Symposium - Review Article

Nanoparticles - A paradigm for topical drug delivery

Abstract

Topical drug delivery is still a challenge due to the difficulties in controlling the active pharmaceutical ingredient (API) fate within the skin. Due to the safety of the component material and controlled release abilities, nanoparticles offer an excellent opportunity for the rational delivery of drugs to the desired target site and hence these carrier systems are effectively used for topical delivery of variety of active principles for both pharmaceutical as well as cosmetic purposes. Recently, solid lipid nanoparticles (SLNs) have shown a great potential as carriers for topical administration of active substances, principally owing to the possible targeting effect and controlled release in different skin strata. Also, nanostructured lipid carriers (NLCs) are a new type of topical delivery system offering improved performance in terms of drug loading and long-term stability with the ability to form highly concentrated dispersions. Another invention in the field of topical drug delivery is the use of micellar nanoparticles (MNPs) that offer a potentially fast and inexpensive pharmaceutical development model by using drugs already proven safe and effective to create new proprietary formulations. These novel drug delivery systems have gained much interest as they combine both the technology of lipid sciences and nanosciences, and hence may be better alternative carriers.

Key words:
Carrier systems, lipid nanoparticles, topical drug delivery

Introduction

Nanotechnology has evolved to be an integral part of the twenty-first century. Nanotech-enabled products find applicability in almost everything we touch on a day-to-day basis, such as medicines, pharmaceuticals, chemicals, biologics, and information technology. In particular, the pharmaceutical industry has been energized with breakthroughs in nano-engineering, especially in the fields of drug delivery and formulation development.[1] Nanopharmaceuticals have blossomed into a billion-dollar industry because of these compounds' inherent ability to overcome solubility and stability issues, localize drug delivery, as well as to diagnose via *in vivo* imaging. A budding interest in nanopharmaceuticals has generated a number of advancements throughout recent years with a focus on engineering novel approaches to drug delivery and formulation. During the past two decades, researchers involved in the development of pharmaceuticals have understood that drug delivery is a fundamental part of drug development, and a wide range of drug delivery systems have thus been designed. Ideally, all these systems improve the stability, absorption, and therapeutic concentration of the drug within the target tissue, as well as permit reproducible and long-term release of the drug at the target site. In addition to reducing the frequency of drug administration and thus improving patient comfort, novel drug delivery systems offer protection and improve the pharmacokinetics of easily degradable peptides and proteins, which often have short half-lives *in vivo*. For the pharmaceutical industry the field of drug delivery represents a strategic tool for expanding drug markets, because new delivery technologies could repackage classical drugs, offering a competitive edge after the expiry of patents and avoiding competition from generics. Demonstrating this advantage clearly, 13% of the current global pharmaceutical market is related to the sale of products that include a drug delivery system.[2] These

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advancements in drug delivery have facilitated the targeting of specific tissues. With the advent of nanotechnology; these targeted tissues are now becoming specific organelles within individualized cells.[3]

Nanotechnology in Topical Drug Delivery

Topical administration of drugs is still a challenge in pharmaceutics and drug delivery due to the difficulties in controlling and determining the exact amount of drug that reaches the different skin layers. The physicochemical characteristics of the active pharmaceutical ingredient (API) as well as vehicle are responsible for the drug differential distribution in the skin. Different strategies have been used to increase local soft tissue bioavailability of a number of drugs for topical administration. One such strategy includes formulation of API within nanometric particulate carriers, in particular of lipid origin, more precisely referred as lipid nanoparticles. Due to the safety of the component materials and controlled as well as prolonged release abilities, these nanodevices possess a great potential and have generated a large interest in the industrial and academic worlds. In fact, they have been proposed and investigated for many different applications and all the administration routes.[4] For prolonged topical drug delivery, the novel lipid nanoparticles, i.e., solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs) and micellar nanoparticles (MNPs) have a promising potential as new drug delivery systems.[5] The present article deals in detail with the above mentioned drug delivery systems including their description, potential advantages and applications.

Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLNs) were introduced at the beginning of the 1990s. These are sub-micron size range colloidal carriers (50–1000 nm) for prolonged drug delivery which combine several advantages of other innovative carrier systems like polymeric nanoparticles, emulsions and liposomes. The main features of SLN are the excellent physical stability, protection of incorporated labile drugs from degradation, good tolerability, biodegradation and site-specific targeting. A clear advantage of SLNs over polymeric nanoparticles is associated with the fact that the lipid matrix is made from physiological lipids, which decreases the danger of acute and chronic toxicity. Different approaches are available for the production of finely dispersed SLN dispersions, viz. high-pressure homogenization (hot or cold), micro emulsion-based SLNs preparations, solvent emulsification evaporation, solvent emulsification diffusion technique, using a membrane contactor, ultrasonication, double emulsion method or supercritical technique.[6]

Literature studies reveal that SLNs as a topical carrier were used for topical delivery of several drugs including clotrimazole, prednicarbate betamethasone 17-valerate, glucocorticoids, podophyllotoxin, and isotretinoin.[6-8] Mei *et al*. reported that triptolide topical anti-inflammatory therapy was favored by its entrapment in SLN. This strategy guaranteed an improved availability of the drug at the site of action, reducing contemporary the needed dose and thus, dose dependent side effects like irritation and staining[9] Suthanut, *et al.* and Bhalekar, *et al.* formulated SLNs using extracts of Kaempferia parviflora and miconazole nitrate, respectively. The SLN formulations were evaluated for their transdermal permeability as well as skin targeting effect in comparison with conventional gel formulations. The results indicated that the SLN formulations with skin targeting may be a promising carrier for topical delivery.[10,11] The ability of SLNs as a promising particulate carrier having controlled drug release, improved skin hydration, and potential to localize the drug in the skin with no skin irritation was demonstrated by Pallavi Pople and Kamalinder Singh.[12] Jenning *et al.* proved that sustained release becomes important with active ingredients that are irritating at high concentrations or to supply the skin over a prolonged period of time with a drug To demonstrate this effect Glyceryl behenate SLN were loaded with vitamin A and the release profiles were studied using Franz diffusion cells. A good correlation between polymorphic transitions and increased drug release was observed in this study.[13]

Though SLN have the chance to be exploited as delivery system in commercial products, they have some limitations, which include-

- Limitation of drug load by the solubility of the drug in the solid lipid,
- Drug expulsion phenomenon when lipid crystallizes to the stable b-form
- Particle concentration in the aqueous dispersions ranging from about 1% to a maximum of only 30%.

Hence in order to overcome these limitations a new lipid carrier, the NLC was developed.[14]

Nanostructured Lipid Carriers

Nanostructured lipid carriers (NLCs) consist of a lipid matrix with a special nanostructure. This nanostructure improves drug loading and firmly incorporates the drug during storage. These NLCs can be produced by high-pressure homogenization and the process can be modified to yield lipid particle dispersions with solid contents from 30–80%. Because of the high consistency of NLC dispersions, they can be used as topical dosage forms without further processing. Drug release from NLCs occurs by diffusion and simultaneously by lipid particle degradation in the body. In some cases it might be desirable to have a controlled fast release going beyond diffusion and degradation. Increase in temperature and water evaporation leads to an increase in drug release rate Based on these cyclosporine-lipid particles were developed to treat psoriasis.[15]

Souto *et al*. studied the promising potential of NLCs as new drug delivery systems for antifungal agents. In his study, two different imidazole antifungals (clotrimazole and ketoconazole) have been used as model drugs for the study of the topical features of aqueous NLC dispersions.[5] NLCs containing ketoprofen and Naproxen as the APIs provide supplementary evidences that these delivery systems have a targeting and prolonged release effect with great potentials in dermal delivery.[4] Ricci *et al*. carried out the *in vitro* and *in vivo* evaluation of indomethacin (IND) release through the skin from NLCs prepared by ultrasonication.[16] Uner, *et al*. worked on improving the chemical stability of ascorbyl palmitate (AP) in a colloidal lipid carrier for its topical use. For this purpose, AP-loaded NLC and for comparison, a nanoemulsion (NE) were prepared employing the high pressure homogenization technique AP was found most stable in the NLC formulation indicating importance of the carrier structure.[17]

Micellar nanoparticles

Although the transdermal drug delivery field has enjoyed a significant amount of research effort and technological breakthrough, there has not been much corresponding innovation taking place in the field of topical drug delivery. The majority of the dosage forms are limited to traditional creams, ointments, and gels. Some of the new additions have been sprays, foams, and patches. MNP technology can be exploited to design improved topical dosage forms that deliver the API locally in an efficient and controlled manner. Micellar nanoparticle (MNP) technology was invented in the mid-1990s Scientists at Novavax developed and patented MNP technology and subsequently rolled out the first nano-engineered transdermal lotion product (Estrasorb) in 2003. MNP is a nanotechnology-based formulation that has achieved a breakthrough in transdermal therapeutics. The formulation represents a robust and versatile delivery system that can accommodate a range of therapeutic compounds having varying physicochemical properties. MNP-based emulsions (lotions) are attractive alternatives for systemic drug delivery via topical application. The technology allows high concentrations of drug to penetrate the skin and functionally create a drug depot in the stratum corneum and epidermis. This route of delivery provides similar advantages of patch technology in avoiding both contact with the gastrointestinal tract and hepatic first-pass effects, and is cosmetically more acceptable to many patients. In broad terms, MNP is a multiphasic nanoemulsion which presents the API in a more readily bioavailable form. There are five basic components of an MNP system: (i) one or more APIs; (ii) solvent; (iii) stabilizer; (iv) oil; and (v) aqueous medium. Depending upon the physicochemical properties of the API and the dose requirements, drug loading up to 20% (w/w) can be achieved. For topical or transdermal administration, MNPs can be classified as a type of microreservoir-dissolution-controlled system that can be tailored to deliver drugs topically.

MNP technology has been applied for estrogen replacement therapy with 17b-estradiol in Estrasorb A constant and controlled infusion of the drug from the topically applied estradiol emulsion maintained the drug at therapeutic levels for prolonged periods of time providing a "depot effect". Several small-molecular weight compounds have been evaluated to prove the versatility and expandability of the MNP technology. A testosterone MNP formulation (Androsorb) has completed phase I clinical evaluation for two indications: hormone replacement therapy in hypogonadal males, and to treat sexual dysfunction in females. Using MNP technology, it is possible to tailor drug deposition, disposition, and permeation kinetics through altered composition, drug loading, droplet size, etc. This concept has been demonstrated using acyclovir as the model drug. Commercially, Zovirax cream, a topical acyclovir product indicated for the treatment of recurrent herpes labialis (cold sores) is available. The product needs to be applied topically five to seven times a day for 4–7 days. A comparative investigation (*in vitro* using Franz cell–cadaver skin assembly) was carried out with a MNP formulations and Zovirax cream. Both the formulations had a drug loading of 5% w/w. The product was applied to the skin (donor compartment), and drug that permeated across the skin as well as that retained within skin layers was estimated. It was clear from the data that the amount of drug retained within skin was about twofold higher for the MNP formulation than the commercial cream.

In addition, the inherent antimicrobial nature of the MNP vehicle would be beneficial from a therapeutic and packaging perspective. Based on these benefits, the MNP technology could offer a novel perspective to the field of topical drug delivery – especially for non-steroidal anti-inflammatory drugs (NSAIDs), antifungals, antibacterials, antivirals, antispasmodics, and vasodilatory drugs.[18]

Conclusion

The success of a new developed pharmaceutical formulation is related to the fact that it is able to deliver the active substance to the target organ at therapeutically relevant levels, with negligible discomfort and side effects, increasing the patient compliance to the therapeutics. Regarding this respect, the route of administration is of major relevance. Topical administration of active substances offers several attractions compared to traditional routes, e.g., it avoids the hepatic first-pass metabolism, it has the potential of long-term controlled release with avoidance of the topical peak-through plasma profiles associated with frequent dosage regiments, Direct as well as indirect evidences substantiate the early reports on the usefulness of nanoparticles as carriers for topical administration, stimulating new and deeper investigations in the field. Even though, the mechanisms by which prolonged release occurs are not completely understood, the novel approaches in nanomedicines were

able to extend the therapeutic effect of the embedded active molecules providing their prolonged release in the epidermis. The current review provides supplementary evidences that the novel nanoparticulate delivery systems have a targeting and prolonged release effect with great potentials in dermal delivery. As we achieve greater disease understanding, especially at the molecular level, there will be greater opportunity for targeted delivery of therapeutic agents by discovering differences between normal and diseased tissues and cells. Together with these advances and developments of newer generations of 'design-specific' nanomaterials, the future of nanotechnology for delivery of drugs looks very bright.

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