RECENT ADVANCES IN SOLID LIPID NANOPARTICLES AND CHALLENGES

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ABSTRACT
Most of the active pharmaceutical ingredients (APIs) under development are poorly water soluble and have poor bioavailability. Nanotechnology is an approach to overcome the challenges of conventional drug delivery systems. The solubility, in vivo stability, intestinal absorption, route of administration, targeting, effectiveness and side effects are the challenges that push the researchers toward exploring a new drug delivery. Nanoparticles made from solid lipid are alternative novel colloidal drug carrier to alter and improve the pharmacokinetic and pharmacodynamics properties of drug molecules. The present review focused on increasing awareness about nanotechnological field in drug delivery with the emergence of several approaches based on solid lipid like Solid lipid nanoparticles, Nanostructured lipid carriers, Lipid drug conjugates, Polymer lipid hybrid nanoparticles for improving medical therapeutics. Hence, solid lipid nanoparticles hold great promise for reaching the goal of controlled and site specific drug delivery and have attracted wide attention of researchers.

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INTRODUCTION

A large fraction of established and, in particular, newly developed drug substances are poorly water soluble. This leads to pharmaceutically important consequences such as poor bioavailability or difficulties with developing formulations. There is thus an urgent need for adequate options to deliver such drugs to the patient. One interesting possibility is the use of colloidal lipid dispersions as drug carrier systems. Compared to many other materials used as drug carriers, in particular to polymers, lipids are regarded as a more physiological option and a high biocompatibility is expected. Naturally, lipophilic drugs in particular should benefit from an incorporation into the lipophilic matrix of lipid carriers. This review will focus on lipid emulsions and, in particular, solid lipid nanoparticles [1].

The use of nanotechnology in drug delivery could revolutionize current therapies and is set for rapid advancements. This is due to the unique properties of nanomaterials, including large surface:mass ratio (i.e. large functional surface), ease in engineering tissue-targeted nanoparticles, and higher loading capacity due to reduced drug expulsion during storage compared with micro-sized systems, which increases their ability to carry natural and synthetic chemical compounds [2].

Recent updates have shown that new drug development is not the prime concern for efficient drug therapy. The main reasons for therapy failure include:

I. poor drug solubility excluding i.v. injection of aqueous drug solution.
II. poor absorption, rapid metabolism and excretion (e.g. proteins, peptides etc).
III. drug distribution to non-targeted sites combined with high drug toxicity (e.g. anticancer drugs).
IV. high fluctuations in drug plasma levels due to unpredictable bioavailability after peroral administration, including influence of food on plasma levels (e.g. cyclosporine).

To troubleshoot these formidable problems, a novel and promising nano-drug carrier system, solid lipid nanoparticles, was introduced [2-4]. Although opportunities to develop nanotechnology based efficient drug delivery systems extend into all therapeutic classes of pharmaceuticals, the development of effective treatment modalities for the respiratory, central nervous system and cardiovascular disorders remains a financially and therapeutically significant need. Many therapeutic agents have not been successful because of their limited ability to reach to the target tissue. Additional problems include drug instability in the biological milieu and premature drug loss through rapid clearance and metabolism. However, nanotechnology for drug delivery applications may not be suitable for all drugs, especially those drugs that are less potent because the higher dose of the drug would make the drug delivery system much larger, which would be difficult to administer (Sahoo et al. 2003). One nanoparticle class that has been widely used in drug delivery is lipid-based nanoparticles. Compared to liposomes and emulsions, solid particles possess some advantages, e.g. protection of non-incorporated active compounds against chemical degradation and more flexibility in modulating the release of the compound. At the beginning of the 1990s, the advantages of solid particles, emulsions and liposomes were combined by the development of the ‘solid lipid nanoparticles’ (SLNs) (Muller et al. 2002; Bunjes et al. 2006) [6-10].

The important goals for research of nanotechnologies in drug delivery include [11]:

I. Decrease in toxicity while maintaining therapeutic effects.
II. Specific drug targeting and delivery.
III. Biocompatible and greater safety.
IV. Development of safe medicines.

<table>
<thead>
<tr>
<th>PROPERTY</th>
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<th>POLYMER NANOPARTICLES</th>
<th>LIPOSOMES</th>
<th>LIPID EMULSION</th>
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<td>No</td>
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<td>Avoidance of RES</td>
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Solid lipid nanoparticles (SLN) are aqueous colloidal dispersions, the matrix of which comprises of solid biodegradable lipids (Swathi et al. 2010) [12].
During the last ten years, different substances have been entrapped into lipid nanoparticles ranging from lipophilic and hydrophilic molecules, including labile compounds, such as proteins and peptides. Some common solid lipids used to make solid lipid nanoparticles (SLNs) include triglycerides (eg, Compritol 888 ATO and Dynasan 112), carnauba wax, beeswax, cetyl alcohol, emulsifying wax, cholesterol, and cholesterol butyrate [13-15].

**Advantages of SLN**

I. Use of biodegradable physiological lipids which decreases the danger of acute and chronic toxicity and avoidance of organic solvents in production method [16-17].

II. Improved bioavailability of poorly water soluble molecules.(Fahr and Liu 2007) [18].

III. Site specific delivery of drugs, enhanced drug penetration into the skin via dermal application [19-20].

IV. Possibility of controlled drug release and drug targeting [21-24].

V. Protection of chemically labile agents from degradation in the gut and sensitive molecules from outer environment [25].

VI. SLNs have better stability compared to liposomes.

VII. Enhance the bioavailability of entrapped bioactive and chemical production of labile incorporated compound.

VIII. High concentration of functional compound achieved.

IX. Lyophilization possible

**Disadvantages of SLN**

I. Poor drug loading capacity.

II. Drug expulsion after polymeric transition during storage.

III. Relatively high water content of the dispersions (70-99.9%).

**Advanced modifications of solid lipid nanoparticles**

Although SLN have numerous advantages of controlled and targeted drug delivery increased stability of incorporated drug, there are some limitations too [26].

I. Limitation of drug load by the solubility of the drug in the solid lipid.

II. Drug expulsion phenomenon when lipid crystallizes to the stable β-form.

III. Particle concentration in the aqueous dispersions ranging from about 1% to a maximum of only 30%.

**Figure 1:** Structure of solid lipid nanoparticle

**Figure 2:** Drug expulsion phenomenon when lipid crystallizes to the stable β-form

During storage it was observed that drug was expelled out of SLN. The reason behind expulsion of drug was the highly ordered crystalline lipid matrix which was leaving very little space for drug molecules. To overcome the limitations of SLN,
nanostructured lipid carriers (NLCs), Lipid drug conjugate (LDCs) and Polymer lipid hybrid nanoparticles (PLNs) were introduced. These carrier systems overcome observed limitation of conventional.

Nanostructured lipid carriers (NLCs): Nanostructured lipid carriers, introduced at the turn of the millennium, represent a new and improved generation of SLNs and are made of a solid lipid matrix entrapping liquid lipid nano-compartments, the blend being solid at body temperature. This new generation of lipid carriers (NLCs) was introduced to overcome the problems associated with SLNs, such as limited drug loading capacity, drug expulsion during storage and adjustment of drug release, long-term physical stability of the suspension etc. NLC is composed of solid lipids and a certain amount of liquid lipids with improved drug loading and increased stability on storage thereby reducing drug expulsion. NLCs have been explored for dermal delivery in cosmetics and dermatological preparations. The goal was to increase the drug loading and prevent drug expulsion. This could be visualised in three ways. Three models of NLCs were proposed. In the first model, also known as imperfect type NLCs, particles are prepared from a lipid mixture of spatially different lipids (like glycerides) composed of different fatty acids. Use of spatially different lipids leads to larger distances between the fatty acid chains of glycerides and general imperfection of the crystal lattice. This would provide more space for accommodation of guest molecules in molecular form or as amorphous clusters. High drug loading could be achieved and drug expulsion from the lipid matrix during storage could be prevented with this model, due to distortion of the crystal lattice. This suggests that an increased number of imperfections leads to increased drug loading capacity and one could say that the perfection of the NLC system lies in the imperfectness in its crystal lattice.

The second model is also known as multiple type NLC, where drugs showing higher solubility in oils than in solid lipids can be dissolved in oil and yet be protected from degradation by the surrounding solid lipids. Multiple type NLCs are analogous to w/o/w multiple emulsions since these are oil-in-solid lipid-in-water dispersions.

The third model, also known as amorphous type NLC, prevents the ongoing expulsion of the drug caused by crystallization or transformation of the solid lipid. Here, the particles are solid but crystallization upon cooling is avoided by using special lipids such as hydroxyl octacosanyl, hydroxyl stearate, isopropyl myristate, etc. The NLCs have mainly been investigated in the topical and dermatological preparations in the delivery of clotrimazole, ketoconazole, other antifungal imidazoles and ascorbyl palmitate.

![Figure 3: Different types of NLC: I-highly imperfect matrix; II-multiple O/F/W type; III-non-crystalline amorphous NLC.(versus SLN with high crystallinity)](image)

Lipid drug conjugates (LDCs): A major problem of SLNs is the low capacity to load hydrophilic drugs due to partitioning effects during the production process. Only highly potent low dose hydrophilic drugs may be suitably incorporated in the solid lipid matrix. In order to overcome this limitation, the so called LDC nanoparticles with drug loading capacities of up to 33% have been developed. LDC enables the incorporation of both hydrophilic (e.g., doxorubicin and tobramycin) and lipophilic (e.g., progesterone and cyclosporine A) drugs.

Polymer lipid hybrid nanoparticles (PLNs): Polymer-lipid hybrid nanoparticles hold great promise as a drug delivery vehicle in the treatment of a myriad of diseases such as breast cancer. A PLNs comprises three distinct functional components:

I. hydrophobic polymeric core to encapsulate poorly water-soluble drugs
II. hydrophilic polymeric shell to enhance PLN stability and circulation half-life
III. lipid monolayer at the core and shell interface to promote drug retention inside the polymeric core.

Interactions among these components play an important role for successful fabrication and performance of PLNs. These hybrid NPs combine the merits of both liposomes and polymeric nanoparticles, two of the most popular drug delivery vehicles approved for clinical use, thereby serving as a robust drug delivery platform. It has been shown in vitro that hybrid NPs possess the ability of carrying poorly water-soluble drugs with high encapsulation and loading yields, tunable and sustained drug release profiles, excellent serum stability, and differential targeting of cells [27,28].
Challenges

Many types of nanoparticles drug delivery systems are in various stages of investigation. These particles have been fabricated from various materials with unique architectures to serve as a possible drug vehicle to treat a particular disease. The real thrust of the current therapy for the puzzling diseases is in the direction of developing new powerful drugs. The next generation of drugs will involve more complex biological or chemical entities and gene therapy. The solubility, in vivo stability, intestinal absorption, route of administration and targeting, effectiveness, and/or the side effects of these new drugs are among the challenges that push researchers toward exploring a new drug delivery strategy.

A major idea behind the development of solid lipid nanoparticles was the hypothesis that a solid lipid nanoparticulate carrier would offer the potential for sustained or controlled drug release by immobilisation of the drug within a solid matrix. The physical and chemical stability of such particles might also be increased due to the presence of a solid particle core. Such a carrier system would thus combine the advantages of fluid-like lipid-based colloidal particles (good biocompatibility of ingredients and ease of production) with those of polymeric nanoparticles (solid matrix). Solid lipid nanoparticles can be based on a broad range of solid lipids with quite different degrees of polarity, ranging from the rather non-polar triglycerides and waxes through glyceride mixtures to fatty acids and emulsifying wax. Their preparation requires the use of surfactants as stabilisers, which include natural substances such as phospholipids and bile salts but also many other kinds of surface active agents, e.g. non-ionic surfactants such as poloxamers, polysorbates, etc [30].

The composition of the dispersions has to be adapted to the intended way of administration (e.g. only a very limited number of excipients can be used in parenteral formulations) but also depends on the preparation method. Although nanotechnology in drug delivery has been successful, as evidenced by some nano drug products in the market, not all approaches have met with the same success. New nanomaterials being developed come with challenges which have to be surmounted. For solid lipid nanoparticles, the situation is much more complex since the solid state of the particle core causes several additional phenomena. The lipids used for the preparation of solid lipid nanoparticles are crystalline substances, which means that the particles will also crystallize on solidification. Thus, they will show all the features of crystalline materials. This includes a solid–liquid transition at a certain temperature and the occurrence of various crystalline modifications if polymeric raw materials are used which is often the case for lipids (e.g. triglycerides). Chemical composition characterised by their particle size distribution and their surface properties are important for stability against coalescence. Problems with the stability of the dispersions have also been related to alterations caused by polymorphism and increase in crystallinity. Both the crystallisation behaviour and the kinetics of polymorphic transitions can be modified by the type of emulsifier used for the stabilisation of the nanoparticles. However some of the challenges encountered have been and are still being tackled by modification of the physicochemical characteristics of the nanomaterials to improve on properties such as long circulation in the blood, increased functional surface area, protection of incorporated drug from degradation, crossing of biological barriers and site-specific targeting [31].

Another challenge of research and development (R&D) of nanomaterials for drug delivery is large scale production. The development and quality control of solid lipid nanoparticle dispersions thus require the investigation of more parameters than emulsions. Apart from the common techniques, such as particle size characterisation, the particle shape and, in particular, the solid state properties (in particular the crystalline status and melting behaviour) need to be carefully monitored. There is always a need to scale up laboratory or pilot technologies for eventual commercialization [31].

A number of nano drug delivery technologies may not be scalable due to the method and process of production and high cost of materials employed. The challenges of scaling up include low concentration of nanomaterials, agglomeration and the chemistry process it is easier to modify nanomaterials at laboratory scale for improved performance than at large scale. Maintaining the size and composition of nanomaterials at large scale is also a challenge. Despite the number of patents for nano drug delivery technologies, commercialization is still at its early stage. This is partially due to the fact that most of the research studies in nano drug delivery are carried out by researchers in academia. Therefore, for these technologies to get to the market there has to be increased partnership with the pharmaceutical companies. Unfortunately, a number of the major pharmaceutical industries are yet to consider nanotechnology as one of their priorities due to lack of regulatory guidelines and challenges of scaling up. However, it is envisaged that with the expiration of more patents and market loss, more pharmaceutical industries will take up the production of nano drug products in order to compete favourably. Advances in nano drug delivery technology also provide new challenges for regulatory control. There is an increasing need to have regulations that would account for physicochemical and pharmacokinetic properties of nano drug products, which are different from conventional drug products [31].

The United States Food and Drug Administration (FDA) and the European Medicines Evaluation Agency (EMEA) have taken the initiative to identify some possible scientific and regulatory challenges. Furthermore, the International Organization for Standardization has set up a technical committee (TC 229) for the field of nanotechnologies to develop standards pertaining to terminology and nomenclature, measurement and characterization; and health, safety and environment amongst other standards. These standards are still under development [30]. With increased R&D work on nano drug delivery, emerges concerns about the safety of the nanotechnologies in humans. Some of the nanomaterials are biodegradable while some are not; furthermore, the side effects of the by-products present a huge concern. Materials which may be safe at macroscale may not be at nanoscale since there may be change in physicochemical characteristics at nanoscale. These nanomaterials may not clear completely from the body and their accumulation may have several possible effects. Safety and possible impact nanomaterials should not be considered for the patient population alone but also for the entire manufacturing and disposal processes [31].

Conventional safety measures in a pharmaceutical factory may not be appropriate for the development and fabrication of nanomaterials. Also extra measures are to be taken to protect the environment from increased envisaged negative impacts of nanomaterials. Although reduced cost to the patients is envisaged to be one of the advantages of nanotechnology since fewer materials...
are expected to go into production as compared to bulk production; it is doubtful if this will be so, as successful commercialization will be expensive. There is also the general public reluctance to embrace nanotechnology based on the unavailability of documented safety guidelines [31]. Although solid lipid nanoparticles have now reached a more mature stage of development, latter mostly refer to an improved administration of poorly water-soluble drugs. Solid lipid nanoparticles should be highly interesting carrier candidates for drug substances that localise at the particle surface since their often platelet-like shape offers much space for the association with such drugs. On the other hand, they usually display an even more complex physicochemical behaviour than lipid emulsions. Such aspects need to be carefully balanced in order to choose an optimal carrier system for a given delivery task. Another challenge for researchers exploring a new drug delivery strategy is in vivo biodistribution of solid lipid nanoparticles, will mainly depend on the route of administration and interactions of SLN with biological surroundings which, in general, include two types of processes: distribution processes (adsorption of biological materials on the particle surface and desorption of SLN components into the biological surrounding) and enzymatic processes (lipid degradation by lipases and esterases). Physiological or physiologically related lipids or waxes generally constitute the SLNs. Therefore, the in vivo fate of the carrier, to a large extent, occurs through the pathways of transportation and metabolism present in the body. Lipases, the enzymes present in various organs and tissues of the body, are most responsible for SLN degradation. Lipases split the ester linkage and form partial glycerides or glycerol and free fatty acids. Activation by an oil/water interface, which opens the catalytic centre, is a prerequisite for lipases to act. Solid lipid nanoparticles show different degradation rates, in vitro, by the lipolytic enzyme pancreatin lipase as a function of their composition (lipid matrix, stabilizing surfactant.

**Peroral administration**

Aqueous dispersions or SLN-loaded traditional dosage forms (tablets, capsules, pellets or powders in sachets) may serve as peroral administration forms of SLN. Pandey et al. formulated and evaluated the chemotherapeutic potential of solid lipid nanoparticles incorporating antitubercular drugs following oral administration to mice and suggested that oral SLN based antitubercular drug therapy forms a sound basis for reducing dosing frequency and improving patient compliance for better management of tuberculosis [32]. Zhang et al. administered orally insulin-loaded SLN and WGA-modified SLN to rats and demonstrated that both of these formulations promoted the intestinal absorption of insulin after oral administration [33].

**Parenteral administration**

Parenteral drug delivery took a major leap after successful development of the submicronic parenteral fat emulsion in the 1960s. Quick commercialization of submicron emulsion based products, such as Diazemuls (diazepam) and Diprivan (propofol), indicated the interest of pharmaceutical industries in colloidal carriers. Wissing et al. reviewed, in detail, the bioactivity of SLN after parenteral administration, i.e. tolerability, toxicology, cellular uptake, albumin adsorption, pharmacokinetics, tissue distribution and drug targeting [34].

Reddy et al. studied the influence of the route of administration on tumor uptake and biodistribution of etoposide loaded solid lipid nanoparticles in mice bearing Dalton’s lymphoma after subcutaneous, intravenous and intraperitoneal injections. It was observed that subcutaneous injection reduced the biodistribution of SLN to all the tissues studied, whereas intravenous injection resulted in lower levels of etoposide-loaded SLN in RES rich organs compared to free etoposide. SLN experienced significantly higher brain distribution after intraperitoneal injection, indicating its potential application in targeting etoposide to brain tumors [35].

**Transdermal administration**

Since the epidermal lipids are found in high amounts in the penetration barrier, lipid carriers (liposomes, SLN, NLC etc.) attaching themselves to the skin surface and allowing lipid exchange between the outermost layers of the stratum corneum and the carrier appear promising. Incorporation of SLN dispersion in an ointment or gel, by reduction of the lipid content of the SLN dispersion, is necessary to achieve a formulation that can be easily administered to the skin.

**Pulmonary administration**

Growing attention has been given to the potential of pulmonary route as an alternative to the non-invasive local and systemic delivery of therapeutic agents using lipid particles, since it provides a large absorptive mucosal area. The lung offers a large surface area for drug absorption and the alveolar epithelium allows rapid drug absorption. The superior physicochemical characteristics of SLNs make them more suitable as an appropriate delivery system due to correlation between the diameter within the nanometric range, biocompatible composition and deep-lung deposition ability. Prolonged drug serum concentration and lung retention are both achievable by means of the particulate colloidal drug carrier system including SLNs [36].

**Ocular administration**

Eyes are among the most readily accessible organs in terms of their location in the body, yet drug delivery to eye tissues is particularly problematic. Delivery of drugs via nanotechnology-based products fulfils three main objectives, enhanced drug permeation, controlled drug release and higher targeting potential. Attama et al. prepared sodium diclofenac loaded lipid nanoparticles combining the homolipid from goat (goat fat) and a phospholipid, with high encapsulation efficiency applying hot high-pressure homogenization technique. Administration of this formulation to bioengineered human cornea demonstrated sustained release of the analgesic drug. Furthermore, permeation of sodium diclofenac through the corneal construct was improved by surface tailoring of nanoparticles with phospholipid, which showed better performance for ocular administration [37].
Targeted delivery

One of the most challenging aspects in pharmaceutical research is targeted delivery of drug molecules to a specific organ, tissue or specific cellular sites. By developing colloidal delivery systems such as liposomes, micelles and nanoparticles, a new frontier was opened for improving drug delivery [38,39].

However, despite these challenges, nano drug delivery is a development that cannot be ignored and so the challenges will be tackled with time.

Application SLNs find potential applications in the following areas of interest:

Cosmetics

SLN as topical vehicles for sunscreens, anti-acne and anti-ageing actives Lipid nanoparticles proved to have a synergistic effect of the UV scattering when used as vehicles for molecular sunscreens. Advantages taken from these observations are the possibility to reduce the concentration of the molecular sunscreen, consequently its potential side effects, as well as the costs of formulation of expensive sunscreens. In addition, lipid nanoparticles can be explored to formulate sunscreen products with lower and medium sun protection factor. The loading capacity of lipid nanoparticles depends mainly on the miscibility of the active in the lipid selected for their production. It can range from about 4% (e.g. ferulic acid), 25% (e.g. tocopherol), or even up to 50% and more, in case of well lipophilic active lipophilic actives [40-42].

SLN as topical vehicles for perfumes, fragrances and repellents Prolonged release of perfumes has the advantage of creating a once-a-day application with prolonged effect over several hours. This was demonstrated to be possible with the use of lipid nanoparticles in comparison with typical o/w emulsions. The release can be slowed down by incorporating perfumes/fragrances in a SLN instead of an oil droplet. In the first 3h, similar release patterns were observed between lipid nanoparticles and oil droplets because of the release of perfume from the outer layers of the particles. During the remaining 10 h, the release from SLN was prolonged. After 6 hr 100% of perfume was released from the emulsion, but only 75% was released from SLN. This property can also be advantageous for the delivery of insect repellents to be applied onto the skin.

SLN have also been employed for dermal application of cosmeceuticals like molecular sunscreens and as carriers for UV blockers. Cosmetic benefits of lipid nanoparticles include enhancement of the chemical stability of actives, film formation on skin, controlled occlusion, skin hydration, drug targeting, enhanced skin bioavailability and physical stability of lipid nanoparticles as topical formulations. An in vivo study showed increased skin hydration, by 31%, after 4 weeks after addition of 4% SLN to a conventional cream formulation [40-42].

Topical delivery

The biggest progress in the field of nanotechnology has allowed the scientists to develop the carriers of drug to improve the penetration of skin and also in targeting to specific skin layers such as podophyllotoxin, tretinoin, isotretinoin, flurbiprofen, psoralen, vitamin A. Lipid-based nano-formulation fulfills three main objectives: controlled drug release, enhanced drug permeation and site specific drug delivery. Similar to liposomes they are composed of well tolerated excipients and due to their small particle size they possess adhesive properties leading to film formation on the skin. Moreover they ensure increased penetration of drug into the epidermis by close contact with the stratum corneum. However the drug free nanoparticles can be used to improve occlusive properties. Dermal penetration barriers contain a high concentration of epidermal lipids and lipid based carriers appear to be promising by attaching themselves to the skin surface, allowing lipid exchange between the outermost layers of stratum corneum. Schafer Korting et al. 2002 has investigated that well tolerated lipid nanoparticles are suitable for glucocorticoids targeting to viable epidermis however long term glucocorticoids treatment can cause skin atrophy so prednicarbonato (PC-0.25%) was incorporated in lipid nanoparticles and it was found that PC is much more efficiently incorporated in lipid nanoparticles (>90%) as compared to prednisolone (50-56%), when identical procedure for production was employed. The targeting effect of prednicarbonato was seen after incubating time of 6h. This accelerated drug release was shown due to water evaporation from the skin surface, as a result there was polymorphic transition of lipid structures of lipid nanoparticles. For designing dermal delivery system, it is important to understand principles of drug incorporation into carrier and their permeation through the skin. There are methods which can quantify the drug at the target site. They are fluorescence spectroscopy employing dyes as model agents and paraelectric spectroscopy. A research carried out by fluorescence spectroscopy to check upon the distribution of lipophilic model dye within the skin strata and appendages after application of lipid nanoparticles system revealed that the drug penetration in SLNs increased about four folds as compared from the uptake followed by the cream [43-47].

Nasal delivery

Nasal administration was a promising alternative noninvasive route of drug administration due to fast absorption and rapid onset of drug action, avoiding degradation of labile drugs (such as peptides and proteins) in the GI tract and insufficient transport across epithelial cell layers. In order to improve drug absorption through the nasal mucosa, approaches such as formulation development and prodrug derivatization have been employed. SLN has been proposed as alternative transmucosal delivery systems of macromolecular therapeutic agents and diagnostics by various research groups. In a recent report, coating polymeric nanoparticles with PEG gave promising results as vaccine carriers. The role of PEG coating of polylactic acid nanoparticles in improving the trans mucosal transport of the encapsulated bioactive molecule. This concept can be useful for solid lipid nanoparticles [49].
Brain delivery

Nanosystems employed for the development of drug delivery systems intended for CNS targeting. SLNs can improve the ability of the drug to penetrate through the blood-brain barrier and is a promising drug targeting system for the treatment of central nervous system disorders. The most formidable obstacles that often impede drug delivery to the brain are characterized by the presence of relatively impermeable endothelial cells with tight junctions, enzymatic activity and the presence of active efflux transporter mechanisms like P-glycoprotein. However, the bioacceptable and biocompatible nature of SLNs makes them less toxic compared to polymeric nanoparticles and they are taken up by the brain because of their lipidic nature. SLNs below 200 nm have increased blood circulation and hence an increase in the time during which the drug remains in contact with BBB and is taken up by the brain. In vivo well tolerable solid lipid nanoparticles (SLNs) using different types of polysorbate as stabilizers were produced. The influence of the different surfactants on in vitro adsorption of human plasma proteins was investigated using two-dimensional polyacrylamide gel electrophoresis (2-DE).

One approach of drug targeting is the incorporation of the substance into colloidal carriers such as polymeric nanoparticles, or solid lipid nanoparticles (SLNs) which have been used for intravenous injection. The next challenge is to direct the colloidal drug carriers to the desired site of action e.g. tumor tissue or brain. After intravenous injection, particles immediately interact with plasma proteins. The adsorbed plasma protein patterns are regarded as the determining factor for the in vivo fate of the carriers. The blood–brain barrier (BBB) represents a strict barrier for water-soluble, charged and high molecular weight drugs [49-51]. Mistry et al. suggested that the existence of a direct nose-to-brain delivery route for nanoparticles administered to the nasal cavity and transported via the olfactory epithelium and/or the trigeminal nerves directly to the CNS is relevant in the field of drug delivery as well as new developments in nanotechnology [39].

Chemotherapy

Cancer is characterized by the formation of abnormal tissues known as neoplasm. Developed basically due to change in the way cells proliferate and differentiate. Currently, cancer fighting drugs are toxic to both tumor and normal cells, thus the efficacy of chemotherapy is always limited by the side effects of the drug. Some nanoscale devices can be targets to the cancer cells. This increases the selectivity of the drugs toward the cancer cells and will reduce the toxicity for normal tissue. The effectiveness of cancer therapy in various solid tumors depends upon adequate delivery of therapeutic agent to tumor cells. Inadequate delivery of drugs to tumor cells leads to regrowth of tumor cells and even result in development of resistant cells. Several drug delivery systems were introduced namely liposomes, microparticles, supramolecular bio-vectors, polymeric conjugates and nano-particulates to facilitate effective chemotherapy with the anti-cancer agents.

The introduction of doxorubicin long circulating liposome in the market for cancer therapy has brought a renewed interest in the field of targeted drug delivery to cancer. Due to drawback of these carrier systems such as physical instability, difficulties in scale-up, lack of specific tumor targeting and cytotoxicity of the polymers, research groups have focused on nanoparticles prepared using lipid matrices. There are many reports describing potentials of lipid nanoparticles for parenteral delivery particularly for the treatment of cancer. In another research tamoxifen citrate and tamoxifen citrate loaded nanoparticles were administered by intravenous injection in rats and the pharmacokinetic parameters were determined. The $t_{1/2}$ and mean residence time of TC-loaded SLNs in plasma was about 3.5-folds ($p < 0.001$) and 3-fold ($p < 0.001$) higher, respectively than free tamoxifen, this indicates the potential of TC-loaded SLNs as a long circulating system in blood. Thus the above mentioned solid lipid nanoparticles can be a beneficial system to deliver tamoxifen to cancer tissues through enhanced permeability and retention (EPR) effect.

The biodistribution of colloidal carriers and delivery of incorporated drugs to the target sites after intravenous administration are mainly determined by their physicochemical properties such as size, surface charge and surface hydrophobicity through their recognition or non recognition by the body’s reticulo-endothelial system. The rapid removal of colloidal particles by the macrophages of the RES is a major obstacle to targeting tissues elsewhere in the body, such as bone marrow and solid tumors.

Several reports appeared on incorporation of polyethylene glycol (PEG) moieties for prolonged blood circulation and charged lipids to modify the biodistribution of lipid nanoparticles. The SLNs were loaded with an anticancer agent; tamoxifen citrate (TC). The TC-loaded TSSLN (tristearin SLN) showed lower entrapment efficiency (78.78%) compared to the TPSLN (tripalmitin SLN) and glycerol behenate SLN (GBSLN) (98.64%). Long circulation half-life of the intravenously administered TC-loaded TSSLN compared to the plain TC solution indicates their possible potential use in the drug delivery to cancer tissues by enhanced permeability and retention (EPR) effect.

Colloidal drug delivery systems without specific delivery usually show a strong tendency to accumulate rapidly in the phagocytic cells of the reticuloendothelial system (RES). Similar phenomenon was found in Camptothecin SLNs. Compared with the commercial emulsion, SLNs showed a higher uptake by RES tissues such as liver and spleen. Therefore, the SLNs containing β-elemene might be an attractive candidate for the treatment of liver cancer. Different kinds of drugs have been incorporated in SLNs, including lipophilic and hydrophilic drugs, small molecular and large molecular biological drugs, but SLNs containing volatile oil has seldom been reported. Being incorporated in the solid matrix of the SLNs, β-elemene might be well protected and providing targeted release different from that of commercial emulsion. Paclitaxel commonly known as yew tree, has antineoplastic activity particularly for ovarian carcinoma, breast cancer, colon, head and neck cancer etc. It is a hydrophobic molecule, which was earlier stabilized in 50:50 mixture of polyethoxylated castor oil (Cremphor EL), however cremophor is associated with number of side effects such as hypersensitivity, nephrotoxicity and neurotoxicity etc. The incorporation of paclitaxel in solid lipid nanoparticles gave promising results by eliminating the need for Cremophor EL and also improved drugs efficacy. This application extends the function of solid lipid nanoparticles as reservoir systems and penetrates into accessible sites, such as tumor and other than mononuclear system. The slow release of paclitaxel from solid lipid nanoparticles suggests that the paclitaxel might be incorporated into lipid matrix of
Nanoparticles. In 1999, the complete patent rights for production of SLNs by high pressure homogenization have been acquired by Skye Pharma AG (Muttenz, Switzerland), a drug delivery company specialized in oral delivery, but also having the potential for parenteral production [49].

Protein and peptide delivery

Increasing attention has been paid to the pulmonary route for systemic delivery of peptide and protein drugs, such as insulin. The SLN production is based on solidified emulsion (dispersed phase) technologies. Therefore, due to their hydrophilic nature most of proteins are expected to be poorly microencapsulated into the hydrophobic matrix of SLN, tending to partition in the water phase during the preparation process, which is further enhanced by the use of surfactants as emulsion stabilizers. Therapeutically relevant peptides (e.g. calcitonin, cyclosporine A, somatostatin), protein antigens (e.g. hepatitis B and malaria antigens) and model protein drugs (e.g. bovine serum albumin and lysozyme) have been investigated for drug release kinetics, protein stability and in vivo performance [49].

Future perspectives

The future vision of lipid nanoparticles – SLNs as drug delivery systems is to develop a self-actuated therapy with good perspectives to be marketed very successfully. The reason for this is that they were developed considering industrial needs, e.g. scale up, qualification and validation, simple technology, low cost, regulatory excipient status (e.g. GRAS), tolerability etc. Research must continue to develop a therapy through localized medical implants.

Yih et al. (2002,2005) had developed bio-micro electro mechanical (BioMEMS) micropumps for controlled localized drug delivery systems such as hydrogel nanoparticles. These systems when implanted, will be able to determine the necessary dose via sensory systems. The implants are normally designed to operate for a long period of time, possibly months. The stability and usefulness of nanoparticles delivery systems might be influenced by time. Thus, further studies are essential to evaluate their efficacy over time when encapsulated and stored. The smart NLC as the new generation offer much more flexibility in drug loading, modulation of release and improved performance in producing final dosage forms such as creams, tablets, capsules and injectables. In addition, research must continue in such a direction to provide improved efficacy, drug loading, targeting and lowering of the drug dose, thereby overcoming the toxicity challenges of this carrier system. Structure and dynamics of SLNs on the molecular level, both in vitro and in vivo, stability, targeting, toxicity and aspects related to interactions of SLNs with their biological surrounding pose a challenge that should be explored in the near future by various research groups around the globe. Implantable devices or nanochips promise improved therapeutics in various disease management and may be potentially applied as antitumor therapy, gene therapy, or vaccines. Nanochips be used to assist in repairing damaged tissue, detecting mutated genes, or detecting high hormone levels indicative of certain malignancies. It is capable of triggering immediate responses to inflamed, ischemic, or neoplastic tissues and simultaneously provide therapy. Surprisingly, a silicon based nano-channel has already been developed to deliver antitumor agents locally with zero order kinetics.

CONCLUSION

SLN constitute an attractive colloidal drug carrier system due to successful incorporation of active compounds and their related benefits. The present review has focused on increasing awareness about nanotechnological field in drug delivery with the emergence of several promising approaches like solid lipid nanoparticles, nanostructured lipid carriers, lipid drug conjugates etc. for improving medical therapeutics. The concept of surface modification is further increasing the importance of SLN among traditional colloidal drug carrier systems. Hence SLN offer an economical and patient-friendly device for administration of drugs by various routes to maximize effectiveness while avoiding adverse effects on non-target tissues.

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