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SOLID LIPID NANOPARTICLES; THE BENEFICIAL CARRIER FOR THE DELIVERY OF LIPID SOLUBLE DRUGS

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ABSTRACT

The review focused on the potential method of preparation, characterization and application of the solid lipid nanoparticles. The solid lipid nanoparticles are used for the chemotherapy of parasitic infection, cancer etc. solid lipid nanoparticles are used for the effective medication of proper concentration to the site of action. Nanoparticles are the solid colloidal particles ranging in 1-1000 nm. The methods use to prepare the solid lipid nanoparticles produce the different size, surface characteristic and the stability. It is the optional for the drug delivery such as emulsion, microparticles, liposomes and niosomes etc. The stability and surface characteristic can be improved by using suitable technique for preparation of nanoparticles. It is also easy to enhance the solubility of lipophilic drugs and their bioavailability. The biodistribution of the solid lipid nanoparticles is possible due to their nano size.

Keywords: *Nanoparticles, microparticles, liposomes, emulsions, nanoparticles.*

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INTRODUCTION

Great progress to treat the various diseases has been done by use of one of drug delivery system including solid lipid nanoparticles (SLN). SLN's which is the colloidal drug carrier systems. SLN are same as the nanoemulsions, conflicting in lipid character. The liquid which used as in emulsions can be substituted by a lipid solid particle (at room temperature) in SLN by means of (high-melting point) glycerides or waxes. SLN's are growing with significance as another drug carrier to polymeric nanoparticles. Controlled drug delivery and enhancement of bioavailability of entrapped drugs through modification of dissolution rate (study) and improvement of tissue distribution.

In the 1960s, the first safe (parenteral) fat emulsion (Intra lipid) was urbanized by Wretlind for parenteral nutrition. This was the introduction of a new delivery system for lipophilic (lipid soluble) drugs, which also can included easily into the form of oil droplets. Successful market products are DIPRIVAN And DIAZEMULS. The main benefit of such carrier system is the decreasing of side effects caused during the injection site. The main drawback is the critical physical stability of

the drug which contains emulsions due to a drop of the zeta potential (ZP) (which can lead to agglomeration, drug expulsion and finally breaking of the emulsion). Another motivating carrier systems are the liposomes. They have explained for the earliest time by Bangham et al. in the 1960. Trade products (DaunoXome, Ambisome, Alveofact and Doxil) had been develop in order to diminish toxic side effects of the incorporated highly potent drugs which result in enhance the efficacy of the treatment

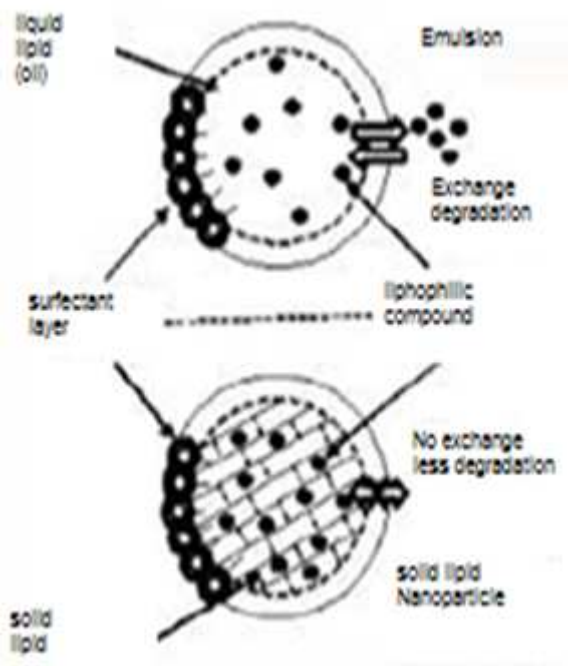

Fig 1:- solid lipid nanoparticles

Polymeric nanoparticles made up of non-biodegradable and biodegradable polymersare yet another modern carrier system. Advantages of these particles will be controlled release system of the incorporated drugs and site-specific targeting. The cytotoxicity of the polymers after the internalization into the cells is a crucial and often discussed aspect. Also the large scale production of polymeric nanoparticles is challenging once. Thus, this carrier system has still now not been relevant for the pharmaceutical market.

In the middle of the 1990s, the concentration of different research batches directed on alternative nanoparticles made up of solid lipids. The advantage combine by solid lipid nanoparticles of further innovative carrier systems e.g. physical stability, protection of incorporated labile drugs to avoid degradation, controlled release of drug, excellent tolerability of drug, while at the same time minimizing the related problems. SLN formulations for a different application routes (oral, parenteral, dermal, occular, pulmonary, rectal etc) had been developed. Thoroughly characterized the in vivo and in vitro. SLN will be produced by replace the liquid lipid (oil) of an o/w type emulsion by a solid lipid particles or a blend of solid lipids particles, i.e. the lipid particle matrix presence solid at mutually room temperature and body temperature. SLN are calm of 0.1% (w/w) to 30% (w/w) solid lipid particles isolated in an aqueous phase medium and when essential stabilized with preferably 0.5% (w/w) to 5% (w/w) surfactant. The incorporation of cosmetic and pharmaceutical actives is possible. The average size of particle of SLN will present in the submicron range, (ranging from 40 to 1000nm).

A first product has been recently introduced to the Polish market (NANOBASE, YAMANOUCHI) as a topically (applied) moisturizer. SLN has the chance to be exploited as delivery system in the commercial products. But there are three limitations of the SLN system as following:

1. Drug expulsion phenomenon (when lipid crystallizes to the stable b-form).
2. Particle concentration in the aqueous dispersions range from about 1% to 30%.
3. Limitation of drug load by the solubility of the drug in the solid (lipid.)

These limitations were solved by a lipid particle with the controlled nanostructure, the nanostructured lipid carrier (NLC). In the NLC, very different lipids were blended to form the matrix, i.e. solid lipids and liquid lipids. Due to their change in structure they cannot fit together very fine to form a perfect crystal form, the matrix containing a lot of imperfections to accommodate drug in molecular form and amorphous clusters form.

In the second generation of the lipid nanoparticles technology, the particles were produce by using blends of solid lipids and liquid lipids (oils). To obtain such blends for the particles matrix, liquid lipids are mixed with solid lipids, rather in a ratio of 30:70 up to a ratio of 99.9:0.1, because of the oil in these mixtures a melting point depression compared to the pure solid lipid is observed, but the blends obtained, in this case are solid at body temperature. This second generation of nanoparticles also called nano-structured lipid carriers (NLC). The whole solid content of NLC should be enhanced up to 95%. This second generation of submicron size particles can be loaded with the cosmetic and pharmaceutical actives as well.

However, as a distinct advantage of the SLN compared to polymeric nanoparticles, they can be produced by using high pressure homogenization identical to parenteral O/W emulsions. This technique is well established on the large scale since the fifties and already available in the pharmaceutical industrial area. The production lines for parenteral emulsions are in most cases equipped with temperature control units because of an increased temperature facilitates emulsion production. The meaning of this is existing production lines can be used for producing SLN by the hot homogenization technique.

PRINCIPLES OF DRUG RELEASE FROM SLN

The common principles of drug release from lipid nanoparticles can be explained below; drug release is inversely proportional to the partition coefficient of the drug. Surface area increases due to smaller particle size in nanometer range which results in higher drug release. Slow release of drug could be accomplished when the drug is equally dispersed in the lipid matrix. This phenomenon of drug dispersion depends on type of SLN and drug entrapment (set up) model of SLN.

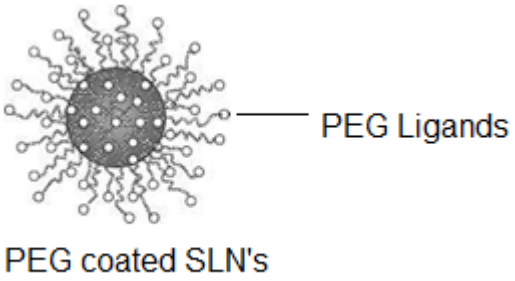

Fig. 2:-Schematic diagram of SLN coated with Poly ethylene glycol and molecular residues of PEG.

Crystalline form of the lipid carrier substance and high flexibility of the drug result into the fast drug release from system. Crystallization degree and mobility of drug are inversely proportional to each other. The drug incorporation model of solid lipid nanoparticles is crucial to the drug release pattern. [1]

Fast primary drug release (burst effect) happens in the first 5 minutes in the drug-enriched shell model (i.e., about 100% within <5 min) as because of the outer most layer of the particles due to the larger surface area of drug (i.e. smaller particle size) decomposition on the particle surface. The burst release phenomenon can reduces with increasing the particle size and contineous release of drug obtained when the particles size will be adequately larger, i.e. lipid microparticles. The nature of surfactant used in the system and its concentration i.e. which will interact with the outer most shell to affect its structure, should be observed as the further significant factor, because a lower surfactant concentration results into a minimum burst and prolonged drug release. In the drug-enriched core model, the release of drug will be membrane controlled and is governed by the Flicks law of diffusion since the lipid surrounds to the drug as a membrane.[2]

SOLID LIPID NANOPARTICLE (SLN)

SLN are particles made from solid lipids (i.e. Lipids solid at room temperature and also at body temperature) and stabilized by surfactant. By

definition, the lipids can be highly purified triglycerides, complex glyceride mixtures or even waxes. The first patents have been granted in 1993 and 1996 and contain claims on different production methods of SLN. The main features of SLN are the excellent physical stability, protection of incorporated labile drugs from degradation, controlled drug release (fast or sustained) depending on the incorporation model, good tolerability and site specific targeting. Potential disadvantages such as insufficient loading capacity, drug expulsion after polymorphic evolution during storage and somewhat high water content of the dispersions (70-99.9%) had been observe. The drug loading capacity of predictable SLN is limited (generally up to approximately 25% with regard to the lipid matrix, up to 50% for special actives such as Ubidecarenone) by the solubility of drug in which the lipid can be melt, the arrangement of the lipid matrix and the polymorphic state of the lipid matrix. Therefore, the use of more complex lipids (mono-, di-, triglycerides, and different chain lengths) is more sensible for higher drug loading. The transition to highly ordered lipid particles is also the reason for drug expulsion. Directly after production, lipids crystallize partially in higher energy modifications with more imperfections in the crystal lattice.

PREPARATION OF SLN

METHODS OF PREPARATION OF SOLID LIPID NANOPARTICLES

The following six types of methods are used for preparation of solid lipid nanoparticles. The more useful and easy one method is high pressure homogenization. All six methods are explained below. In high pressure homogenization shear stress and cavitation force is used.

a) High Pressure Homogenization

It is a reliable and powerful technique, which is used for the production of SLNs. High pressure homogenizers push a liquid with high pressure (100-2000 bar) through a narrow gap (in the range of a few microns). The fluid accelerates on a very short distance to very high velocity (over 1000 km/h). Very high shear stress and cavitation forces disrupt the particles down to the submicron range. Generally 5-10% lipid content is used but up to 40% lipid content has also been investigated. Two general approaches of HPH are hot homogenization and cold homogenization; work on the same concept of mixing the drug in bulk of lipid melt.[3,4]

In high pressure homogenization technique lipids are pushed with high pressure (100-200 bars) through a narrow gap of few micron ranges. So shear stress and cavitations are the forces which cause the disruption of particle to submicron range. Normally, the lipid contents are in the range of 5-10%. In contrast to other preparation technique high pressure homogenization does not show scaling up problem. Basically, there are two approaches for production by high pressure homogenization, hot and cold homogenization techniques. For both the techniques the drug is dissolved or dispersed or solubilized in the lipid being melted at approximately 5-10ºc above the melting point.

i) Hot Homogenization Technique

Hot homogenization is conducted out at temperatures above which the melting of the lipid occour. it can consequently be viewed as the homogenization of (dispersed system) an emulsion. The melting of a pre-emulsion of the drug loaded lipid occour and the aqueous emulsifier phase (same temperature) should be achieved by high-shear mixing device. Above the melting point temperature of the lipid the HPH of pre-emulsion should be carried out. In general, higher temperatures result in lower particle sizes due to the decreased viscosity of the inner phase. However, high temperatures increase the degradation rate of the drug and the carrier. Further, one should remember that the high pressure homogenization increases the temperature of the sample (approximately 108°C for 500 bar). Increasing the homogenization pressure or the number of cycles often results in an

increasing of the particle size of lipid due to high kinetic energy of the particles.[5]

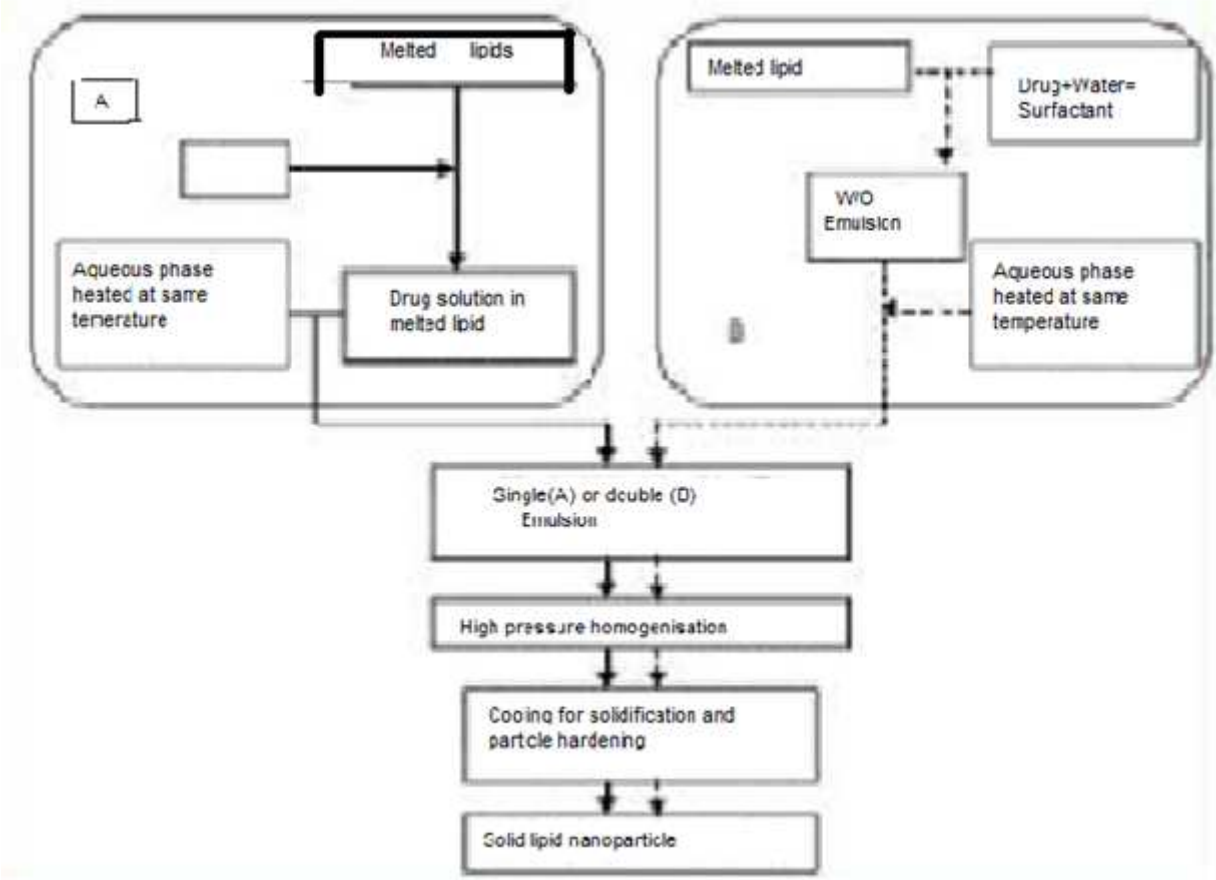

Fig. 3: Solid lipid nanoparticles preparation by hot homogenization process.

In hot homogenization technique the drug loaded melted lipid is dispersed under stirring by high shear device (e.g. Ultra Turrax) in the aqueous surfactant solution of same temperature. The pre-emulsion obtained is homogenized by using a piston gap homogenizer (e.g. Macron LAB 40/60 or APV-2000) and the produced hot o/w nanoemulsions is cooled down to room temperature. At room temperature the lipid recrystallizes and leads to formation of Nanoparticles.

ii. Cold Homogenization Technique

Cold homogenization has been developed to overcome various problems associated with hot homogenization such as: Temperature-induced drug degradation, drug distribution into the aqueous phase during homogenization, Complication of the crystallization step of the nanoemulsion leading to a number of modifications and/or super cooled melts.[6,4] In this technique the drug containing lipid melt is cooled, the solid lipid ground to lipid micro particles and these lipid micro particles are dispersed in a cold surfactant solution yielding a pre-suspension. Then this pre-suspension will be homogenized at or below room temperature, the force is strong enough to break the lipid micro particles directly to solid lipid nanoparticles.

The problem which occour during hot homogenization technique can be avoided by cold homogenization technique. Such as, the temperature mediated accelerated degradation of the drug payload, Partitioning and hence degradation of drug into the aqueous phase during

homogenization process. First step in between cold and hot homogenization is same.

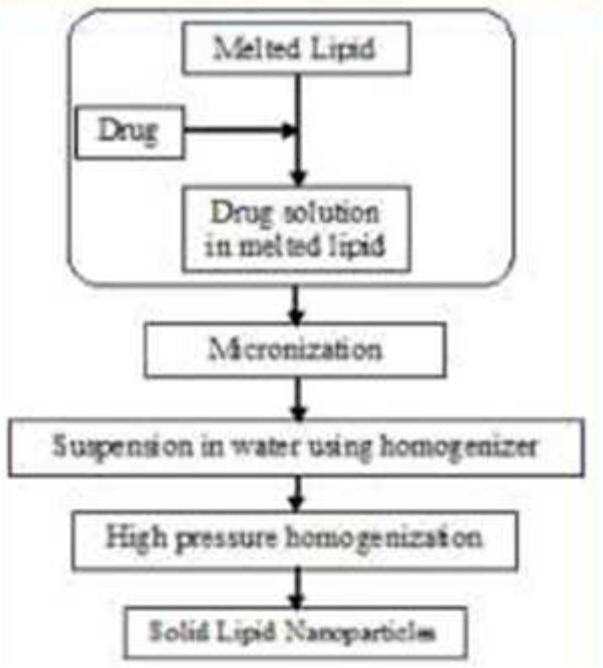

Fig 4:- solid lipid nanoparticles by cold homogenization

b) Ultrasonication/High Speed Homogenization

SLNs are also prepared by ultrasonication or high speed homogenization techniques. For smaller particle size combination of both ultrasonication and high speed homogenization is required. Potential metal contamination and physical instability like particle growth upon storage are the major drawbacks of this technique.[7,8]

c) Solvent Evaporation/ Emulsification

SLNs are also prepared by solvent evaporation method. Sjostrom and Bergenstahl described a production method to prepare nanoparticles dispersions by precipitation in o/w type emulsions. The lipophilic material is dissolved into a water-immiscible organic solvent (e.g. cyclohexane) that is emulsified into an aqueous phase. During the evaporation of the solvent, the precipitation of the lipid in aqueous medium results into nanoparticles dispersion(giving the nanoparticles of 25 nm mean size). Siekmann and Westesen also prepared solid lipid nanoparticles of 30 to 100 nm by dissolving tripalmitin in

chloroform. This solution was emulsified in an aqueous phase by high pressure homogenization. The emulsion can be evaporated under reduced pressure(40-60 mbar) and the organic solvent can be removed out from emulsion.[9,10]

d) Supercritical Fluid Method

This is an alternative method of preparing SLNs by particles from gas saturated solutions (PGSS). This technique has several advantages such as (i) avoid the use of solvents; (ii) Particles are obtained as a dry powder, instead of suspensions, (iii) mild pressure and temperature conditions. Carbon dioxide solution is the best solvent for this method.[11,12,13]

e) Micro emulsion Based Method

This method is based on the dilution of micro emulsions. As micro emulsions are two-phase systems composed of an inner and outer phase (e.g. o/w-micro emulsions). They are formed by stirring an optically transparent mixture at 65-70°C. An optically transparent mixture composed of a lower melting fatty acids (e.g. stearic acid), an emulsifier (e.g. polysorbate20, polysorbate 60, soy phosphatidyl choline and taurodeoxy cholicacid sodium salt), co-emulsifiers (e.g. butanol, sodium monooctyl phosphate) and water.

The hot micro emulsion is dispersed in cold water (2-3°C) under stirring. Excipients like butanol are less favorable with respect to regulatory aspects. From the technical point of view precipitation of the lipid particles in water is the dilution of the system that leads to reduction of solid content of SLN dispersion. For some technological operations it is desirable to have a high lipid solid content, e.g. 30%. The SLN dispersion can be used as granulation fluid for transferring in to solid product (tablets, pellets) by granulation process, but in case of low particle content too much water needs to be removed. Considering micro emulsions, the temperature gradient and the pH value fix the product quality in addition to the composition of the micro emulsion. High-temperature gradients facilitate rapid lipid crystallization and prevent aggregation. Due to the

dilution step; achievable lipid contents are considerably lower compared with the HPH based formulations.[14,15,]

f) Spray Drying Method

Spray drying method is an alternative technique to the liopophilization. Freitas and Mullera suggested the use of lipid with melting point more than 70° C by using this method. The best results were gained with SLN concentration of 1% in a solution of trehalose in water or 20% trehalose in ethanol-water mixture system.[16]

Characterization Of Solid Lipid Nanoparticles:

1. Particle Size Determination
2. Drug Entrapment Efficiency
3. X-Ray Diffraction
4. Differential Scanning Calorimeter

1) Particle Size Determination

The particle size of solid lipid nanoparticles can be determine by the Laser diffractometry (LD). The size distribution of solid lipid nanoparticles depends upon poly dispersity index. To prepare the droplets of solid lipid nanoparticles in sufficient range, proper input of energy is require. The fine dispersion is directly depends upon the stirring rate, temperature, emulsification time etc. The mean and width of solid lipid nanoparticles measured by Laser Diffractometer.[27,28]

2) Drug Entrapment Efficiency (EE%)

Accurately weight quantity of solid lipid nanoparticles. The amount of drug present within the nanoparticles can be determined by the U.V. Spectrometer. By the following equation we can measure the Entrapment Efficiency,[29]

$$\text{Entrapment efficiency}(\%) = \frac{W_{\text{initial drug}} - W_{\text{free drug}}}{W_{\text{initial drug}}} \times 100$$

3) X-Ray Diffraction

This method is commonly used to determine the crystal and amorphous nature of drug entrapped within the case of nanoparticles. The diffraction pattern of the graph by using this method can be helpful to check the crystallinity and amorphous nature of drug. The sharp peak is obtained in case of drug present in the crystals form and they are in order.[30]

4) Differential Scanning Calorimeter

It is analytical probe for the investigation of melting point or phase transmission and recrystallization nature of solid lipid nanoparticles. The sample and reference are heated to the same temperature and melting temperature of both sample is determined. Organic compound usually show a marked melting point (increasing range of melting temperature of the sample may have impurities. Temperature difference between sample and reference is calculated and impure sample is identified i.e. for purification and identification purpose it is useful.[31]

APPLICATIONS OF SOLID LIPID NANOPARTICLES

1) Oral Delivery

Oral administration of SLNs will possible as aqueous dispersion or after transforming in to dosage form i.e. tablets, pellets, capsules or powder in sachets. For the production of the tablets the aqueous SLN dispersion can be used as a substitute of a granulation fluid in the granulation process. On the other hand SLN can be transferred to a powder (e.g. by spray drying) and added to the powder mixture. For the production of pellets the SLN dispersion can be used as wetting agent in the extrusion process. SLN powder can be used for the filling of hard gelatin capsules.[17,18]

However, the evaluation of the stability of colloidal carriers in Gastric fluids is important in order to predict their correctness for oral administration. Critical parameters have been widely ignored in the design of new and efficient colloidal drug carrier systems for oral use:

1. Their stability is depended upon contact with GI fluids since they consist of biodegradable materials and particle size in nano range increases the surface area for enzymatic degradation.

2. Particles aggregate due to environmental situation of the GI tract primary reduce in the interaction ability of particles with the intestinal mucosa.

2) Parentral Delivery

SLNs can be administered intravenously, intramuscularly, subcutaneously or to the target organ, because of their smaller size. The particles are determined from the circulation by the liver and the spleen. SLN formulations can be used for systemic body distribution with a minimized risk of blood clotting and aggregation leads to embolism. SLNs formulations also provide a sustained release depository of the drug when administered subcutaneously or intramuscularly.[20,21]

3) Topical Delivery

Topical applications of lipid nanoparticles have been used with capable results either for therapeutic or cosmetic purposes. SLN have shown some defensive activity on skin surface, such as a UV-blocking potential. SLN may be formulated in creams, gels, sprays. The small particle sizes are observed for SLN dispersions with low lipid matter (up to 5%).[24] The disadvantages for dermal administration are the small concentration of the isolated lipid and the little or low viscosity. In the majority cases, incorporation of the SLN dispersion in gel or an ointment is necessary in order to achieve a formulation which can be applied to the surface of skin. The administration step implies additional decline of the lipid content. It may be suitable for direct application on the skin. Unfortunately, in most cases, the increase in lipid content is related with a large increase of the particle size.[25]

4) Rectal Delivery

When quick pharmacological effect is required, in some conditions, parentral or rectal administration is favored predictable rectal delivery of drugs and it is also very useful for pediatric patients all over in the world due to its easy application. In the interim, therapeutic efficacy and plasma levels of rectally administered dosage form reported to be higher as compared to those given intramuscularly or orally in the same dose of administration. This area seems very open to analysis, particularly when the profit of rectal course are taken into deliberation. PEG coating seems to be a shows potential approach on rectal delivery and accordingly, improvement of bioavailability.

5) Controlled Release Of Perfumes And Repellents

SLNs are used to include perfumes. The perfume Allure was included in SLN and the release studied was compared with a nanoemulsions of the same lipid content and surfactant composition. The initial release was similar; this could be due to the attendance of perfume in the outer shell of the SLN. The release of the perfume from SLN was late further to 8 hr. This open the prospect of developing allow long lasting perfume formulations depend on the prolonged release of the perfume from lipid matrix.[26]

6) Nasal Administration

Nasal administration has (due to fast absorption) a promising alternate non-invasive route of drug administration and onset of drug action, avoiding degradation of labile drugs (such as peptides and proteins) in the GI tract and poor transport across epithelial cell layers. In order to get superior drug absorption through the nasal mucosa, approaches such as formulation development and prodrug derivatization had been engaged. SLN had been proposed as substitute transmucosal delivery systems of macromolecular therapeutic agents and diagnostics by various research groups. Moreover, hydrophilic coating of SLN drug will have the interaction and transport of SLN through the nasal mucosa and therefore bring great reimbursement and observance as nasal drug carriers. In a current report, coating polymeric nanoparticles with PEG will give hopeful results as vaccine carriers.

CONCLUSION

Lipid carriers has bright future, because of their intrinsic property to improve the bioavailability of lipophilic drugs with low aqueous solubility. Obvious advantages of SLN includes the occurrence of physiologically tolerable lipids, the fast and effective production processes including the possibility of large scale production, prevention of organic solvents and the possibility to produce high concentrated lipid suspensions. Lipophilic drugs are the potential candidates for solid lipid nanoparticles. These compounds showing improved bioavailability in the presence of lipids (dietary or lipid-based formulation) are absorbed via the intestinal lymph and evade the absorption in portal blood supply. The most difficult route will be i.v. injection which requires absolute control of the particle size phenomenon. The results obtained with the dermal application are encouraging and most likely this will be the main important of the SLN. SLN offers an economical and patient-friendly device for administration of drugs by different routes. Hydrophilic substances coating of SLN is very important in the treatment of various diseases like cancer and tuberculosis.

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