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NANOTECHNOLOGY BASED APPROACHES FOR TRANSDERMAL DRUG DELIVERY

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ABSTRACT

The transdermal route of administration is recognized as one of the potential route for the local and systemic delivery of drugs. Transdermal drug delivery is a convenient method of drug administration enabling physicians to provide controlled delivery of drugs to patients with minimum discomfort. Compared to oral and parenteral routes, the transdermal route has the advantages of reducing gastrointestinal side effects and reducing drug degradation. However, the poor permeability of the stratum corneum often limits the topical administration of novel drug formulations. Though, there are various chemical and physical methods; to promote transdermal drug permeation by the disruption of the skin barrier. Although effective, tend to produce allergic reactions, skin irritation, and sensitization. Nanotechnology is a booming branch of science that also aids in the area of drug delivery and therapeutics. Several research findings proved that nanotechnology based drug delivery approaches are far more efficient for transdermal delivery than other conventional drug delivery systems. In present article, efforts have been taken with the intention to get thorough information of the mechanism of transdermal delivery along with a comprehensive review of diverse nanotechnology based approaches adopted for transdermal delivery till date.

KEYWORDS: Drug delivery, Nanocarriers, Transdermal delivery, Nanoemulsion, Nanoemulgel.

INTRODUCTION

In the present era not too many new molecules are hitting the market due to the fact that most of the drugs are either poorly soluble or not permeable. Hence continuous demand for new methods and technologies is the demand. Various methodologies have been explored in the past decade to deliver the drug through skin.[1] As skin has a inherited barrier property and allows penetration of only selected drugs molecules. This characteristic of skin has been explored recently for delivering of drugs through skin using nano particulate matters. In research and medicine field the small particle size coupled to their unique chemical and physical properties is thought to underlie their exploitable biomedical activities. Here, we review current toxicity studies of Nanoparticles with clinical potential. The so-called 'proof-of-principle' approach, whereby ultra-high nanoparticles concentrations are used.[2]

The drug can be delivered using nanotechnology by using various formulation aspects like nano emulsion, nanosuspension, nanoemulgel etc. The nanoemulsion is one of the most efficient dispersed nanosystems of droplet size ranging to submicron size. Nanoemulsion are generally transparent or semi transparent system characterized by high stability. The nanoemulgel formulated as transdermal delivery system for poor water soluble drug (Eg. ketoprofen) in order to overcome the troubles associated with its oral delivery.[3] Various nanoemulsion components (oil, surfactant, and co-solvents) were selected on the basis of solubility and emulsification ability. Carbomer 940 was added as gel matrix to convert nanoemulsion into nanoemulgel. Drug loaded nanoemulsions and nanoemulgels were characterized for various parameters like particle size, viscosity, spreadability, rheological behavior and permeation studies. Nanoemulgel containing 6% oleic acid as oil, 35% Tween 80, and Transcutol P as surfactant cosurfactant mixture, 56.5% water, 2.5% drug, and 0.6% carbomer was concluded as optimized formulation (NG6). The *ex vivo* permeation profile of optimized formulation was compared with nanoemulsion and marketed formulation (Fastum). Nanoemulgel showed significantly higher ($P < 0.05$) cumulative amount of drug permeated and flux along with lower lag time and skin retention than marketed formulation. Hence, the study shows that nanoemulgel formulation can be used as a feasible alternative to conventional formulations with advanced permeation characteristics for transdermal application.[4]

They are characterized by high stability. Submicron droplet size and high surfactant concentration makes it an efficient transdermal delivery vehicle. The slow progress in the efficacy of the treatment of several diseases has suggested a growing need for a multidisciplinary approach to the delivery of therapeutics to target tissues. Transdermal drug delivery systems (TDDS) or patches are controlled-release devices that contain the drug either for localized treatment of tissues underlying the skin or for systemic therapy after topical application to the skin surface. TDDS are available for a number of drugs, although the formulation matrices of these systems may differ. They differ from conventional topical formulations in the following ways.

- They have an impermeable occlusive backing film that prevents intensive water loss from the skin beneath the patch;
- The delivery of the drug is primarily by diffusion and concentration gradient; hence matrix of the patch maintains the drug concentration gradient within the device after application so that drug delivery to the interface between the patch and the skin is sustained.
- TDDS are kept in place on the skin surface by an adhesive layer ensuring drug contact with the skin and continued drug delivery.[5]

In order to enhance drug transdermal absorption, different methodologies have been investigated, developed, and patented. Improvement in physical permeation-enhancement technologies has led to renewed interest in transdermal drug delivery. Some of these novel advanced transdermal permeation-enhancement technologies include iontophoresis, electroporation, ultrasound, microneedles to open up the skin, and more recently the use of transdermal nanocarriers.[6]

Structure of the Skin

The structure of skin is depicted in **Figure 1**. Various parameters affect drug release like particle size and shape, physical stability and cellular uptake of the nanoparticulate materials. During the processing parameters such as stirring rate, temperature, type and amount of dispersing agent as well as the viscosity of the organic and aqueous phases also have affect on the final characteristic of the formulation. Zeta potential of a dispersion is necessary for dispersion stability system are affected by certain Transdermal drug administration systems can be delivered only to drugs with a particle range from submicron to few micron levels and of certain charge preference. For instance, cationic compounds have a positive effect on skin

permeation, since the skin carries a negative surface charge due to phosphatidylcholine[7] and carbohydrates found in mammalian cells contain negatively charged groups, Therefore, nanoparticles with predominant positive charge would enhance permeation owing to the selective nature of the skin barrier, only a small pool of drugs can be delivered systemically at therapeutically relevant rates. Besides great potency, the physicochemical drug characteristics often evoked as favourable for percutaneous delivery include moderate lipophilicity and low molecular weight. However, a large number of pharmaceutical agents do not fulfill these criteria.[8] This is especially true for macromolecules, such as insulin, human growth hormone or cyclosporine, which are very challenging from the drug delivery point of view. The physicochemical properties of ideal drug for transdermal delivery include.

- Molecular weight less than approximately 1000 Daltons.
- Affinity for both lipophilic and hydrophilic phases. Extreme partitioning characteristics not ideal.
- Low melting point.
- Should be potent, with short biological half life and be non-irritating.[8]

Factors Affecting Transdermal Permeability[1,2]

The factors controlling transdermal permeability can be broadly placed in the following cases.

I. Physico-chemical properties of the penetrant molecules

1. ***Partition coefficient:*** Drugs having both lipid and water solubilities are favorably absorbed through skin. Transdermal permeability coefficient shows a linear dependency on partition coefficient. A lipid /water partition coefficient of one or greater is generally required.
2. ***pH conditions:*** The pH value of higher or very low can be destructive to the skin. With moderate pH values the flux of ionisable drugs can be affected by changes in pH that alter the ratio of charged and uncharged species and their transdermal permeability.
3. ***Penetrant concentration:*** Increasing concentration of dissolved drug causes a proportional increase in flux. At higher concentration, excess solid drug function as reservoir and help to maintain a constant drug concentration for a prolonged period of time.

II. Physico-chemical properties of drug delivery systems

1. ***Release characteristic:*** Solubility of the drug in the vehicle determines the release rate. The mechanism of drug release depend on the following factors.

a) Whether the drug molecules are dissolved or suspended in the delivery system,
b) The interfacial partition coefficient of the drug from the delivery system to skin,
c) pH of the vehicle,

2. ***Enhancement of transdermal permeation:*** Majority of drugs will not penetrate the skin at rates sufficiently high for therapeutic efficacy. The permeation can be improved by the addition of permeation enhancer into the system.

III. Physiological and pathological condition of skin.

1. ***Reservoir effect of horny layer:*** The horny layer especially is deeper layer, can sometimes act as a depot and modify the transdermal permeation of drugs. The reservoir effect is due to irreversible binding of a part of the applied drug with the skin.
2. ***Lipid film:*** The lipid film on the skin surface acts as a protective layer to prevent the removal of moisture from the skin and helps in maintaining the barrier function of stratum corneum.
3. ***Skin hydration:*** Hydration of stratum corneum can enhance permeability. Skin hydration can be achieved simply by covering or occluding the skin with plastic sheeting, leading to accumulation of sweet. Increased hydration appears to open up the dense, closely packed cells of the skin and increases its porosity.
4. ***Skin temperature:*** Raising the skin temperature results in an increase in the rate of skin permeation; this may be due to availability of thermal energy required for diffusivity.
5. ***Regional variation:*** Difference in nature and thickness of the barrier layer of skin causes variation in permeability.
6. ***Pathological injuries to the skin:*** Injuries that disrupt the continuity of the stratum corneum, increases permeability due to increased vasodilation caused by removal of the barrier layer.
7. ***Cutaneous self metabolism:*** Catabolic enzymes present in the epidermis, may render the drug inactive by metabolism and the topical bioavailability of the drug.

Advantages of Transdermal Preparations

Delivery of drugs through skin has certain merits and some of them are.

- Convenient and pain free administration.
- Avoid first pass hepatic effect.

- Cost effective.
- Drug can be delivered at predetermined controlled manner.
- Potent drugs can be delivered through this route.
- In case of emergency, patch can be removed easily.
- Drugs with low therapeutic index can also be delivered through this route.[9]

Disadvantages of Transdermal Preparations

Inspite of its potential to deliver the drugs through skin barrier, it has some inherited limitations and some of which are.

- Drug loading is a limiting factor.
- Not all the drugs can be delivered through this route.
- Drugs which need high blood supply cannot be delivered through this route.
- Due to the slow penetration, fast onset of action is not possible.
- Special equipments and technology is required to manufacture TDDS.[10]

The primary function of nanomedicine is to diagnose with minimizing the side effects using noninvasive route. The advantage is to provide the drugs and other materials in the nanometer scale which can alter the characteristics and bioactivity of materials. Some of the characteristics that can be explored are solubility, increase in surface area, controlling release profile and site-targeted delivery systems. These nanocarriers can be administrated into the organisms by various routes like topical and transdermal routes. For the obvious reasons, drug dosing and side effects are mitigated using these nano particles. Improvement in permeation enhancement methodologies has led to renewed interest in transdermal drug delivery using iontophoresis, electroporation, ultrasound, microneedles to open up the skin and more recently the use of transdermal nanocarriers and penetration enhancers.[11]

Routes of Drug Penetration through the Skin

There are basically three ways through the intact barrier may be identified i.e. the intercellular route, transcellular route and follicular penetration (**Figure 2**). The intercellular lipid route lies between the corneocytes, interlamellar regions in the stratum corneum, which has less ordered lipids and more flexible hydrophobic chains. Fluid lipids in skin barrier are important for transepidermal diffusion of the lipidic, hydrophilic and hydrophobic molecules migrating through intercellular lipid layers of such molecules. The transcellular route contemplates the crossing through the corneocytes and the intervening lipids. Intracellular macromolecular matrix in the stratum corneum does not contribute directly to the skin

diffusive barrier but supports in mechanical stability. Transcellular diffusion is as such not important for transdermal drug transport.[12]

Recently, follicular penetration has become a major focus of interest due to the fact that drug targeting to the hair follicle is of great interest in the treatment of skin diseases. However, follicular orifices occupy only 0.1% of the total skin surface area. For this reason, it was assumed to be a non-important route for drug penetration. Such follicular pathways have also been proposed for topical administration of polystyrene nanoparticles.[12]

Do's and Don'ts of Using Nanocarriers for TDDS

Various carrier systems have been proposed in order to improve the transport of drugs through the skin, enabling drug retention and allowing a modified release.[13] Skin penetration is as such important to contamination by microorganisms and chemicals, drug delivery to skin (topical treatments) and through skin (transdermal treatments), and skin care (cosmetics).[14]

As such the main advantages of microparticles and nanoparticles over conventional formulations such as creams, ointments, gels, and foams, is that the latter ones have different absorption characteristics and aesthetic properties. But they also possess certain limitations, such as poor penetration and uncontrolled drug release. It happens because using a traditional system, drug delivery is sometimes rapid and topical or plasma concentrations can hit beyond maximum therapeutic range. However, for the case of nanoparticles a relatively smaller amount of the drug is required primarily due to the targeted nature of delivery.[15] Topical or transdermal drug deliveries have many advantages over the other conventional routes which include less side effects, increased compliance, controlling the release pattern, and bypassing hepatic firstpass. Nanoencapsulation of drugs increases their efficacy and are better tolerated. Nanocarriers as drug delivery systems were first intended for use in parenteral or oral routes of administration. However skin application of these nanocarriers, and especially for liposomes, polymeric and lipidic nanoparticles, also makes sense when considering film formation and occlusive effects, local effects in the skin and systemic effects (deeper drug permeation). In potential uses apart from issues with surface effects the nanocarrier has to overcome the subcutaneous barrier in order to deliver the drug more or less deeply into skin layers.[16,17] Reduction in particle size results in increased lipid content on nanoparticle (**Figure 3**). Applications dependent on skin penetration that have received special attention include transdermal delivery of nano- and microparticles by hair follicles, especially for

nanoparticles which penetrate hair follicles very efficiently targeting the skin immune system in order to develop new strategies mainly for the vaccines, and in skin disorders.[18,19]

Marketed Products[20-22]

Some of the marketed transdermal formulations are listed in **Table 1**.

Characterization of TDDS systems

Drug solubility determination

The determination of solubility of the drug in the transdermal/dermal matrix early in the formulation process can avoid crystallization problem, which is one of the instabilities in transdermal drug delivery systems (TDDS). This instability in the matrix which could be due to supersaturation makes the formulation metastable and upon storage results in changes in the liberation/release rate of the drug from the formulation.[23]

Particle size and zeta potential

Light scattering is an important way of characterizing colloidal and macromolecular dispersions and could be useful in assessing properties of particulate TDDS (E.g. Ethosomes).[24] The particle size and size distribution are primarily measured using wet laser diffraction sizing otherwise called dynamic light scattering (DLS).[25] Size of formulation can also be determined using dynamic light scattering (E.g. using a Zetasizer). This is necessary to ascertain the possible effect of the size on drug release and penetration across barriers in transdermal and dermal delivery as well as to monitor stability over time. The zeta potential of a formulation is very important. It is determined using Zetasizer or by other means, and gives information on the charge of the particles and the tendency of the particles in a formulation to aggregate or to remain discrete.[26]

Surface area

The absorptive surface area of the drug particles and surface area on the skin has a direct impact on the penetration capacity.[21] More the Surface area, enhanced will be the absorption. The different areas on the body has different thickness and surface area, hence this also should be kept in mind depending on the release pattern of the drug needed. Usually scopolamine patch is used on the back of ear and nicotine patch is usually applied on the back of ear.[27]

Stability

Physical and chemical instabilities of carrier systems often limit their widespread use in medical applications. Instabilities in nanocarrier formulations are caused by hydrolysis or oxidation of the phospholipid molecules and are indicated by leakage of the encapsulated drug and alterations in vesicle size due to fusion and aggregation. Changes in size and size distribution, entrapment efficiency and aggregation of vesicles are very important parameters in monitoring stability.[28, 29]

Novel Technologies for Dermal and Transdermal Application

Nanoparticles for dermatological applications such liposomes and other vesicular systems as well as other types of nanosized drug carriers such as solid lipid nanoparticles, nanostructured lipid carriers, polymer-based nanoparticles and magnetic nanoparticles have been developed. These have in one way or the other overcome the issues associated with the shortcoming of the traditional TDDS such as ointments, gels etc.[30] Different carrier systems have been proposed in an attempt to favor the transport of drugs through the skin, enabling drug retention and in some cases allowing a controlled release.[31] Skin penetration is essential to a number of current concerns, e.g. contamination by microorganisms and chemicals, drug delivery to skin (dermatological treatments) and through skin (transdermal treatments), and skin care and protection (cosmetics). Physicochemical properties of nanocarrier systems determine the interaction with biological systems and nanocarrier cell internalization.[32] The main physicochemical properties that affect cellular uptake are size, shape, rigidity, and charge in the surface of nanoparticles. The most used and investigated nanocarriers for dermal/transdermal drug delivery in the pharmaceutical field include liposomes, transfersomes, ethosomes, niosomes, dendrimers, lipid and polymer nanoparticles, and nanoemulsions. In general, the advantages and limitations of using nanocarriers for transdermal drug delivery are their micron size, their high surface energy, their composition, their structural configuration.[33,34]

Nanoemulsions

Nanoemulsions are isotropic dispersed systems of two non-miscible liquids, normally consisting of an oily system dispersed in an aqueous system, or an aqueous system dispersed in an oily system but forming droplets or other oily phases of nanometric sizes.[35] They are thermodynamically unstable systems, in contrast to microemulsions, because some nanoemulsions need high energy to produce them. They are susceptible to Oswald ripening,

and as a consequence susceptible to creaming, flocculation, and other physical instability problems associated with nanoemulsions.[36] Despite this, they can be stable (metastable) for long periods due to their small size and the use of appropriate surfactants. Amphiphilic drugs can be formulated in nanoemulsions. They are nontoxic and nonirritant systems, and they can be used for skin or mucous membranes and parenteral and non-parenteral administration in general, and they have been utilized in the cosmetic field.[37]

These can be prepared by various methods which include three methods mainly: high-pressure homogenization, microfluidization, and phase-inversion temperature. Transdermal delivery using nanoemulsions has limitations due to the stability issues inherent to this dosage form. There are various commercial products available in the market some e.g. of drugs using nanoemulsions for transdermal drug delivery are gamma tocopherol, caffeine, plasmid DNA, aspirin, methyl salicylate, insulin and nimesulide.[38] Presently, transdermal nanoemulsion formulations are not developed as much as nanoparticles or liposomes due to the inherited stability problems. The use of these nanocarriers to deliver analgesics, corticosteroids, anticancer agents, etc, is very important, as these drugs are able to act immediately because they do not need to cross extra barriers.[39]

Nano Implants

The versatility of the implantable systems has been increased significantly by the use of nanotechnology. The entire delivery systems along with its components has been reduced to the extent where only minimum invasion is required.[40] Different approaches have been used to put in use to stabilized the implant. These technologies have helped to customized drug-release mechanisms to achieve of drug-release profiles including programmable, cyclic, pulsatile or continuous.[41]

Nanocarrier Advantages[42,43]

- They can be formulated as liquids, foams and cream.
- They are non toxic and non irritant.
- Easily applied to skin and mucous membrane.

Limitations

- They are subject to Oswald ripening.
- Surface charge has effect on stability.
- Variable kinetics of distribution and clearance.

Regulations on TDDS

Safety, efficacy and toxicological issues are the most important issues for a drug delivery system. Safety is an obvious concern for the fast growth of nanoparticles mediated drug delivery.[27]

Federal regulatory agencies such as the United States Food and Drug Agency (USFDA) have established guidelines describing the kind of safety tests that should be conducted in animals in order to have a new drug approved for use in clinical trials and in order to get approval of a new drug application (NDA) for marketing. The rationale and circumstances for conducting reproductive, mutagenicity, carcinogenicity, irritation, and sensitization studies have already been mentioned.[37,43] The studies for pharmaceutical products intended for use in humans as described according to are the requirements of the United States, Japan, and Europe because these areas represent the largest pharmaceutical markets in the world today. These requirements have been developed at the International Conference on Harmonization to provide uniformity among the three regions. Phases I, II, and III refer to the different phases of human clinical trials. Phase I refers to the initial trials, limited to one or a few doses to determine absorption, pharmacokinetics, and an initial estimate of safety. Phase II refers to larger scale studies to establish safety and to get an initial estimate of clinical efficacy. Phase III refers to the final, large-scale, multicenter trials aimed at establishing efficacy requirements for acute, sub-acute, and chronic toxicity.[44] The Food and Drug Agency (FDA) paradigm for regulation of new products is based on the concepts of risk management, which includes identification, analysis and control of risk. The regulation and approval by the FDA is on a ‘‘product by product’’ basis, with the overall regulation process falling into three stages: premarket approval, premarket acceptance and post-market surveillance.[44]

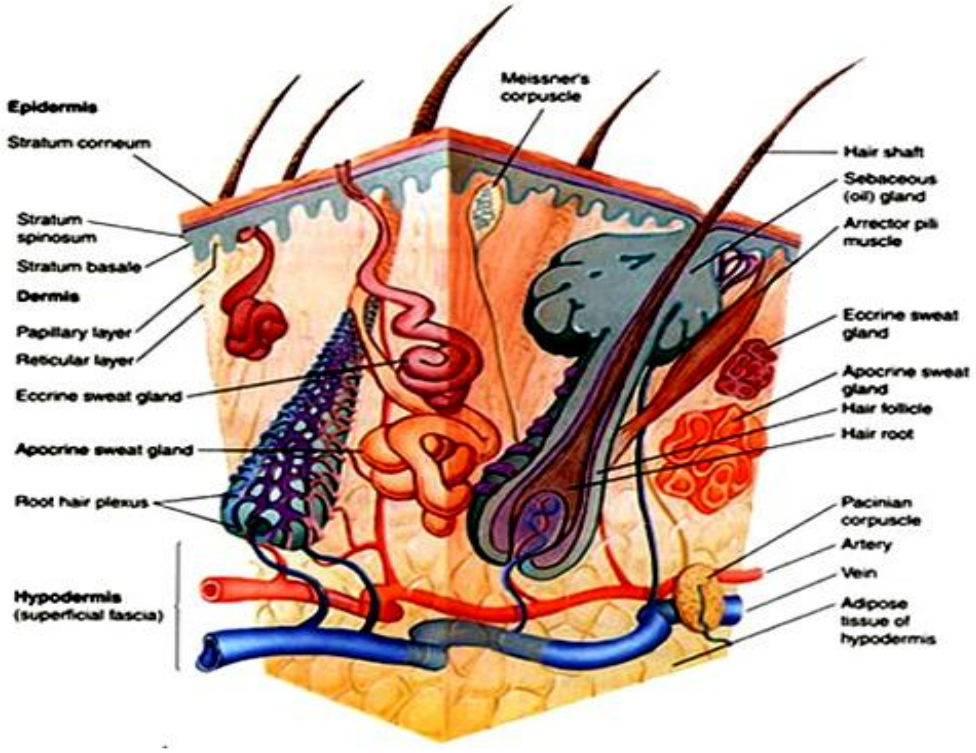

Figure 1: Structure of skin.

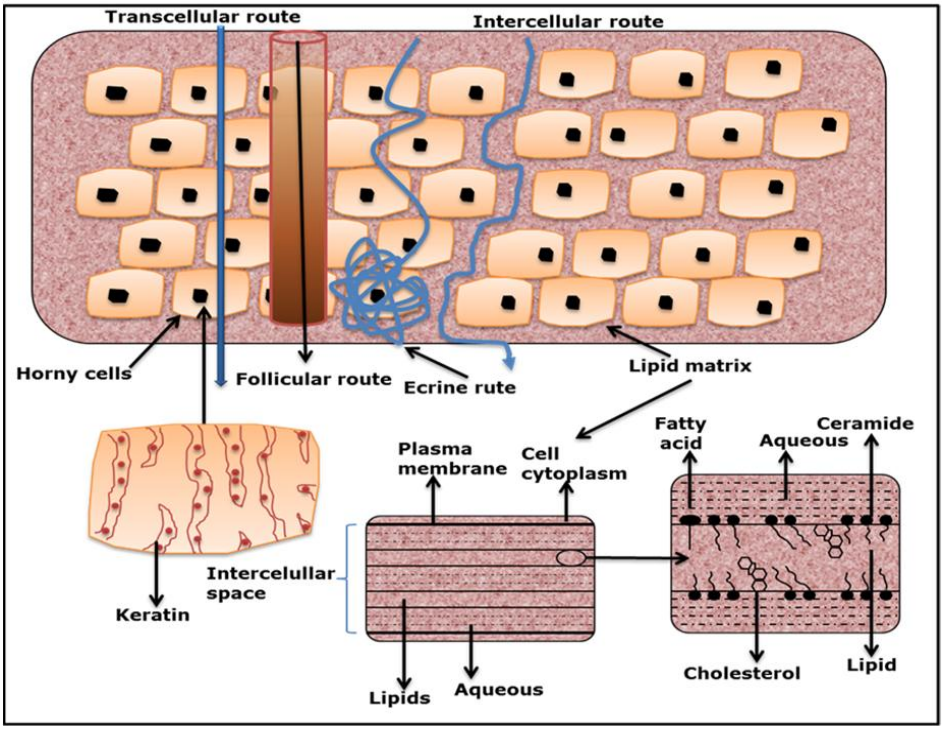

Figure 2: Transcellular and intercellular route of drug penetration/absorption.

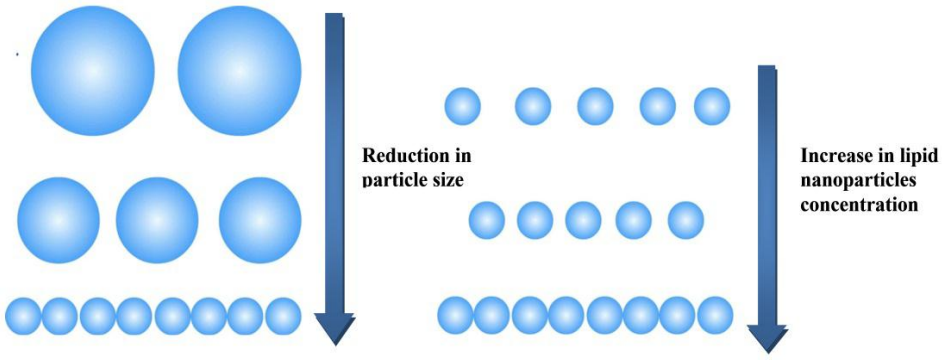

Figure 3: Effect of particle size reduction on the lipid content of nanoparticles.

Table 1: Marketed transdermal formulations.

Drug	Tradename	Manufacturer
Fentanyl	Duragesic	Alza Pharmaceuticals
Nitroglycerine	Nitrodisc	Searle, USA
Nicotine	Ncotrol	Mcneil consumer Products ltd
Habitraol	Isosorbide dinitrate	Novartis
Testosterone	Androderm	GSK
Clonidine	Catapress	Alza/Boehinger Ingelheim
Lidocaine	Lidoderm	Cerner Multum, Inc.
Scopolamine	Transderm Scop	Alza/Novartis
Minoxidil 4%	Nanominox	Sinere, Germany
Acyclovir	Supravir Cream	Trima, Israel
Estradiol	Climara	3M Pharmaceuticals
Ethinyl estradiol	Ortho evra	--

CONCLUSIONS

Nanotechnology based drug delivery systems are useful functional tools that had wide use in the pharmaceutics and therapeutics. The versatility and multi-functional characteristics of these nano systems makes them capable of alleviating the undesirable properties of drug molecules. As the most desirable attribute for a drug carrier is its ability to deliver drug to the targeted site, nanosystems are potent enough for the same. Thus, diverse nanosystems implied for transdermal delivery of drugs in view of approaches like nanoparticles, nanoemulsions, nano-implants, liposome, dendrimers and carbon nanotubes etc. would be a versatile means of constructing a new class of novel transdermal drug delivery systems.

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