o/w emulsion, which was furthersonicated using aprobesonicator (Vibracell ™ 700 W; Sonics, USA) at 75°C. This step produced o/wnanoemulsion, which was immediately placed inadouble walled plastic box filled with ice to cool it down rapidly. The liquid nano droplets of melted lipid transformed into solid nanoparticles at lowtemperature and produced solidnanoparticledispersion. The basic rule for the formulation of SLN/NLC is to maintain process temperature at least 5 °C above the melting point of the solid lipid. As the melting point of the solidlipids were around 60–70°C, the processing temperature was selected 75°C.[17]

The procedure for the preparation of these formulations was the same as that described above for the LCNPs. Then 0.5 mL of PEG-15 hydroxy stearate was added to 0.25 mL of dimethyl sulfoxide incorporated with 5 mg of BMK-20113, and this solution was mixed until clear. The BMK-20113 solution was added to 4.25 mL of the HP-β-CD solution and then vortexes until clear. The prepared LCNPs and HGC were stored at 4°C for further evaluation. The amount of TET, the amount of glyceryl monoolein, and the ratio of poloxamer 407 to glyceryl monoolein were selected as the factors that were used to optimize the dependent variables, which included encapsulation efficiency and drug loading. A three-factor, five-level central composite design was constructed to optimize the formulation. [21] Nanostructured cubic lyotropic liquid crystalline colloidal particles (Cubosomes) are of interest for applications such as drug and biomedical imaging agent encapsulation systems. Maintaining the stability and integrity of these nanoparticles over time is essential for their storage and application. [24]

Synthesisofliquid-crystal–nanoparticle hybrids: The synthesis of NP hybrids is of course largely determined by the nature of the nanoparticle, and is affected by factors such as the synthetic method used to prepare the inorganic species, the presence of coligands (stabilisers) and the surface chemistry of the particular material under investigation. Furthermore, the relative ease and flexibility of synthesis of the organic ligand(s) means that their design is tailored to the particular surface chemistry and morphology characteristics of the

NP under investigation, ensuring a suitable anchoring group and structuredirecting groups are present in the molecular structure. In the case of Au NPs, which are by far the most extensively investigated, there are two main methods used for the preparation of hybrids; the first being direct synthesis of the NPs in the presence of the ligand of interest by using a modified Brust–Schiffrin procedure, and the other being a two-step process in which the NPs are first synthesised with a protective layer (e.g., a simplealkanethiol), followed by solvent-mediated ligand exchange to give the desired product (Figure).

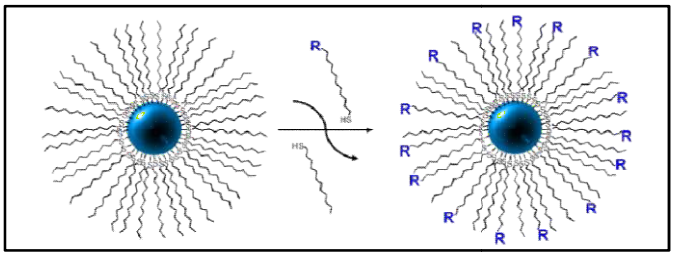

Figure 8. The solvent-mediated lig and exchange process, illustrated for the partial exchange of thiols at the surface of anoble-metal nanoparticle; R represents a proto-mesogenic moiety. [25]

Organicnanop articles: Dendrimers, micelles, liposomes and ferritin, etc. are commonly knows the organic nanoparticles or polymers. These nanoparticles are biodegradable, non-toxic, and some particles such as micelles and liposomes has a hollow core also known as nanocapsules and are sensitive to thermal and electromagnetic radiation such as heat and light. The organic nanoparticles are most widely used in the biomedical field for example drug delivery system as they are efficient and also can be injected on specific parts of the body that is also known as targeted drug delivery.

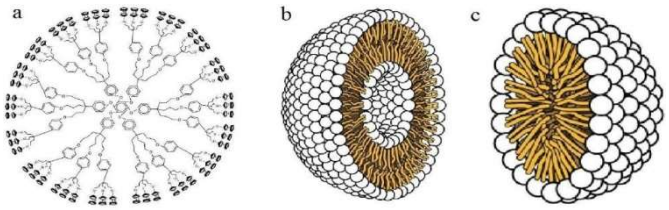

Figure 9. Organicnanop articles: a –Dendrimers, b–Liposomesandc–micelles. [28]

Formulation of RHTSLN: SLN were formulated by homogenization and ultra sonication method. Formulation procedure was divided into two parts in which one part contained lipid and drugwhileotherpart contained aqueous solution of surfactant and stabilizer. Drug and lipid mixture was melted 5 _C above the melting point of lipid. Aqueous part was heated at the same temperature. When both parts attain equilibrium, the aqueous phase was incorporated into lipid phase and emulsified using highspeed homogenizer (HSH, Kinematica AG, Polytron PT 1600 E, Switzerland). Temperature was maintained constant throughout the emulsification process. Primary emulsification was followed by ultrasonication using a probe sonicator (SONICS, VibraCell, VC 505, USA) and temperature was kept constant. Resulting lipidic dispersion was cooled down at room temperature for 15 min to obtain RHT SLN.

Composition of liquidcrystallinenanop articles: LCNPs are self-assembled structures and can be easily formed by the combination of biocompatible lipids and aqueous phases. Certain stabilizers and additives may be added to enhance the stability and efficacy ofLCNP formulation (Table 1). The factors that are essential for the formation of LCNPs are amphiphilic molecules, aqueous solvent, and temperature.

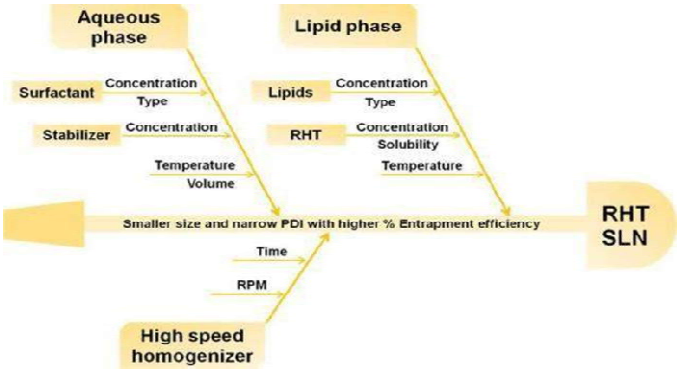

Figure 10. Ishikawadiagramillustrating CPP affecting on CQA of RHTSLN

Composition of liquidcrystallinenanoparticles: LCNPs are self-assembled structures and can be easily formed by the combination of biocompatible lipids and aqueous phases. Certain stabilizers and additives may be added to enhance the stability and efficacy of LCNP formulation (Table 1). The factors that are essential for the formation of LCNPs are amphiphilic molecules, aqueous solvent, and temperature.

Lipids: Lipids are the biocompatibleamphiphiles that have been used in the formulation of LCNPs. Incontact with the aqueous medium, lipids undergo self-assembly to reduce the unfavorable interactions between their lipophilic part and the aqueous medium. To date, many lipids that have the ability to formlyotropicliquidcrystals have been reported in the literature. Glycerylmonooleate (GMO) and GMO-like lipids (e.g. monolinolein) were among the first lipids to be reported. Other examples of lipids include lecithin, phytantriol, silicone, and hydrogenated castor oil.

Stabilizers/surfactants: The dispersions of nanoparticles can be prevented from aggregation by the addition of stabilizers. Pluronic® polymers preventflocculation of LCNPs. The commonest Pluronic® polymeris Pluronic® F127, which is a triblock copolymer of ethylene oxide and propylene oxide. Brij-78 is another example. Ethoxylated phytosterol is a natural, non-polymeric surfactant, which.

Additives: Additives are added to improvedrug efficacy in LCNP formulations. Non-polarad ditives are added in hexosomes to imparts tability at room temperature. This is because hexosomes are normally formed at higher temperatures. Examples of additives include PEG, propylene glycol, cetostearyl alcohol, and tetradecane. Silica has been used to stabilize cubosome made of GMO. [5]

Characterization of RHTSLN: For characterization, three batches of optimized RHT SLN were formulated and they were characterized for physicochemical, morphological, diffusion and histopathological parameters as shown below.

Particlesize, PDIand Zeta Potential: Particle size, PDI and zeta potential measurements were performed by photon correlationspectroscopy using Zetasizer (Nano-ZS90, Malvern, Worcestershire, UK). Before measuring size,case of zeta potential, due to application of an electric field, particles move with a velocity related to theirzetapotential which is measuredusing atechniquecalled phase analysis light scattering andgets converted to the zeta potential by inbuilt software.

% Entrapment efficiency (%EE): The %EE of formulated RHT SLN was determined by centrifugation method. Samples were taken in centrifugetubes and centrifuged at 10000 rpm for 20min at room temperature in order toobtainpellet of lipidnanop articles. Supernatant was collected, suitablydiluted with methanol and analyzed for free drug content by UV spectroscopy. %EE was calculated by following equation:

%EE¼= Totala mount of RHT- Amount of free RHT / Total amount of RHT

The actual amount of AE entrapped in the LCNPs was calculated as the difference between the initial amount of AE used in the preparation of LCNPs and the amount of unentrapped AE separated in the filtrate, as determined spectrophotometrically at λmax =431 nm. [12,19,22,23,26]

Biological Assay: The formulation equivalent to 10 mg of RHT was diluted 10 times with methanol and final dilution was made with mobile phase. Samples were prepared and RHT content was determined by means of HPLC method. [8] The biological assays to evaluate the impact of these nanoparticles on the cell viability constitute an important aim of this work. Two different methodologies, image analysis and Alamar Blue assay, were applied in investigating the cytotoxicity of the LNPs. Studies were performed using threem different cell lines, namely, Swiss 3T3 mouse fibroblasts (3T3), human epithelial cervical carcinoma (HeLa), and human embryonic kidney (HEK 293T) cells. Treatments were applied to actively proliferating cells (1 day after seeding). In the case of 3T3, cell line observations were made through an inverted fluorescence microscope. [14,19]

Zeta potential: ZP is an essential parameter that could influence the colloidal stability of nano-sized drug delivery systems. Although MO is a neutral lipid, a negative ZP was observed during the optimization of LCNPs. This could be ascribed to the adsorption of hydroxyl ions on the surface of the LCNPs and also the commercial MO containing free oleic acid that may contribute to the negatively charged ZP. Such higher ZP could be beneficial in maintaining the stability of LCNP dispersions and preventing their aggregation. [12]

X-raydiffraction (XRD): X-ray diffraction analysis of sample was carried out to characterize the physical form i.e. amorphous or crystalline nature of glimepiride in sample of optimized batch in an X-ray diffractometer (D8 Advance, Bruker) with Cu Kα radiation (λ=1.54060 A°). The scanning rate 100/min and diffraction angle 2 was 10-800. [13]

Measurement of viscosity: Viscosity measurements of prepared topical NLCs based gel were measured by Brookfield viscometer using spindle no. 63 with the optimum speed of 10rpm; viscosity was found to be 3776cps.

Extrudability study: Extrudability was based upon the quantity of the gel extruded from the collapsible tube on the application of acertainload. More the quantity of gelextruded shows better extrudability. It was determined by applying the weight on the gel-filled collapsible tube and recorded the weight on whichgel was extruded from the tube. Extrudability of gel required 170 grams of weight to extrude a 0.6 cm ribbon of gel in 6 seconds. [16]

Stability Study: Chemical stability of tacrolimus entrapped in the liquid crystalline nanoparticle formulations was assessed during storage period at 25_C and 37_C for 1 month. Particle size evolution during the storage period was also analyzed. On the basis of this study it was considered that there was no significant change in the formulation and so we can conclude that formulation was stable after 1-month study at accelerated stability study.[22,23]

Scanning Electron microscopy: Scanning electron microscopy (SEM) is giving morphological examination with direct visualization. The techniques based on electron microscopy offer several advantages in morphological and sizing analysis; however, they provide limited information about the size distribution and true population average. For SEM characterization, nanoparticles solution should be first converted into a dry powder, which is then mounted on a sample holder followed by coating with a conductive metal, such as gold, using a sputter coater. [26]

Evaluation of nanoemulsion

Nanoemulsion Droplet Size Analysis: Droplet size distribution is one of the important physicochemical characteristics of a nano-emulsion, was measured by a diffusion method using a light-scattering particle size analyzer Coulter LS-230. It measures the size distribution using the diffusion of laser light by particles. It is used to measure the droplets size distribution, like 0.5 ml emulsion was introduced in the measure compartment (125 mlof water). The results were presented as the volume distribution.

Polydispersity Index: The average diameters and polydispersity index of samples were measured by photon correlation spectroscopy. The measurements were performed at 25oC using a He-Ne laser.

Viscosity Determination: The viscosity of the formulations was determined as such without dilution using a Brookfield DV III ultra V6.0 RV cone and plate rheometer using spindle.

Refractive Index: The refractive index, n, of a medium is defined as the ration f the speed, c, of a wave such as light or sound in a reference medium to the phase speed, vp, of the wave in the medium. n=c/vp It was determined using an Abbes type refractrometer (Nirmal International) at 25 ± 0.5°C.

pH: The apparent pH of the formulation was measured by pH meter.

Transmission Electron Microscopy (TEM): Morphology and structure of the nanoemulsion were studied using transmission electron microscopy. Combination of bright field imaging at increasing magnification and of diffraction modes was used to reveal the form and size of nanoemulsion droplets. Observations was performed as, a drop of the nanoemulsion was directly deposited on the holey film grid and observed after drying. [7]

Morphology and Dispersibility: The morphology of the microparticles was examined by a light microscope (Olympus) with digital image capabilities. One drop of the freshly prepared microsphere suspension was poured onto a slide and sealed with a cover glass. With the highest magnitude of amplification, the morphology, size uniformity, and aggregation or coalescence of the microspheres were studied. The images were captured using a personal computer running on built-in software.

Particle Size and Zeta Potential Measurement: The particle size of the prepared microparticles was determined by using a Cilas□ 1064 laser diffraction analyzer, yielding the mean size and size distribution. Only the samples with the aimedsize range were measured for zeta potential using a Zetasizer Nano ZS analyzer at a scattering angleof 173 ° at a temperature of 25 °C.

Determination of Drug Encapsulation Efficiency: The amount of encapsulated CPX in the microspheres was calculated by the difference between the amount of CPX added to the microsphere forming solution and the measured non-entrapped CPX remaining in the external phase after microsphere formation. After formation, the microsphere suspension was centrifuged for 10 min at 15,000 rpm and the supernatant was analyzed for the non- entrapped CPX by HPLC with UV detection at 260 nm. The chromatographic method was carried out isocratically. Themobile phase consisted of1.25%acetic acid in watermethanol (75:25) and the flow rate was set at 1 ml/min. Separation was achieved by using an Inersil C18 (250 mm x 4.6 mm, 5m) analytical column connected to an Inersil C18 (50mmx4.6mm,5m) guard column. The column temperature was 40 oC. Calibration curves were obtained over concentration ranges of 0.004 mg/ml to 0.5 mg/ml. [4, 20, 21, 24].

Drug Content (Assay): The standards and requirements were maintained accordingly and an accurately weighed portion of the powder equivalent to about 10mg of Sorafenib tosylate was transferred to a 10mL volumetric flask containing 7.4 pH. It was shaken by mechanical means for 1h then it was filtered through a Whattman filter paper (No.1) and diluted to 1mL with 7.4 pH. and absorbance was measured against blank at 264nm.

Invitrocorneal permeation study: Corneal permeation characteristics of tropicamide-loaded cubic ophthalmic nanoformulation were comparatively evaluated with the commercially available conventional ophthalmic preparation (Tropicacyl 1%, (w/v)) using isolated porcine eyes cornea as model. Fresh whole eyeballs were obtained from the local butcher shop immediately after slaughtering and transported to the laboratory in cold normalsaline with in an hour.There ceptor compartment contained 11.5ml off reshly prepared phosphate buffered saline (PBS) pH 7.4 maintained at 35±0.5 _C under magnetic stirring. Area available forcorneal permeation was 0.785 cm2. The test formulation (1 ml) was placed in the donor compartment over the cornea. An aliquot of 1ml of the sample was withdrawn from receptor compartment at fixedtime intervals and analyzed for the contents of tropicamide.

Ocular tolerance: Ocular irritancy potential of tropicamide-loaded cubic ocular nanoformulation was assessed employing Hen's Egg Test Chorioallantoic Membrane (HET-CAM). HET-CAM study is established alternative technique to the Draize rabbit eye test to check potential irritation effects in the eye. Ten-day-old fertilized hen's eggs were procured from a poultry farm. The eggs were placed in a stand with the equatorial side up where a small window was opened to expose the CAM. Only eggs with an air sac and live embryo were used for further testing. An aliquot of 0.5 ml of the test samples were placed directly onto the CAM's surface and CAM was observed for 5 min for appearance of any of the following phenomena: hemorrhage, vasoconstriction, and coagulation for which a score was calculated.

Invivomydriatic activity: Tropicamide produces a rapid mydriatic response and therefore bioavailability was assessed by measuring pupildiameter. The protocol for invivomy driatic study in rabbit was designed and an approval of institutional animal ethics committee was obtained. All tests were carried out on non- anesthetized Albino rabbits procured from disease free small animal house of Lala Lajpat Rai University of Veterinary and Animal Sciences. Three albino rabbits with equivalent pupil light response were used in the study. Each rabbit was acclimatized to the laboratory testing conditions for 1 h prior to initiating the study. [15]

Invitro drug release studies: *In vitro* drug release studies of glimepiride loaded PLA nanoparticles were performed to determinethepercentageof drug released from the nanoparticlesin gastricfluid and intestinal fluid. The *in vitro*drug release study of optimized formulation (R3 and R9) with same concentration surfactants was performed forthefirst two hoursat pH1.2and atphosphatebuffer pH 6.8 fornext 12 hrs. Therelease patterns of glimepiride from nanoparticles are shown in Figure. The drug released from the nanoparticles was found to be in the range of 14.46 to 16.89 % in first 2 hrs at pH 1.2 and 73.72 to 78.12% up to 12 hrs at pH 6.8. From the drug release behavior it was observed that if the polymer concentration increase drug release decreases due to the high viscosity of PLA which on contact with the dissolution medium, surface of nanoparticles become wet and forms viscous gel layers. As the concentration of PLA increases viscosity of the gel layers increases while the diffusion coefficient of drug decreases.

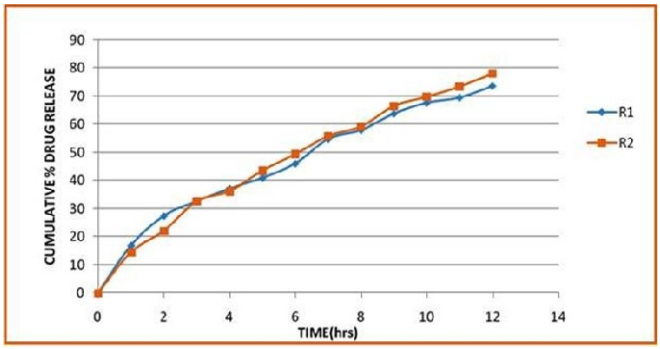

Figure 11. % cumulative drug release from sustaine drelease Glimepiride-Loaded PLA Nanop articles
Notes: R1-cumulative % drugrelease drug-polymerratio (1:1), R2-cumulative % drug release drug-polymerratio (1:3).[13,16]

The shape and surface morphology of prepared NLCs was determined by using TEM and SEM. The photomicrographwas takenwhichshown in figure and was found that they wereIt was observed that the percent drug entrapment was decreasing with increasing the concentration of surfactant and on increasing the time of sonication. It is due to the extract out the drug from particles on increasing the mechanical force by sonication and size reduction of size NLCs on increasing the concentration of surfactant due to their surfactant action. Stability study data was revealed that the optimized formulation stable after 3 mo of storage at 4°C while at 25-28±2°C, the formulation was found unstable.

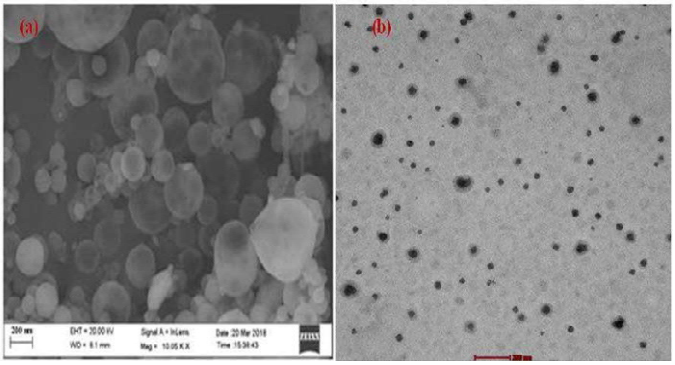

Figure 12. SEM(a) and TEM (b) photomicrograph of optimized NLCs formulation at 1000KX

This was dueto the high penetration ofdocetaxel-loaded NLCs into cancer cells. The valueof IC50 for docetaxel and docetaxel-loaded NLCs was found to be 0.2 µg/ml and 0.1µg/ml following 24 hr and 48 hr incubation, respectively which was more than 5-fold lower as compared to free docetaxel.

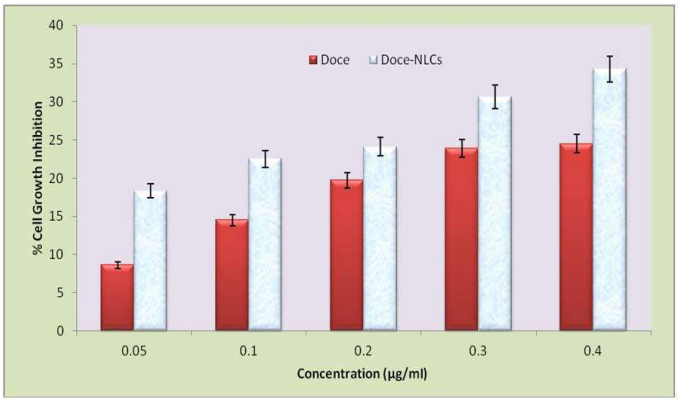

Figure 13. *In vitro*cytotoxicity of DOCE and DOCE-NLCs formulations (Percent Cell Growth Inhibition Assay) on skin cancer cell line, the value represents as mean±SD (n=6). [16]

Application of Solid Lipd Nanoparticles (SLNs):

Applications of Metallic Nanoparticles: The various characteristics of different nanoparticles relative to bulk metals are summarized below.

Catalyst function: Reaction efficiencies can been hanced since the specific surface area of such nanoparticles is large compared with existing particles; to the extent that the surface terrace is regular at the atomic level, a hyperactivecatalyst with high selectivity canbemade: forexample, Au nanoparticles.

Electrical function: Since super conductivity transition temperaturerises so that particle diameter is small (less than 1 nm), it can be used to make high temperature super conductivity material.

Mechanical function: Since the mechanical characteristics improve, mechanical strength can be sharply raised by mixing the nanoparticles with metals or ceramics.

Magnetic function: The attractive force of amagneticmetal increases on reduction of the particle diameter, such that soft-magnetic materials can be made in the form of an alloy of nanoparticles.

Application of Nanoparticles in Paints: One of the most interesting aspects of metal nanoparticles is that their optical properties depend strongly upon the particle size and shape. The nanoparticles attracted attention as color materials and the possibility of their use has been examined invarious fields. Spraying with the clear colored coating containing the nanoparticles increased the depth of the red background even more, and since the car is in the shade there is almost no diffuse reflection.

Figure 14. Photographofacar to which was applied a clear coating containing gold nanoparticle sonared colored base coating.

Application in Chemical Catalysis: Ni, Pd, Ag, and Pt have been used as typical metal catalysts in chemical reactions. However, the dissociative adsorption of hydrogen or oxygen molecules cannot be carried out on an Au smooth surface and at a temperature of less than 200 °C. Therefore, such a gold material is inactive as a catalyst in hydrogenation and oxidation reactions.

Application of Nanoparticles in Micro-wiring: Metal nanoparticle paste is used for circuit pattern formation of a printed wired board in the electronic industry. Formation of nanoparticle wiring can usean ink-jet method, a method that is both inexpensive and requires shorter times than vacuum evaporation and photolithographic methods that are typically used. Generally, Au is used to make the metal nanoparticle paste.

Application of Nanoparticles in Medical Treatments: Just as the surfaceplasm on resonanceis seen in a metal nanoparticle, an increase in the quantity of nanoparticles raises the scattering intensity. Taking advantage of this feature, the application to specifi c molecule recognition in a living body tissue is expected. The imaging at various wave lengthsis performed by achange in the shape of then anop article. [27]

Cosmetics and Sunscreens: The conventional ultraviolet (UV) protections unscreen lacks long-term stability during usage. The sunscreen including nanoparticles such as titaniumdioxide provides numerous advantages. TheUV protection property of titaniumoxide and zincoxidenanop articles as they are transparent to visible light as well as absorb and reflect UV rays found their way to be used in some sunscreens. Some lipsticks use iron oxide nanoparticles as a pigment.

Medicine: Nanotechnology has improved the medical field by use of nanoparticles in drug delivery. The drug can be delivered to specific cells using nanoparticles [32]. The total drug consumption and side effects are significantly lowered by placing the drug in the required area in required dosage. This method reduces the costandside effects. There production and repair of damaged tissue (Tissue engineering) can be carried out with the help nanotechnology. The traditional treatments such as artificial implants and organtransplants canbe replaced by tissue engineering. One such example is the growth of bones carbon nanotube scaffolds. [28,31]

In Tumour Therapy: It has been studied that naked gold nanoparticles inhibited the activity of heparin- binding proteins such as VEGF165 and bFGF *in vitro* and VEGF induced angiogenesis *in vivo*. Further work in this area has been reported that onto the surface of AuNPs heparin binding proteins areabsorbed and were subsequently denatured.

In Rheumatoid Arthritis: Scientists from the University of Wollongong (Australia) have built a new class of anti-arthritic drug which could be used by gold nanoparticles and it has fewer side effects. Rheumatoid arthritis is an autoimmune disease that occurs when the immune system does not function properly and attacks a patient"s joints. [29]

Energy Harvesting: Due to scarcity of fossil fuels scientist have been shifting their research interests in the development of different strategies which can help in generating renewable energies from easily available resources at cheap cost. NPs are the suitable candidate for this purpose due to their large surface area, opticalbehavior and catalytic nature. NPs are widely used to generate energy from photoelectrochemical (PEC) and electrochemical water splitting. [30]

Applicationsinenergy harvesting: Recent studies warned us about the limitations and scarcity of fossil fuels in coming years due to their nonrenewable nature. Therefore, scientists shifting their research strategies to generate renewable energiesfromeasilyavailableresources atcheapcost.TheyfoundthatNPsarethebestcandidate forthis purpose due to their, large surface area, optical behavior and catalytic nature. [33]

Advantages: Some of the advantages of using nanoparticles as a drug delivery system areas follows;

Ease of manipulation of the particle size and surface characteristics of nanoparticles so as to achieveboth passive and active drug targeting after parenteral administration.

1. Thenanoparticlesurfacecanbemodifiedtoalterbiodistributionofdrug swithsubsequentclearanceof the drug so as to achieve maximum therapeutic efficacy with minimal side effects of the drug.
2. Controlled release and particle degradation characteristics can be readily modulated by the choice of matrix constituents.
3. Drug loading is relatively high and drugs can be incorporated into the systems without any chemicalreaction; this is an important factor for preserving the drug activity.

Site-specific targeting can be achieved by attaching targeting ligands to surface of particles or use ofmagnetic guidance. [32]

CONCLUSION

We have demonstrated that NLCs are promising colloidal Nano systems for dermal delivery of Docetaxel through the invitroand invivo studies. NLCs suspension enhances Docetaxel permeability and picks it up to cancer cells and decreases cell viability at different concentration. According to cell uptakestudy, a substantial improvement in there striction of cancer cell was found. Further studies are necessary for the determination of long-term Docetaxel-NLCs stability andthe lack of cytotoxicity on the various untargeted organs to exploit this carrier can be used for the treatment of skin cancer. The current study adopted the development of new PEGylated LCNPs of AE. The AE-PEGylated LCNPs could be tailored with □96% drug encapsulation efficiency and nanometric range. The solubility enhancement property of MO-based system was assessed. Furthermore, the prepared formulation showed good serum stability and hemocompatibility with higher cytotoxic effects and cellular uptake in MCF-7 cells compared with free drug. Liquid crystal nanoparticles provide controlled release ofthe drug and these systems are used as drug carriers for lipophilic drugs, to enhance the solubility and bioavailability of poorly water-soluble drugs and to reduce the doses regimen through nanoparticles, as a drug delivery system.

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