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A REVIEW: NANOSTRUCTURED LIPID CARRIER AS DRUG DELIVERY SYSTEM

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ABSTRACT

Nanostructured lipid carriers (NLCs) are novel pharmaceutical formulations which are composed of physiological and biocompatible lipids, surfactants and co-surfactants. Over time, as a second generation lipid Nano carrier NLC has emerged as an alternative to first generation nanoparticles. This review article highlights the structure, composition, various formulation methodologies, and characterization of NLCs which are prerequisites in formulating a stable drug delivery system. NLCs hold an eminent potential in pharmaceuticals and cosmetics market because of extensive beneficial effects like skin hydration, occlusion, enhanced bioavailability, and skin targeting. This article aims to evoke an interest in the current state of art NLC by discussing their promising assistance in topical drug delivery system. The key attributes of NLC that make them a promising drug delivery system are ease of preparation, biocompatibility, the feasibility of scale up, non-toxicity, improved drug loading, and stability.

KEYWORDS: Nanostructure lipid carrier, Lipid, Topical, Skin.

INTRODUCTION

Nano particulate carriers, with their Nano scale dimensions and distinct properties, have shown great promise as delivery systems in the recent years. Their advantages include protection of the active ingredient by providing protection against moisture, physiological pH and enzymes, enhanced bioavailability, dose reduction, controlled drug release, prolonged circulation time, improved intracellular penetration and targeted delivery to specific sites or organs by surface modifications of the carriers. They also act as carriers for a variety of molecules including peptides and proteins, contrast agents, antibodies, RNA, etc. A variety of

Nano carriers such as Nano crystals, nanotubes and nanowires, liposomes, polymeric nanoparticles, hydrogels, dendrimers and lipid nanoparticles have been designed for drug delivery and diagnostic purposes.Lipidic drug delivery systems have gained attention in the past few decades primarily due to their biocompatibility as compared to polymeric and inorganic Nano particulate delivery systems, in addition to their capability of permeating challenging physiological barriers, especially the blood-brain barrier (BBB) due to their lipophilicity, even without surface modifications. Further, ease of preparation, cost-effectiveness and the feasibility of large-scale production is making these delivery systems more attractive

- **Types of NLCDepending on the location of incorporated drug moieties in NLC, following three types of morphological models has been proposed**

1) **Type I :- Imperfect Crystal Model**
2) **Type II :- Amorphous Model**
3) **Type III :- Multiple Type**

1) **NLC type I (imperfect crystal model)**

Imperfect crystal type NLC consists of a highly disordered matrix with many voids and spaces which can accommodate more drug molecules in amorphous clusters. These imperfections in the crystal order are acquired by mixing solid lipids with adequate amount of liquid lipids (oils). Due to varying chain length of fatty acids and the mixture of mono- di-, and triacylglycerol's, the matrix of NLC is not able to form a highly ordered structure.

2) **NSL type II (amorphous model**)

Amorphous type NLC is formulated by carefully mixing lipids in such a way as to minimize the drug leakage due to process of crystallization. Specific lipids such as hydroxyl octacosanyl, hydroxyl stearate, and isopropyl myristate or dibutyl adipate form solid yet non-crystalline particles. The lipid matrix exists in a homogenous amorphous state.

3) **NSL type III (multiple type)**

Multiple type NLC is oil/ lipid / water type. Lipophilic drugs are more soluble in liquid lipids than solid lipids. This idea leads to the development of multiple type NLC using high liquid lipid content. Oil moieties, at low concentrations, are effectively dispersed in the lipid matrix. The addition of oil beyond its solubility induces phase separation forming small Nano compartments of oil encircled in the solid matrix.

Type II model offer advantages like high drug entrapment efficiency, controlled drug release and minimized drug leakage.

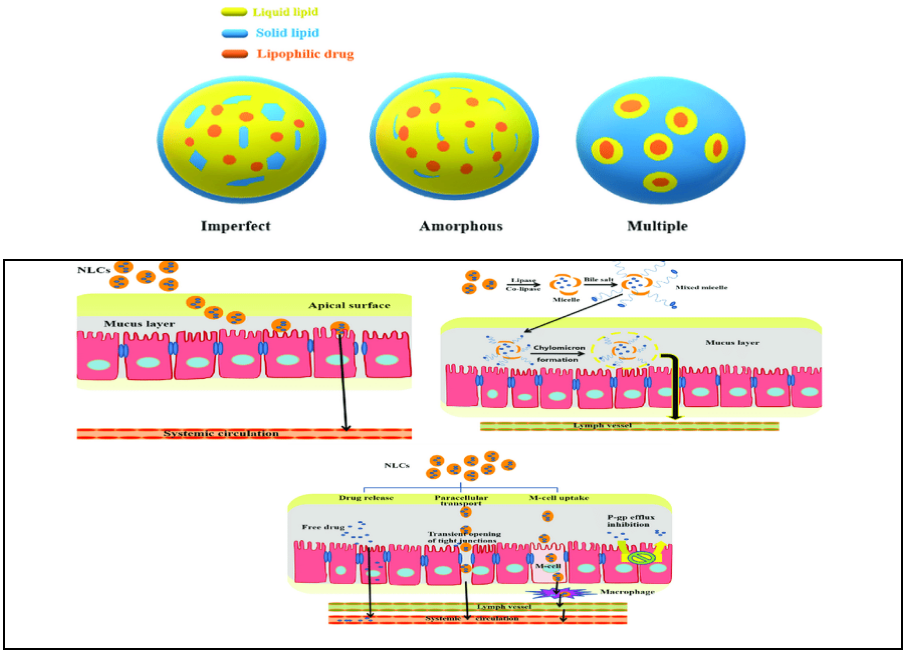

Fig.No: Multiple Type II

Application of NLC

1) Cosmetics

Recently NLCs have been developed based on the controlled Nano structuring of particle matrix which provides immense advantages with respect to loading capacity and long term stability. The various forms in which NLC dispersions can be given are gel, cream, lotion, ointment. The beneficial aspects associated with these NLCs in cosmaceuticals are very broad which lies in, enhancing skin bioavailability of active ingredients, film formation and controlled occlusion, UV protection, penetration enhancement and epidermal targeting, enhancement of physical and chemical stability and *in vivo* skin hydration.

The easily oxidized black currant seed oil is incorporated in NLCs which are able to protect it against oxidation and enhance the stability of the final product. A prolonged release profile can also be obtained for the perfumes and insect repellents by incorporating them in NLCs.

2) Chemotherapy

Recent studies have shown that NLCs not only enhanced the efficacy and stability but also reduced side effects of many cytotoxic drugs. Different Nano systems have been developed with anti-cancer drugs, for example, the albumin–paclitaxel nanoparticles were approved in

early 2005 in the chemotherapy for metastatic breast cancer; etoposide NLCs were found to be cytotoxic against human epithelial-like lung carcinoma cells; stabilization and prolonged release of topotecan NLCs in treatment of refractory ovarian and small-cell lung cancer.

Advantages of incorporating anti-cancer drugs in NLCs include.

i. high drug loading efficiency
ii. prolonged release profile
iii. Increased chemical stabilization.
iv. Increased cytotoxicity.

As these NLCs avoid some potential problems associated with SLN, such as drug leakage during storage and decreased loading capacity. They act by prolonging the exposure of tumor cells to anti-tumor drug and enhancing permeability and retention effect to further increase the therapeutic effect. It has also been reported that hyaluronic acid coated NLC could prolong the circulation time of paclitaxel (PTX) in blood and increase the accumulation of PTX in the tumor.

3) Neutraceuticals

Nutraceuticals are bioactive compounds, which provide medicinal or health benefits, including the prevention, and treatment of diseases. Among them, the carotenoids are one of the most important groups of natural pigments, because of their wide distribution in plant tissues, structural diversity and numerous functions.

Hesperetin (5,7,3′-trihydroxy-4′-methoxy flavone) belonging to flavones which is useful in chemically induced mammary tumor genesis, colon carcinogenesis, heart attack and blood pressure was also successfully encapsulated in NLCs that showed good acceptance, homogeneity, improved taste and enhanced therapeutic effects.

4) In food industry

Because of its good stability and high loading capacity, the NLCs are widely applied in the pharmaceutical field. It was seldom reported that the NLC was applied as a nutritional supplement carrier in food industry for the capsule and beverage preparations. However, there are certain difficulties related to the raw material supply, availability and environmental factors due to which there is still a great risk for food industry to invest in this area. NLCs for food application were developed to enhance the physicochemical stability and bioavailability.

5) Gene delivery and Gene therapy

Transfer of genes to mammalian cells is the most challenging task to achieve efficient and safe gene therapy. Gene delivery systems are basically divided into two types, viz., viral and non-viral vectors. Viral vectors have been extensively investigated because of their high transfection efficiencies while non-viral vectors have the benefits of low immunogenicity and ease of preparation). Lipopolyplexes are used as Nano medicines for successful and efficient gene delivery. These are prepared by combination of gene (RNA/DNA), polycations, and lipids. They are mainly preferred for gene delivery in treatment of various cancers.

Oral Application

a) Enhancement of oral bioavailability
b) Treatment of GIT local diseases
c) Mitigation of drug associated toxic effect

Cutaneous Application

a) Formation of film above the skin surface. This film could consequently improve skin hydration by diminishing water loss and improving drug penetration throughout the SC.
b) Creating controlled occlusive effect due to small particle size. This occlusion improves hydrates the SC, which subsequently increases the diffusion of the actives into the deeper skin layers.
c) Rearrangement of SC lipids, which aids penetration of actives.
d) Miscibility/mixing of NLCs lipid constituents with stratum corneum lipids also helps penetration.
e) Inclusion of surfactant disrupts of skin structure and improves absorptions.

6) Pulmonary Application

Lung offers plentiful advantages as a delivery route for noninvasive actives for localized and generalized acting drugs. If local delivery is desired (as in case of asthma, lung cancer and cystic fibrosis), the particles should be adjusted to be more relevant to be accumulated in targeted pulmonary region. However, respiratory airway systems have biological barriers including mucus, ciliated cells and alveolar macrophages which hurdle pulmonary delivery Controlled release behavior and suitable aerodynamic diameter were obtained. The majority of nebulized NLCs were deposited in alveolar area of mice. Nebulized NLCs particle size was in range of 100–200 nm confirming penetration and accumulation in deep respiratory tract. NLCs proved the superiority above free solution in terms of low incidence of intra-

alveolar bleeding and Normality of lung tissue parenchyma the drug is targeting the upper respiratory tract, it is cleared by ciliated cells whereas those drugs localized in lower respiratory tract, they will be engulfed and digested by alveolar macrophages. Lipid nanocarrires present one of the most suitable systems for pulmonary drug delivery as they can reach lower respiratory tract if their particle sizes are less than 0.5 lm resulting in high drug accumulation and diffusion In addition, smaller particle sizes (less than 260 nm) were reported to avoid macrophagal clearance. Specifically, lipophilic constituents contributes enhanced.

6) Ocular Application

a) Prolongation of drug release and hence residence time of the encapsulated drug.
b) Improvement of ocular bioavailability of the encapsulated drug via both transcellular and paracellular mechanisms.
c) Conquering blood ocular barriers.
d) Fortification of the encapsulated drugs against inactivation by lacrimal enzymes.
e) Raising the patient compliance by decreasing the dosing frequency.

7) Brain Application

To avoid invading by hazards, brain is highly shielded by diffusion restricting barrier called blood brain barrier (BBB). BBB can confines diffusion of the majority of macromolecules (100%) and small (98%).

So, the sole way to reach the brain in therapeutic concentration is via receptor-mediated endocytosis. Surface decorated NLCs enhanced brain delivery of both drugs when compared to NLCs and solution. Khan and coworkers investigated brain delivery by evaluation of anticonvulsant and anxiolytic effects of carbamazepine loaded NLCs.

Advantages and Disadvantages

Sr. no	Advantages	Disadvantages
1	More loading capacity for drugs	Cytotoxic effects related to the nature of lipid matrix and concentration
2	Less water in the dispersion	Irritation and sensitizing action of surfactants
3	Prevent drug expulsion during storage	Application and efficiency in case of protein and peptide drugs and gene delivery systems still needs to be exploited
4	Control and targeted drug release	Stability of lipids
5	Feasibilities of loading both hydrophilic and lipophillic drugs	

6	Use of biodegradable and biocompatible lipids	
7	Avoid organic solvents	
8	Less expensive	
9	Easier to qualify, validate and gain regulatory approval	
10	Better physical stability	
12	Ease of preparation and scale up	
13	Increase of skin hydration and elasticity	
14	Small size ensures close contact with the stratum corneum	

Methods of preparing NLC

1) High pressure homonization technique

This technique is powerful and reliable for the commercial-scale production of NLCs. High pressure used in homogenization technique makes it possible to avoid use of organic solvents in preparations and render them eco friendly. Additionally high-pressure homogenization is easy to scale up and an attractive technique being used in the manufacturing of pharmaceuticals and cosmetics for topical application.

Hot homogenization is performed at elevated temperature and cold homogenization is done below room temperature. Active ingredient is dissolved or dispersed in the molten lipid before to the high pressure homogenization, in both approaches. High pressure (100–2000 bar) moves the fluid in the narrow gap in homogenizer.

2) Hot homogenization

In this approach homogenization is conducted at elevated temperature. The solid lipids are melted at a temperature above 5-10°C above their melting point. A dispersion is obtained by adding liquid lipid and drug to be encapsulated. The mixture is dispersed in aqueous solution of surfactant (s) heated to same temperature by high shear mixing device and leads to formation of pre emulsion. The pre-emulsion is introduced in high pressure homogenizer at controlled temperature. Generally 3 to 5 cycles at 500-1500 bar are sufficient for homogenization. The lipid recrystallizes and causes formation of nanoparticles as nanoemulsion is gradually cooled down. Employment of high temperature during the process may lead to degradation of heat sensitive ingredients. Another problem which may arise is reduction in emulsifying capacity of surfactants due to high temperature as surfactants have cloud point lower than 85°C. This may induce instability to nanocarriers.

3) Cold homogenization

In this technique lipid melt containing active agent is rapidly cooled to being solidify using liquid nitrogen or dry ice, then milled and ground before being dispersed in cold surfactant phase and subsequently homogenized at room temperature. Pressure used in cold process is higher i.e. 5-10 cycles of 1500 bar. This approach minimizes the thermal exposure of drug and well suited for thermolabile drugs. Improved drug entrapment efficiency and uniform distribution of drug within the lipid are other benefits of the method. However it results in nanoparticles of more variable sizes

4) Solvent emulsification evaporation method

In this method, the lipids (solid lipid + liquid lipid) along with drug are dissolved in a water immiscible organic solvent (cyclohexane, chloroform). The obtained mixture is dispersed into aqueous solution of emulsifiers producing an o/w emulsion. Evaporation under reduced pressure is employed to remove solvent from the emulsion. Evaporation leads to the dispersion of nanoparticles in the aqueous phase (by lipid precipitation in the aqueous medium). This method avoids any thermal stress, but usage of organic solvent is a disadvantage. Particle size can vary from 30-100 nm according to the solid lipid and surfactant.

5) Solvent emulsification diffusion method

In this technique, solvent and water are mutually saturated to maintain initial thermodynamic equilibrium. Afterwards, the lipids and drug is dissolved in the water-saturated solvent. Solvent containing drug and lipids are emulsified in a solvent-saturated aqueous emulsifier solution by a homogenizer to form an o/w emulsion. The lipid nanoparticles precipitate after dilution with excess water (ratio: 1:5–1:10) due to diffusion of the organic solvent from the emulsion droplets to the continuous phase. The solvent can be removed by ultrafiltration or lyophilisation. Solvent diffusion is more innovative and most of the solvent employed show a better safety profile compared to volatile solvents.

6) Micro emulsion method

In this approach, the solid lipid is melted, followed by addition of liquid lipid and solubilization of drug in the subsequent mixture. Separately, a mixture of emulsifier, co-emulsifier and water is heated at same temperature. Both the lipid and the aqueous phase are mixed in appropriate ratios and gently stirred to produce thermodynamically stable oil in water hot microemulsion. The hot micro emulsion is quickly dispersed into an excess of

chilled water (0-4°C) with vigorous stirring. The dilution causes the breakdown of microemulsion into a nanoemulsion with ultrafine particles. The ratio of the hot microemulsion to cold water usually lies in the range of 1:10 to 1:50. As the microemulsion is diluted by cold water, the internal lipid droplets recrystallize to form nanosize carriers. The size of the nanoparticles depends on the droplet size of micro emulsion and temperature difference between micro emulsion and ice water. Rapid cooling and hence solidification can prevent the aggregation of particles and lead to production of smaller particles.26 NLC dispersions formed by this method contained large quantity of particles in the micron range; therefore, in this condition, the time of stirring, percentage of lipids, and amount of drug were optimized in order to obtain the appropriate size and higher entrapment efficiency. The method does not require any special equipment or energy for production of NLC; hence it is simple to commercially scale up the technique.

7) Double emulsion technique

This method is mainly used for the production of lipid nanoparticles loaded with hydrophilic drugs. This technique overcomes the problem of escapism of water soluble moiety in aqueous phase from oily phase as investigated in micro emulsion method. In this method, drug is firstly dissolved in aqueous solvent (inner aqueous phase) and then is dispersed in lipid phase (Molten solid lipid + liquid lipid+ lipophilic surfactant+ lipophilic active moiety) to produce primary emulsion (w/o). Both lipid and the aqueous phase are maintained at same temperature. Stabilizer prevents loss of drug to the external phase during solvent evaporation. Afterwards, primary emulsion is dispersed into a large volume of surfactant aqueous solution followed by sonication to form a double emulsion (w/o/w). The lipid nanoparticles are then purified by ultrafiltration or solvent evaporation.

8) Solvent injection technique

It is a viable new technique to manufacture lipid nanoparticles. In this technique, lipids are solubilized in water-miscible solvent (e.g., acetone, methanol, ethanol, isopropyl alcohol) or water-soluble solvent mixture and then rapidly injected into aqueous surfactant solution under continuous stirring. Resultant dispersion is filtered in order to eliminate excess lipid. The technique relies on rapid diffusion of the solvent over the solvent–lipid interfaced with the aqueous phase. The particle size of nanocarriers depends on diffusion rate of the organic solvent through the lipid-solvent interface. This method offers the advantage of easy

handling, efficiency, versatility, no employment of technical equipment (e.g., high-pressure homogenizer) and use of approved organic solvents.

9) Phase inversion technique

It is a novel, cost effective and solvent-free approach for the formulation of lipid nanocarriers that involves the phase inversion from o/w to w/o emulsion.

It involve two steps.

Step 1: - involves mixing of all the ingredients (lipid, surfactant and water) in optimized proportions. The mixture is stirred and temperature is increased at a rate of 4°C to reach up to 85°C from room temperature. Three temperature cycles (85–60–85-60-85°C) are applied to the system to reach phase inversion zone.

Step 2: - results an irreversible shock introduced to break the system, due to dilution with cold water (0oC). This fast addition of cold water causes formation of nanocapsules. Application of a slow magnetic stirring for 5 minutes avoids particle aggregation. Low energy involvement enables the formation of stable transparent dispersions (smaller than 25 nm), which can be used for encapsulation of numerous bioactive compounds.

10) Microfludization method

The technique involves use of a new, patented mixing technology employing high shear fluid device known as microfluidizer. In this process, the liquid is forced at speed up to 400 m/s through micro channels to an impingement area at high operating pressures. Cavitation and the accompanying shear and impact are accountable for the efficient particle size reduction within the "interaction chamber". The technique can be utilized on laboratory as well as production scale.

11) Membrane contractor technique

Membrane contactor is used to identify membrane systems that are employed to "Keep in contact" two phases. The lipid phase, at a temperature above its melting point is placed in a pressurized vessel. It is allowed to permeate through ceramic membrane pores under applied pressure to form small droplets. The aqueous phase, under continuous stirring, flow tangentially inside the membrane module, and brush away the droplets formed at the pore outlets. Cooling of the preparation to room temperature leads to the formation of lipid particles. Temperature of aqueous and lipid phase, aqueous phase tangential-flow velocity

and pressure of lipid phase and membrane pore size are the process parameters affecting size of lipid nanocarriers. The benefits of this new process of membrane emulsification are commercial scalability and control on particle size by fitting optimized parameters.

Stability of nanostructured lipid dispersions

NLCs may contain additional colloidal structures, such as micelles, mixed micelles, liposomes and Nano emulsions which contribute to their stability. There are also some major stability issues during storage, such as particle size enhancement, gelation of the dispersion and drug expulsion from the lipid matrix. Gelation takes place due to formation of the network and lipid bridges between the particles. The physical stability of these dispersions is generally investigated by measurement of particle size (Photon correlation spectroscopy, PCS; Laser diffraction, LD), zeta potential (ZP) and thermal analysis (Differential scanning calorimetry, DSC). Several studies indicated physical stability of SLNs dispersion more than 1 year.

In case of highly concentrated NLC dispersions the particles form a 'pearl-like network', thus undergoing collision and per kinetic flocculation. After the administration of NLCs and their dilution with gastrointestinal fluid, the network is destroyed releasing single, non-aggregated particles. Lipid particle dispersions were produced at identical surfactant concentration, but with low lipid content (below 30%, outside patent coverage) and with 35% lipid. The low particle dispersion aggregated during storage time, the gel-like NLC dispersion remained stable during storage and, after dilution, and single particles were obtained showing no size increase Freely diffusible nanoparticles in low concentration dispersion can collide and aggregate (upper), while in highly concentrated dispersions the particles are fixed in a network, where further dilution with water releases non-aggregated definite nanoparticles.

Strategies employed for overcoming the issues related to stability of NLCs

- Providing good physical stability and dispersability of colloids.
- Improving presence of colloids in blood circulation for systemic use.
- Modulation of interaction of colloids with mucosa for specific delivery requirements and drug targeting
- Acceleration of colloid transport across the epithelium.
- Increasing biocompatibility and decreasing thrombogenicity of drug carriers.

- Providing reservoir function to colloid particles carrying hydrophobic drugs due to hydrophilic coating around the particles.

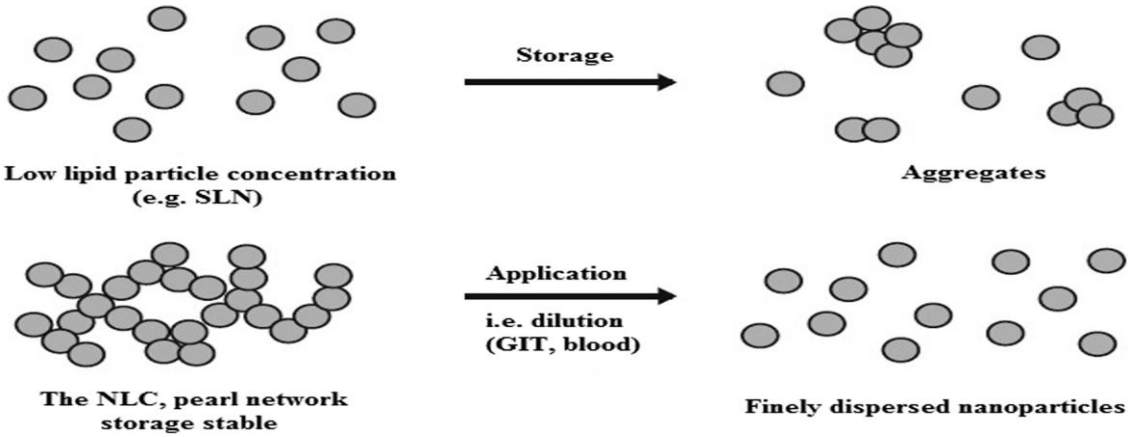

Figure: Stabilization effect in highly concentrated lipid particle dispersions; adopted and modified

Spray drying

In addition to the optimized storage conditions, SLNs/NLCs dispersions can also be spray dried to increase their stability.

However, melting point of the lipid matrix should be more than 70°C for spray drying.

Lyophillization

Efficient way to increase stability is lyophilisation. However, when SLN are lyophilized without cry protectant, the final product commonly results in the aggregation of particles. Some of the most widely used cry protectants are trehalose, sorbitol, glucose, sucrose, mannose and maltose.

CONCLUSION

The lipid nanoparticles like SLN, NLC, LNC, etc. have always been potential carrier systems with good therapeutic applications. The purpose of this work was to highlight the role of NLCs as a novel drug delivery system for various categories of drugs. They are the new generation, smart, flexible systems offering for enhanced drug loading, modulation of release and improved performance in producing final dosage forms such as creams, tablets, capsules and injectable. The article also emphasizes on various production techniques, stability related issues along with the therapeutic and cosmetic applications of NLCs.

LNC (e.g. NLC) of this generation are considered to be one of the major strategies for drug delivery without any modification to the drug molecule because of their rapid uptake, bio-acceptability and biodegradability. The impact of these carrier systems is continuously increasing and thus has bright future prospects. However, their cytotoxic effects related to the nature of matrix and concentration, irritative and sensitizing action of some surfactants are the areas of concern. Their application and efficiency in food, protein and peptide drugs, gene delivery systems and other fields still needs to be better exploited.

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