We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Chapter 6

Nanoparticles for Dermal and Transdermal Drug Delivery

Okoro Uchechi, John D. N. Ogbonna and Anthony A. Attama

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/58672

1. Introduction

The term "nanoscale" refers to particle size range from ~ 1 to 100 nm [1], but for the purpose of drug delivery, nanoparticles in the range of 50 – 500 nm are acceptable depending on the route of administration. The method by which a drug is delivered can have a significant effect on its efficacy. Some drugs have an optimum concentration range within which maximum benefit is derived and concentrations above or below this range can be toxic or produce no therapeutic benefit. 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 [2]. 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 [3]. TDDS are available for a number of drugs, although the formulation matrices of these delivery systems 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 formulation 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; and
- TDDS are kept in place on the skin surface by an adhesive layer ensuring drug contact with the skin and continued drug delivery [4].

Topical or transdermal drug delivery is challenging because the skin acts as a natural and protective barrier. TDDS were introduced into the US market in the late 1970s [5], but transdermal delivery of drugs had been used for a very long time. There have been previous reports about the use of mustard plasters to alleviate chest congestion and belladonna plasters as analgesics. The mustard plasters were homemade as well as available commercially where mustard seeds were ground and mixed with water to form a paste, which was in turn used to form a dispersion type of delivery system. Several methods have been examined to increase the permeation of therapeutic molecules into and through the skin and one such approach is use of nanoparticulate delivery system.

The skin has been an important route for drug delivery when topical, regional, or systemic effects are desired. Nevertheless, skin constitutes an excellent barrier and presents difficulties for the transdermal delivery of therapeutic agents, since few drugs possess the characteristics required to permeate across the stratum corneum in sufficient quantities to reach a therapeutic concentration in the blood [6]. 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.

2. The human skin

The potential of using the intact skin as the port of drug administration to the human body has been recognized for several decades. However, the skin is a very difficult barrier to the ingress of materials allowing only small quantities of a drug to penetrate over a period of time. In order to design a drug delivery system, one must first understand the skin anatomy and its implication of drug-of choice and method of delivery.

The human skin is the largest organ in our body with surface area of 1.8-2.0 m^2. It is composed of three main layers; the epidermis, dermis and hypodermis (subcutaneous layer) (Fig. 1). The skin is a well energized organ that protects the organism against environmental factors and regulates heat and water loss from the body.

3. Routes of drug penetration through the skin

The permeation of drugs through the skin involves the diffusion through the intact epidermis through the skin appendages (hair follicles and sweat glands). These skin appendages form shunt pathways through the intact epidermis, occupying only 0.1% of the total human skin. It is known that drug permeation through the skin is usually limited by the stratum corneum (Fig. 2). Three main penetration routes are recognized (Fig. 3).

http://dx.doi.org/10.5772/58672

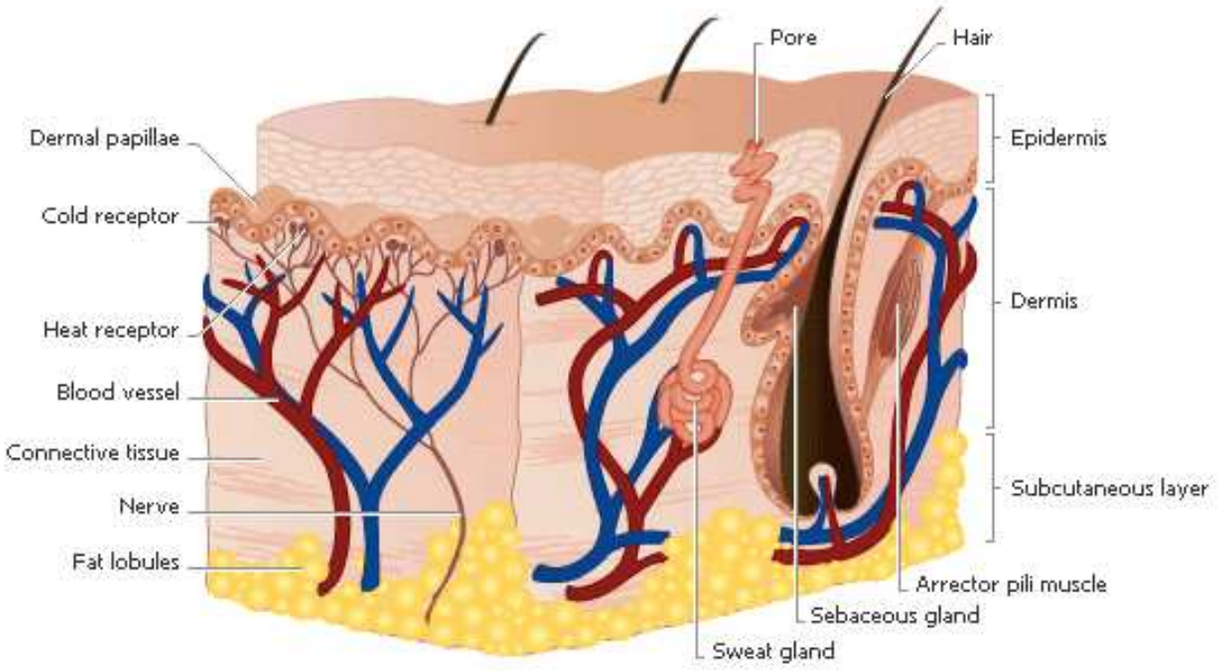
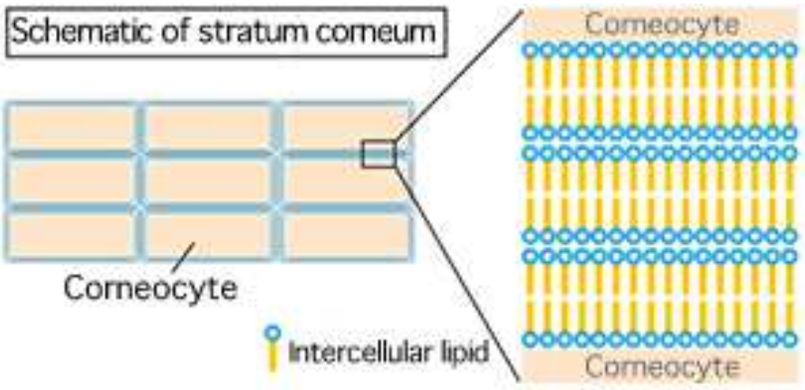


Figure 1. Structure of the skin (http://www.naturalrussia.com/natural/skin/structure.html. Downloaded on April 26, 2014)



(http://www.spring8.or.jp/en/news_publications/press_release/2011/110406/. Downloaded April 26, 2014).

Figure 2. The stratum corneum

3.1. The intercellular lipid route

Interlamellar regions in the stratum corneum, including linker regions, contain less ordered lipids and more flexible hydrophobic chains. This is the reason for the nonplanar spaces between crystalline lipid lamellae and their adjacent cells' outer membrane. Fluid lipids in skin barrier are crucially important for transepidermal diffusion of the lipidic and amphiphilic molecules, occupying those spaces for the insertion and migration through intercellular lipid

layers of such molecules [7]. The hydrophilic molecules diffuse predominantly "laterally" along surfaces of the less abundant water-filled interlamellar spaces or through such volumes; polar molecules can also use the free space between a lamella and a corneocyte outer membrane to the same end.

3.2. The transcellular route

Intracellular macromolecular matrix within the stratum corneum abounds in keratin, which does not contribute directly to the skin diffusive barrier but supports mechanical stability and thus intactness of the stratum corneum. Transcellular diffusion is practically unimportant for transdermal drug transport [8]. The narrow aqueous transepidermal pathways have been observed using confocal laser scanning microscopy. Here, regions of poor cellular and intercellular lipid packing coincide with wrinkles on skin surface and are simultaneously the sites of lowest skin resistance to the transport of hydrophilic entities. This lowest-resistance pathway leads between clusters of corneocytes at the locations where such cellular groups show no lateral overlap. The contribution to transdermal drug transport can increase with pathway widening or multiplication, e.g., that which is caused by exposing the stratum corneum to a strong electrical (electroporation/iontophoresis), mechanical (sonoporation/sonophoresis), or thermal stimulus, or suitable skin penetrants.

3.3. Follicular penetration

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 nonimportant route for drug penetration. But a variety of studies have shown that hair follicles could be an interesting option for drug penetration through the skin [6]. Such follicular pathways have also been proposed for topical administration of polystyrene nanoparticles. They were investigated in porcine skin (*ex vivo*) and human skin (*in vivo*). Surface images revealed that polystyrene nanoparticles accumulated preferentially in the follicular openings. This distribution was increased in a time-dependent manner, and the follicular localization was favored by the smaller particle size. The study also confirmed similarity in the penetration between both membranes (porcine and human skin). In other investigations, the influence of microparticle size in skin penetration has been shown by differential stripping. Nanoparticles can act as efficient drug carriers through the follicle or can be utilized as follicle blockers to stop the penetration of topically applied substances.

4. Main factors for nano-based delivery system

4.1. Particle size, size distribution and zeta potential

Particle size and shape affect drug release, physical stability and cellular uptake of the nanoparticulate materials. The yield and size distribution of each system are affected by certain

http://dx.doi.org/10.5772/58672

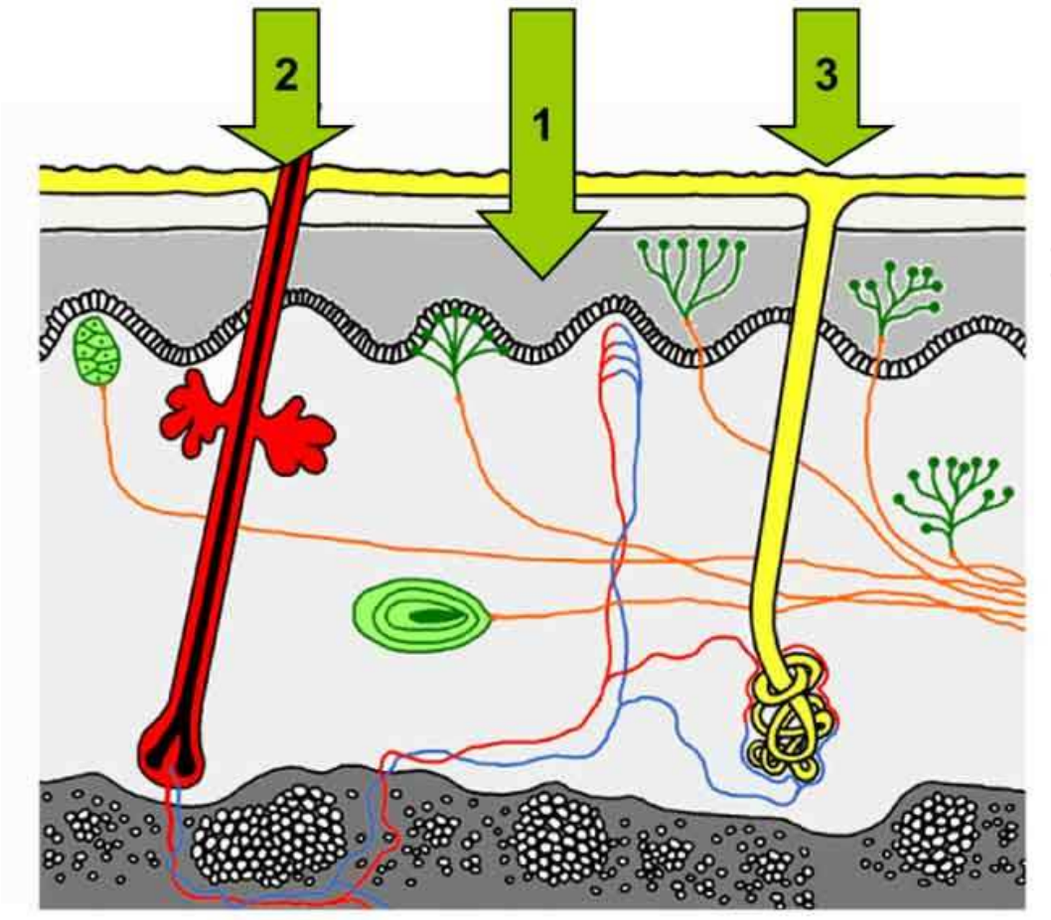


Figure 3. Structure of the skin showing routes of penetration: (1) across the intact horny layer, (2) through the hair follicles with the associated sebaceaous glands, or (3) via the sweat glands (http://www.skin-care-forum.basf.com/en/author-articles/strategies-for-skin-penetration-enhancement/2004/08/12?id=5b9a9164-6148-4d66-bd84-6df76bd6d111&mode=Detail. Downloaded April 26, 2014).

in-process operations and conditions such as stirring rate, temperature, type and amount of dispersing agent as well as the viscosity of the organic and aqueous phases [9,10]. Zeta potential of a dispersion is necessary for dispersion stability [11].

4.2. Surface properties

The attachment of nanoparticles to cell membrane is affected by the surface charge of the particles. Variation of the particle surface charge could potentially control binding to the tissue and direct nanoparticles to cellular compartments both *in vitro* and *in vivo*. Cellular surfaces are dominated by negatively charged sulphated proteoglycans molecules that play pivotal roles in cellular proliferation, migration and motility [12]. Cell surface proteoglyans consist of a core protein anchored to the membrane and linked to one or more glycosaminoglycan side chains (heparan, dermatan, keratan or chondrotine sulfates) to produce a structure that extends away from the cell surface.

Nanoparticles show a high affinity for cellular membrane mainly due to electrostatic interactions [12]. It is known that cell membranes have large negatively charged domains, which should repel negatively charged nanoparticles. The high cellular uptake of negatively charged nanoparticles is related first to the non-specific process of nanoparticles adsorption on the cell membrane and second to formation of nanoparticle clusters [13]. The adsorption of the negatively charged particles at the positively charged sites via electrostatic interaction can lead to localized neutralization and a subsequent bending of the membrane favouring in turn endocytosis for cellular uptake [14]. Thus the formulation of nanoparticles with different surface properties can influence their cellular uptake and intracellular distribution and it is possible to localize the nanoparticles to specific intracellular targets (lysosomes, mitochondria, cytoplasm, etc) by modifying their surface charge [15].

There are some investigations that showed the effect of surface charge, for example polymer charge density of dendrimers was found to significantly impact membrane permeability. The most densely charged polymer facilitates the transport of dye molecule across the membrane [16]. Other investigation showed that lipid coating of ionically charged nanoparticles was able to increase endothelial cell layer crossing 3 or 4 fold compared with uncoated particles, whereas nanoparticles coating of neutral particles did not significantly alter their permeation characteristics across the endothelial cell monolayer [13]. Transdermal drug administration systems have been limited to certain drugs of a range of molecular weight and lipophilicity, 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 [17] and carbohydrates found in mammalian cells contain negatively charged groups. Therefore, nanoparticles with predominant positive charge would promote transdermal permeation.

5. Dermatopharmacokinetics

Dermatopharmacokinetics describe the pharmacokinetics of topically applied drugs in the stratum corneum with pharmacodynamic effects. The smart techniques (tape stripping and microdialysis) use in dermatopharmacokinetic methodology assesses the cutaneous drug concentration at the site of application. Various studies have shown dermatopharmacokinetics to be a reliable and reproducible method for determining bioequivalence, and have indicated that it is applicable for all topical dermatological drug products. Dermatopharmacokinetics refer to the determination of stratum corneum concentration-time curves for topical actives. This is analogous to plasma/urine concentration-time curves for systemically or orally administered drugs, and the concept is clearly adaptable to microdialysis, where drug is determined in the skin compartment in which the microdialysis fibre is positioned (Fig. 4).

Although, this procedure is invasive, it is a method of great potential offering information of high value and relevance. There could be sampling in a compartment within the skin. It is a technically demanding procedure, however, requiring experimental dexterity of high order. The potential for use on diseased skin is a unique and considerable advantage over other techniques, but real challenges remain with respect to reproducibility, sensitivity, applicable drugs, etc.

http://dx.doi.org/10.5772/58672

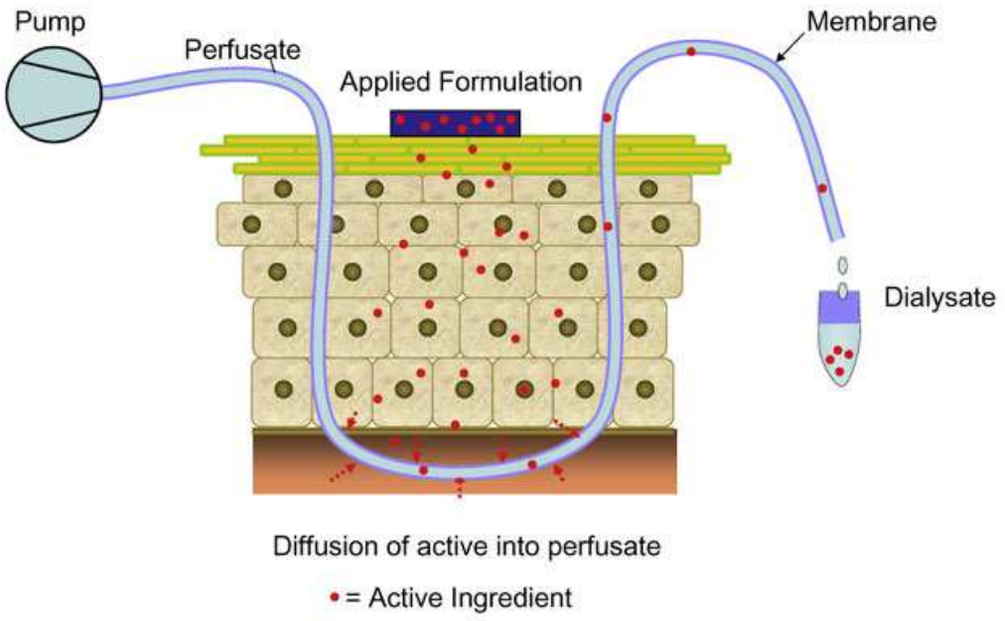


Figure 4. Sampling in the skin by microdialysis (http://www.skin-care-forum.basf.com/en/author-articles/strategies-for-skin-penetration-enhancement/2004/08/12?id=5b9a9164-6148-4d66-bd84-6df76bd6d111&mode=Detail. Downloaded April 26, 2014)

Stratum corneum tape-stripping is a minimally invasive method for determining drug levels in human stratum corneum *in vivo.* It involves repeated application of adhesive tapes on a site that has been treated with a topical formulation and determination of drug levels in stratum corneum collected on tape strips.

The dermatopharmacokinetics approach suggested by the Food and Drug Administration (FDA) proposes to evaluate the level of a topically applied drug in the stratum corneum during its uptake and clearance so as to calculate classic pharmacokinetic parameters [18]. The assumption is that stratum corneum concentration-time curves are directly related to concentration-time curves in the epidermis and dermis.

When applied to diseased skin, topical drug products induce one or more therapeutic responses, where onset, duration, and magnitude depend on the relative efficiency of three sequential processes, namely:

- the release of the drug from the dosage form
- penetration of the drug through the skin barrier, and
- generation of the desired pharmacological effect.

Because topical products deliver the drug directly to or near the intended site of action, measurement of the drug uptake into and drug elimination from the stratum corneum can provide a dermatopharmacokinetics means of assessing the bioequivalence of two topical drug products [19,20]. Presumably, two formulations that produce comparable stratum corneum concentration-time curves may be bioequivalence, just as two oral formulations are judged

bioequivalent if they produce comparable plasma concentration-time curves. Even though the target site for topical dermatologic drug products in some instances may not be the stratum corneum, the topical drug must still pass through the stratum corneum, except in instances of damage, to reach deeper sites of action [21]. In certain instances, the stratum corneum itself is the site of action. For example, in fungal infections of the skin, fungi reside in the stratum corneum and therefore dermatopharmacokinetic measurement of an antifungal drug in the stratum corneum represents direct measurement of drug concentration at the site of action [22]. In instances where the stratum corneum is disrupted or damaged, *in vitro* drug release may provide additional information toward the bioequivalent assessment. In this context, the drug release rate may reflect drug delivery directly to the dermal skin site without passage through the stratum corneum. For antiacne drug products, target sites are the hair follicles and sebaceous glands. In this setting, the drug diffuses through the stratum corneum, epidermis, and dermis to reach the site of action. The drug may also follow follicular pathways to reach the sites of action. The extent of follicular penetration depends on the particle size of the active ingredient if it is in the form of a suspension [21, 23-25]. Under these circumstances, the dermatopharmacokinetic approach is still expected to be applicable because studies indicate a positive correlation between the stratum corneum and follicular concentrations. Although the exact mechanism of action for some dermatological drugs is unclear, the dermatopharmacokinetic approach may still be useful as a measure of bioequivalence because it has been demonstrated that the stratum corneum functions as a reservoir, and stratum corneum concentration is a predictor of the amount of drug absorbed [26].

For reasons thus cited, dermatopharmacokinetic principles should be generally applicable to all topical dermatological drug products including antifungal, antiviral, antiacne, antibiotic, corticosteroid, and vaginally applied drug products. The dermatopharmacokinetic approach can thus be the primary means to document bioavailability/bioequivalence. Generally, bioequivalence determinations using dermatopharmacokinetic studies are performed in healthy subjects because skin where disease is present demonstrates high variability and changes over time. Use of healthy subjects is consistent with similar use in bioequivalence studies for oral drug products.

A dermatopharmacokinetic approach is not generally applicable when:

- a single application of the dermatological preparation damages the stratum corneum
- for otic preparations except when the product is intended for otic inflammation of the skin; and
- for ophthalmic preparations because the cornea is structurally different from the stratum corneum.

6. Ideal drugs for dermal and transdermal delivery

Owing to the selective nature of the skin barrier, only a small pool of drugs can be delivered systemically at therapeutically relevant rates [27]. Few drugs constitute the whole segment of

http://dx.doi.org/10.5772/58672

the transdermal drug market. Besides great potency, the physicochemical drug characteristics often evoked as favourable for percutaneous delivery include moderate lipophilicity and low molecular weight [28]. However, a large number of pharmaceutical agents do not fulfill these criteria. 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 half life and be non-irritating.

Overcoming low skin permeability to xenobiotics can be achieved by a variety of approaches, and is an active field of research. Their effectiveness and applicability will vary from drug to drug depending on the physicochemical nature of the compound. New drug discovery is still a complicated process and generally requires substantial time and monetary investment. Technologies for formulation change provide the benefit of improving pharmaceutical product efficacy and safety as well as patient convenience; these technologies provide a relatively simple approach to creating new pharmaceuticals compared with new drug discovery because the active compounds used in the formulation have already been approved [29-31]. Nnamani *et al* [32] developed and evaluated the antimicrobial activities of an alternative non-invasive, convenient and cost-effective transdermal drug delivery system (TDDS) containing gentamicin in biodegradable polyester-based matrices. Other drugs which have been formulated for dermal and transdermal delivery are nitroglycerin, nicotine, scopolamine, clonidine, fentanyl, 17-β-estradiol, testosterone, Boswellic acid (*Boswellia serrata*) and curcumin (*Curcuma longa*).

7. Advantages of dermal and transdermal drug delivery

Transdermal delivery provides convenient and pain-free self-administration for patients. It eliminates frequent dosing administration and plasma level peaks and valleys associated with oral dosing and injections to maintain constant drug concentrations, and a drug with a short half-life can be delivered easily. All this leads to enhanced patient compliance, especially when long-term treatment is required, as in chronic pain treatment and smoking cessation therapy [3,33,34].

- Avoidance of hepatic first-pass metabolism and the gastrointestinal (GI) tract for poorly bioavailable drugs is another advantage of transdermal delivery. Elimination of the first-pass effect allows the amount of drug administered to be lower, and hence, safer in hepato-compromised patients, resulting in the reduction of adverse effects.
- Transdermal systems are generally inexpensive when compared with other therapies on a monthly cost basis, as patches are designed to deliver drugs from 1 to 7 days.

- The other advantage of transdermal delivery is that multiple dosing, on-demand or variable-rate delivery of drugs is possible with the latest programmable systems, adding more benefits to the conventional patch dosage forms.
- The general acceptability of transdermal products by patients is very high, which is also evident from the increasing market for transdermal products.
- Transdermal route permits the use of a relatively potent drug with minimal risk of system toxicity [35,36].
- In case of toxicity, the transdermal patch can easily be removed by the patient [37].

8. Disadvantages of dermal and transdermal delivery systems

Even though dermal and transdermal delivery systems have a lot of advantages over conventional topical formulation, it still suffer from a lot of limitations. The disadvantages of dermal and transdermal delivery systems according to Ranade and Cannon [38] are that:

- Not all drugs are suitable for transdermal delivery.
- Drugs that require high blood levels cannot be administered.
- The adhesive used may not adhere well to all types of skin.
- Drugs or drug formulation may cause sensitization or irritation which must be evaluated fairly early in the development process.
- The patches may/can be uncomfortable to wear.
- The manufacture requires specialized equipments which results in the formulation being more expensive to manufacture than conventional dosage forms thus the formulation will not be economical for most patients.
- There is always a lag time for drug to penetrate through the skin to the systemic circulation, therefore TDDS is not suitable for drugs requiring rapid onset of action.
- There is a requirement for low dose/high permeable drug. In general a drug with molecular weight less than 400, $\log P_{o/w}$=2-3 and dose less than 10 mg will be the best candidate for transdermal delivery.

9. Characterization of dermal and transdermal delivery systems and their performance

Dermal and transdermal delivery systems are characterized using different methods.

http://dx.doi.org/10.5772/58672

9.1. 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.

9.2. Micromeritic measurements

9.2.1. Particle-size, shape and zeta potential analysis

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. The particle size and size distribution are primarily measured using wet laser diffraction sizing otherwise called dynamic light scattering (DLS) [39]. 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 Zetsizer 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.

9.2.2. Specific surface area

An important parameter of bulk powders is the specific surface area expressed per unit weight. The specific surface area measurement includes the cracks, crevices, nooks, and crannies present in the particles. To include these features in the surface-area measurement, methods have been developed to probe these convoluted surfaces through adsorption by either a gas or a liquid [40-42]. The most widely used surface area measurement technique is the adsorption of a monolayer of gas, typically krypton or nitrogen as the adsorbate gas in helium as an inert diluent, using the method developed by Brunauer, Emmett, and Teller known as the BET method. Surface area affects spreading and occlusivity of TDDS.

9.3. Visualization by transmission electron microscopy

A combination of transmission electron microscopy (TEM) and freeze fracturing otherwise referred to as freeze fracture electron microscopy (FFEM) could be used to visualize skin structures and certain perturbations in the skin. A micrograph image is generated by transmitting a beam of electrons through a specimen appropriately treated to enhance the visualization of skin structural details. High resolution of TEM makes it possible to visualize both structures and transition processes in the epidermis. Using different techniques, epidermal granules [43], Langerhans cells [44] and the lipids in stratum corneum and epidermis [45], amongst others, have been observed. Samples preparation in FFTEM involves freezing the sample and subsequent longitudinal fracturing approximately parallel to the original skin

surface under high vacuum [46]. Further treatment could be done on the sample after which the fracture is viewed under high voltage. This visualization method can provide information on the interaction between the nanoparticle formulation and the skin. Since the fracture will always run along the plane of least resistance, FFEM micrographs of treated stratum corneum often show the lipid coated surfaces of corneocytes or the lipid lamellae.

9.4. Stability

Physical and chemical instabilities of carrier systems often limit their widespread use in medical applications [47]. Instabilities in ethosomes and other 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 [48,49]. Changes in size and size distribution, entrapment efficiency and aggregation of vesicles are very important parameters in monitoring stability. These parameters can be assessed by EM or DLS repeatedly over time at varying storage conditions. It has recently been found that although multilamellar and large unilamellar benzocaine-loaded ethosome vesicles remained substantially stable with time, in terms of drug entrapment yield and particle dimensions, small unilamellar vesicles showed high tendency to form aggregates due to increased surface area exposed to the medium [10]. Such vesicle aggregation indicates instability. In addition, changes in storage conditions led to marked decrease in particle dimensions and drug-entrapping yield with less regular morphology for frozen-and-thawed multilamellar ethosome dispersions, while the untreated multilamellar and unilamellar vesicular dispersions remained homogenous and stable with regard to those parameters assessed over the period [50]. Temperature of formulation and storage conditions affect physical stability of nanoparticle preparations [10,51].

Optical characteristics, viscosity and physical changes such as cracking or creaming are also important in assessing stability of ethosomes. Ethosomes are colloidal disperse systems therefore, cracking and creaming may be observed during storage as in water-in-oil emulsions. The use of an innovative optical analyzer, Turbiscan Lab® Expert, in studying the influence of optical characteristics on long-term stability of vesicular colloidal delivery systems has been advocated [52]. The principle of this measurement is based on the variation of the droplet volume fraction (migration) or mean size (coalescence), thus resulting in the variation of backscattering and transmission signals as a function of time. No variation of particle size occurs when the backscattering profile is within the interval ± 2 %. Variations greater than 10 % either as a positive or negative value in the graphical scale of backscattering are representative of an unstable formulation.

9.5. High-pressure liquid chromatography (HPLC)

It is used to monitor the stability of pure drug substance and drugs in formulation with quantitation of degradation product. A liquid mobile phase is pumped under pressure through a stainless steel column containing particles of stationary phase with a diameter of 3-10 μm. The analyte is loaded onto the head of the column via a loop valve and separation of a mixture occurs according to the relative lengths of time spent by its components in the stationary phase.

http://dx.doi.org/10.5772/58672

and less dense [150]. The vesicles then squeeze through the intercellular spaces into the deeper layers of skin. It has been shown that drug particles are concentrated more on the inside wall than in the core of vesicles [151]. In this position, release of the vesicular content is thermodynamically favored. Owing to the increased affinity, due to its lipid content, the vesicle fuses with the lipid contents of the skin layers and releases its content which then diffuses into deeper layers of the skin or membrane and into systemic circulation. Other mechanisms, such as the free drug diffusion, may be involved in penetration.

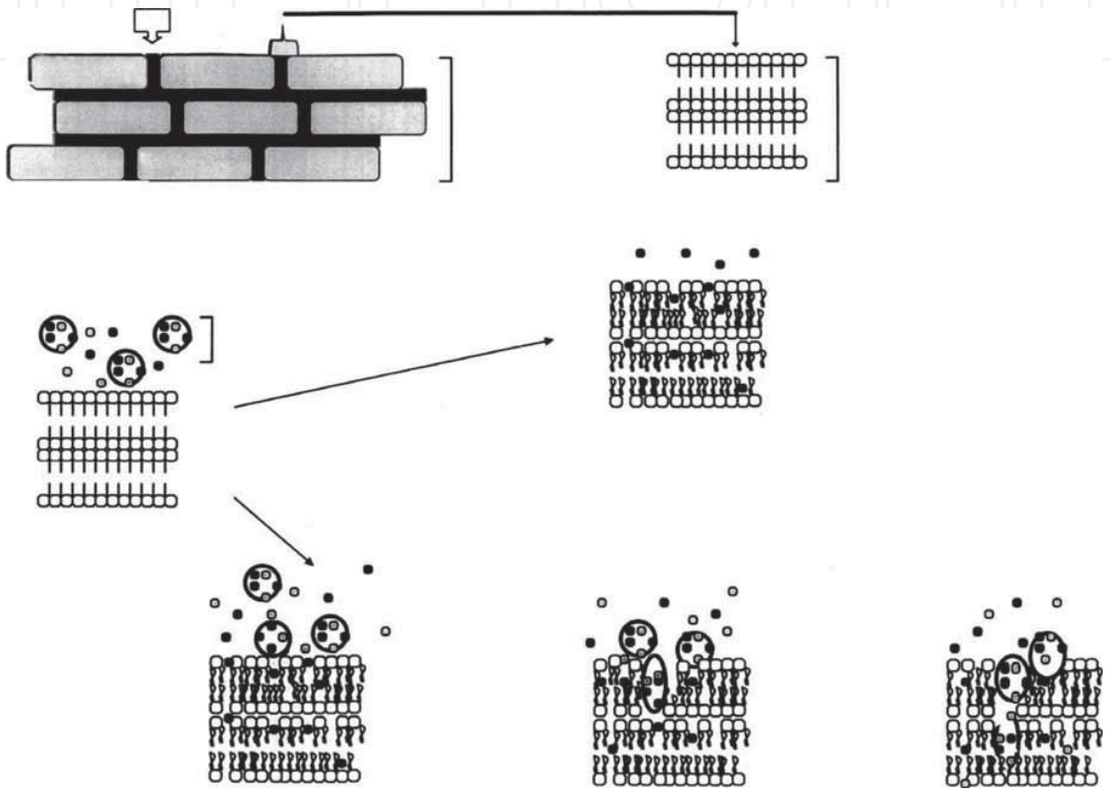


Figure 8. Mechanism of drug delivery from ethosomal vesicular carriers through the skin [46,115]. Note the initial fluidization of the skin architecture.

12. Regulations on dermal and transdermal delivery systems

Safety 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 [152]. Governmental 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. The requirements for acute, subacute, and chronic toxicity

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 [153]. 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.

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 [154]. 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.

Premarket approval: Prior to market introduction of any new pharmaceuticals, high-risk medical devices, food additives, colors, and biologicals, FDA approval is required. The producer/sponsor of the product is responsible for identifying and assessing the risks presented by the product. This party will also be responsible for indicating means to minimize the risks in a product application.

Premarket acceptance: This category refers to products that are often copies of similar products that were approved previously or are products prepared according to approved specifications. For these products, the FDA receives and reviews some form of notice that the products will be marketed and the products undergo a more rapid review process than premarket approval.

Postmarket surveillance: In this category, FDA manages the risks of GRAS products like foods, cosmetics, radiation emitting electronic products and materials such as food additives and food packaging. For products in this category, market entry, and distribution are at the discretion of the manufacturer/producer. These products are generally regulated by the application of good manufacturing practices. FDA takes regulatory action if adverse events that threaten public or individual health occur.

The FDA coordinates policies within itself and with other government agencies. As and when new toxicological risks that derive from the new materials and/or new conformations of existing materials are identified, the FDA will require new tests.

The FDA regulations are for products, not technologies. In addition, the FDA regulates only the claims made by the product sponsor. If the manufacturer makes no nanotechnology claims regarding the manufacture or performance of the product, the FDA may be unaware at the time that the product under review employed nanotechnology. Finally, the FDA has only limited authority over some potentially high-risk products, such as cosmetics. Many products are regulated only if they cause adverse health-related events in use. To date there have been few resources available to assess the risks of these products.

13. Dermal and transdermal formulations on the market

A lot of dermal and transdermal drug delivery systems have been licensed for manufacture after passing through the regulatory approval and trials as specified by different countries example FDA (United States of America). Some of the drugs currently available on the market are presented in Table 3.

Drug	Trade name	Type of transdermal patch	Manufacturer	Indication
Fentanyl	Duragesic	Reservoir	Alza/Janssen Pharmaceutica	Moderate/ Severe pain
Nitroglycerine	Deponit	Drug in adhesive	Schwarz Pharma	Angina Pectoris
	Minitran	Drug in adhesive	3M Pharmaceuticals	
	Nitrodisc	Micro reservoir	Searle, USA	
	Nitrodur	Matrix	Key Pharmaceuticals	
	TransdermNitro	Reservoir	Alza/Novartis	
	Nitroderm TTS	Face	Novartis	
	Diafusor	Matrix	Schering-Plough	
	Transdermal-NTG	Rim	Warner Chilcott Lab	
	Nitrocine	Rim	Kremer Urban	
	Nitro patch	Rim	Adria Lab	
	NTS patch	Rim	Bolar, Major, Qualitest, Bio-Line, Goldline, Geneva, Rugby WarnerChilcott Lab	
Isosorbide dinitrate	Frandol Tape	Matrix	Toaeiyo, Yamanouchi Pharm.	
Nicotine	Prostep	Reservoir	ElanCorp/Lederie Labs	Smoking Cessation
	Nicotrol	Drug in adhesive	Cygnus Inc./McNeil Consumer Products Ltd.	
	Nicotinell	Matrix	Novartis	
	Nikofrenon	Matrix	Novartis	
	Habitraol	Drug in adhesive	Novartis	
Testosterone	Androderm	Reservoir	Thera Tech/ GlaxoSmithKline	Hypogonadism in males
	Testoderm TTS	Reservoir	Alza	
Clonidine	Catapres-TTS	Membrane matrix hybrid type	Alza/Boehinger Ingelheim	Hypertension
Lidocaine	Lidoderm	Drug in adhesive	Cerner Multum, Inc.	Anesthetic

Drug	Trade name	Type of transdermal patch	Manufacturer	Indication
Scopolamine	Transderm Scop	Membrane matrix hybrid type	Alza/Novartis	Motion sickness
Hyoscine	Trasiderm-Scop	Matrix	Novartis	
	Kimite-patch	Matrix	Myun Moon Pharm. Co.	
Minoxidil 4%	Nanominox		Sinere, Germany	Hair growth promoter
Acyclovir	Supravir cream		Trima, Israel	herpes infection.
Many ingredients	Cellutight EF		Hampden Health, USA	Topical cellulite
Estradiol	Climara	Drug in adhesive	3M Pharmaceuticals/ Berlex Labs	Postmenstrual Syndrome
			Noven Pharma/Novartis	
	Vivelle	Drug in adhesive	Alza/Novartis.	
	Estraderm	Reservoir	Women First Healthcare, Inc	
	Esclim	Drug in adhesive	Johnson & Johnson	
Ethinyl Estradiol	Ortho Evra	Drug in adhesive		

Table 3. Currently available medications for transdermal delivery [155,156].

14. Dermal and transdermal delivery of phytopharmaceuticals

Novel drug delivery system is a novel approach to drug delivery that addresses the limitations of the traditional drug delivery systems. Phytopharmaceuticals are pharmaceuticals using traditional compounds derived from botanicals instead of chemicals. Because these natural ingredients are more easily and more readily metabolized by the body they produce fewer if any side effects and provide increased absorption in the bloodstream resulting in more thorough and effective treatments unlike pharmaceuticals produced from chemical compounds which are prone to adverse side effects [157]. The formulation of dermal and transdermal delivery of phytopharmaceuticals is gaining interest owing to the benefits accruable from it. One of the first few attempts to utilize TDDS containing phytopharmaceuticals was investigation aimed to formulate transdermal films incorporating herbal drug components such as boswellic acid (*Boswellia serrata*) and curcumin (*Curcuma longa*), which utilizes skin as a site for continuous drug administration into the systemic circulation [157]. TDDS avoids first pass metabolism of the drug without the pain associated with injection; moreover the system provides a sustained drug delivery with infrequent dosing via zero-order kinetics and the therapy can easily be terminated at any time. For the local action of the drug at the site of administration of TDDS, turmeric are used which is considered a new version of ayuverdic turmeric *poultic*e or *lepa* [158].

Application of vesicular encapsulation holds great promise in the development and use of phytomedicines considering the difficulties of their formulation into stable dosage forms. Certain physicochemical properties of many herbal extracts make their formulation difficult due to stability and processing challenges. By using appropriate techniques, vesicular products of herbal extracts with enhanced stability and efficacy have been produced. A new drug delivery device known as phytosome, composed of phosphatidylcholine, has been developed to overcome the poor absorption of flavonoids, a challenge due mainly to their large molecular sizes and poor miscibility with the lipid contents of cell membrane linings [159]. Phytosomes are well absorbed when taken orally.

Evaluations of phytosomes indicate that a bond is formed between a flavonoid and a phosphatidylcholine molecule to form a hybrid that is highly lipid-miscible. The development and applications of a variety of novel vesicular herbal formulations such as liposomes, phytosomes, transfersomes and ethosomes have been reported [160,161]. Ethosomes, by virtue of their special characteristics, may circumvent the hindrances to successful delivery of phytomedicines. Both soluble and insoluble phytomedines can be encapsulated in ethosomes. Ethosomes also offer protection from premature degradation and increased biodistribution, which would make for improved bioavailability and more beneficial therapeutic outcome for TDDS.

15. Conclusion

From the myriad published studies involving nanoparticles, it is clear that nanoparticles have the potential to effectively deliver drugs across the skin barrier. Conventional liposomes, flexible liposomes, ethosomes, niosomes and ultradeformable liposomes, etc offer potential value as dermal and transdermal drug delivery systems in addition to other lipid nanoparticles.

Author details

Okoro Uchechi, John D. N. Ogbonna and Anthony A. Attama*

*Address all correspondence to: anthony.attama@unn.edu.ng

Drug Delivery Research Unit, Department of Pharmaceutics, University of Nigeria, Nsukka, Enugu State, Nigeria

References

[1] Hatto P (2011) ISO concensus definitions relevant to nanomaterials and nanotechnologies. 4th Annual Nano Safety for Success Dialogue. ISO TC 229and BSI NTI/1 Nano-

technologies Standardization Committees. 29th and 30th March 2011. Brussels. Available from: http://ec.europa.eu/health/ nanotechnology [Last accessed 15 August 2012].

[2] Devi VK, Saisivam S, Maria GR, Deepti PU (2003) Design and evaluation of matrix diffusion controlled transdermal patches of verapamil hydrochloride. Drug Dev. Ind. Pharm. 29:495-503.

[3] Valenta C, Auner BG (2004) The use of polymers for dermal and transdermal delivery. Eur. J. Pharm. Biopharm. 58: 279–289.

[4] Block HL (2010) Biopharmaceutics and drug delivery systems In: Comprehensive Pharmacy Review. Eds. Leon Shargel, Alan H Mutnick, Paul F Souney, Larry N Swanson, Lippincott Williams and Wilkins, USA. pp. 83-96.

[5] Prausnitz MR, Langer R (2008) Transdermal drug delivery. Nat. Biotech. 26(11):1261–1268.

[6] Escobar-Chávez JJ, Díaz-Torres R, Rodríguez-Cruz IM, Domínguez-Delgado CL, Morales RS, Ángeles-Anguiano E, Melgoza-Contreras LM (2012) Nanocarriers for transdermal drug delivery. Research and Reports in Transdermal Drug Deliv. 1: 3–17.

[7] Geinoz S, Guy RH, Testa B, Carrupt PA (2004) Quantitative structure–permeation relationships (QSPeRs) to predict skin permeation: a critical evaluation. Pharm Res. 21:83–92.

[8] Cevc G, Vier IU (2010) Nanotechnology and the transdermal route. A state of the art review and critical appraisal. J. Control. Rel.141:277–299.

[9] Pinto Reis C, Nuefeld RJ, Ribeiro AJ, *et al*., (2006) Nanoencapsulation 1. Methods for preparation of drug-loaded polymeric nanoparticles. Nanomedicine. 2: 8-21.

[10] Maestrelli F, Capasso G, Gonzalez-Rodriguez ML, *et al*., (2009) Effect of preparation technique on the properties and in vivo efficacy of benzocaine-loaded ethosomes. J Liposome Res 19(4): 253-60.

[11] Attama AA, Schicke BC, Paepenmüller T, Müller-Goymann CC (2007) Solid lipid nanodispersions containing mixed lipid core and a polar heterolipid: Characterization. Eur. J. Pharm. Biopharm. 67: 48-57.

[12] Bernfild M, Gotte M, Park PW, Reizes O, Fitzgerald ML, Lincecum J, Zako M (1999) Functions of cell surface heparan sulphate proteoglycans. Annu. Rev. Biochem. 68: 729-777.

[13] Honary S and Zahir F (2013) Effect of Zeta Potential on the Properties of Nano-Drug Delivery Systems - A Review (Part 1).Trop. J. Pharm Res. 12 (2): 255-264

[14] Win KY, Feng SS (2005) Effects of particle size and surface coating on cellular uptake of polymeric nanoparticles for oral delivery of anticancer drugs. Biomaterials 26: 2713–2722.

[15] Patila S, Sandberg A, Heckert E, Self W, Sea S (2007) Protein adsorption and cellular uptake of cerium oxide nanoparticles as a function of zeta potential. Biomaterials 28: 4600–4607.

[16] Wolinsky JB, Grinstaff MW (2008) Therapeutic and diagnostic applications of dendrimers for cancer treatment. Adv. Drug Deliv. Rev. 60: 1037–1055.

[17] Chang JH, Cho MA, Son HH, Lee CK, Yoon MS, Cho HH, Seo DS, Kim KJ (2006a). Characterization and formation of phospholipid nanoemulsion coatings on Mg-modified sericite surface. J. Ind. Eng. Chem, 12: 635-638.

[18] FDA (1998) Guidance for Industry: topical dermatological drug product NDAs and ANDAs- *in vivo* bioavailability, bioequivalence, *in vitro* release and associated studies (Draft).

[19] Shah, V. P. and H. I. Maibach (eds.), 1993, Topical Drug Bioavailability, Bioequivalence and Penetration, Plenum Press.

[20] Shah VP, Flynn GL, Yacobi A, et al., (1998) "Bioequivalence of topical dermatological dosage forms - Methdods of evaluation of bioequivalence," Pharm. Res. 15: 167-171.

[21] Schaefer, H. and T. E. Redelmeir (eds.), 1996, Skin Barrier, Principles of Percutaneous Absorption, Eds, Karger Publishers.

[22] Pershing LK, Lambert L, Wright ED, et al., (1994) "Topical 0.05% betamethasone dipropionate: Pharmacokinetic and pharmacodynamic dose-response studies in humans," Arch Dermatol, 130:740-747.

[23] Allec A, Chatelus A, Wagner N (1997) "Skin distribution and pharmaceutical aspects of adapalene gel," J. Am. Acad. Dermatol. 36: S119-125.

[24] Hueber F, Schaefer H, Wepierre J (1994) Role of transepidermal and transfollicular routes in percutaneous absorption of steroids: *in vitro* studies on human skin, Skin Pharmacology, 7: 237-244.

[25] Illel B, Schaefer H, Wepierre J, Doucet O (1991) Follicles play an important role in percutaneous absorption, J. Pharm. Sci. 80: 424-427.

[26] Rougier A, Rallis M, Kiren P, Lotte C (1990) "*In vivo* percutaneous absorption: A key role for stratum corneum/vehicle partitioning," Arch Dermatol Res. 282: 498-505.

[27] Kalpana SP, Mikolaj M, Courtney LS, Nicole KB, Priyanka G, Audra LS (2010) Challenges and opportunities in dermal/transdermal delivery. Ther. Deliv. 1(1): 109–131.

[28] Bos JD, Meinardi MMHM (2000) The 500 Dalton rule for the skin penetration of chemical compounds and drugs. Ex. Dermatol. 9(3): 165–169.

[29] Tsutomu I, Tohru M (2010) Techniques for efficient entrapment of pharmaceuticals in biodegradable solid micro/nanoparticle. Expert Opinion Drug Deliv. 7(6): 1-11.

[30] Moghimi SM, Hunter AC, Murray JC (2005) Nanomedicine: current status and figure prospects. FASEB J. 19: 311-330.

[31] Marcato PD and Duran N (2008) New aspects of nanopharmaceutical delivery systems. J Nanosci Nanotechnology. 6: 2216-2229.

[32] Nnamani PO, Kenechukwu FC, Dibua EU, Ogbonna CC, Momoh MA, Ogbonna JDN, Okechukwu DC, Olisemeke AU and Attama AA (2013). Bioactivity of gentamicin contained in novel transdermal drug delivery systems (TDDS) formulated with biodegradable polyesters; Afr. J. Pharm. Pharmacol. 7(28): 1987-1993.

[33] Dnyanesh NT, Vavia PR (2003) Acrylate-based transdermal therapeutic system of nitrendipine. Drug Dev. Ind. Pharm. 29: 71–78.

[34] Chandak AR, Verma PRP (2008) Development and evaluation of HPMC based matrices for transdermal patches of tramadol. Clin. Res. Reg. Affairs. 25: 13–30.

[35] Mundargi RC, Patil SA, Agnihotri SA, Aminabhavi TM (2007) Evalua-tion and controlled release characteristics of modified xanthan films for transdermal delivery of atenolol. Drug Dev. Ind. Pharm. 33:79–90.

[36] Mutalik S, Udupa N (2004) Glibenclamide transdermal patches: Physicochemical, pharmacodynamic and pharmacokinetic evaluations. J. Pharm. Sci. 93: 1577–1594.

[37] Chang HI, Perrie Y, Coombes AGA (2006) Delivery of the antibiotic gentamicin sulphate from precipitation cast matrices of polycaprolactone. J. Control. Rel. 110:414-421.

[38] Ranade VV, Cannon JB (2011) Drug Delivery Systems, Third Edition, Taylor and Francis, Boca Raton.

[39] Touitou E, Dayan N, Bergelson L, et al., (2000). Ethosomes-- novel vesicular carriers for enhanced delivery: characterization and skin penetration properties. J. Control. Rel. 65: 403-18.

[40] Martin A, Bustamante P (1993) Physical Pharmacy: Physical Chemical Principles in the Pharmaceutical Sciences, 4th edn, Lippincott Williams & Wilkins, Philadelphia, PA, pp. 436–439.

[41] Newman A.W (1995) Micromeritics in Physical Characterization of Pharmaceutical Solids, (ed. H.G. Brittain), Marcel Dekker, New York, NY, Ch. 9, 254–264p.

[42] Chikazawa M, Takei T (1997) Specific Surface Area in Powder Technology Handbook (eds K. Gotoh, H. Masuda & K. Higashitani), 2nd edn, Marcel Dekker, Inc., New York, NY, Ch. III. 8, pp. 337–349.

[43] Ishida-Yamamoto A, Simon M, Kishibe M, Miyauchi Y, Takahashi H, Yoshida S, O'Brien TJ, Serre G, Iizuka H (2004) 'Epidermal lamellar granules transport different cargoes as distinct aggregates'. Journal of Investigative Dermatology 122(5): 1137-1144.

[44] Demarchez M, Asselineau D, Regnier M, Czernielewski J (1992) 'Migration of Langerhans Cells into the Epidermis of Human Skin Grafted onto Nude-Mice'. Journal of Investigative Dermatology, 99(5): S54-S55.

[45] Holman BP, Spies F, Bodde HE (1990) 'An Optimized Freeze-Fracture Replication Procedure for Human Skin'. Journal of Investigative Dermatology 94(3):332-335.

[46] Norlen L, Al-Amoudi A, Dubochet J (2003) 'A cryotransmission electron microscopy study of skin barrier formation'. Journal of Investigative Dermatology. 120(4): 555-560.

[47] Stark B, Pabst G, Prassl R (2010) Long-term stability of sterically stabilized liposomes by freezing and freeze-drying: effects of cryoprotectants on structure. Eur. J. Pharm. Sci. 41: 546-555.

[48] Lopez-Pinto JM, Gonzalez-Rodriguez ML, Rabasco AM (2005) Effect of cholesterol and ethanol on dermal delivery from DPPC liposomes. Int. J. Pharm. 298: 1-12.

[49] Nakhla T, Marek M, Kovalcik T (2000) Issues associated with large-scale production of liposomal formulations. Drug Deliv. Technol. 2:1-6.

[50] Maestrelli F, Gonza´lez-Rodrı´guez ML, Rabasco AM, *et al*., (2006). Effect of preparation technique on the properties of liposomes encapsulating ketoprofen-cyclodextrin complexes aimed for transdermal delivery. Int. J. Pharm. 312:53-60.

[51] Attama AA, Müller-Goymann CC (2008) Effect of beeswax modification on the lipid matrix and solid lipid nanoparticle crystallinity. Colloids and Surfaces A: Physicochemical and Engineering Aspects. 315: 189-195.

[52] Celia C, Trapasso E, Cosco D, et al (2009) Turbiscan Lab® Expert analysis of the stability of ethosomes and ultradeformable liposomes containing a bilayer fluidizing agent. Colloids Surf B Biointerfaces 72: 155-60.

[53] Watson DG (1999) Pharmaceutical Analysis. A textbook for Pharmaceutical students and Pharmaceutical Chemists. 1st Ed. Churchil Livingstone, UK.

[54] Coderch L, de Pera M, Perez-Cullell N, Estelrich J, de la Maza A, Parra JL (1999) 'The effect of liposomes on skin barrier structure'. Skin Pharmacol. Applied Skin Physiol., 12(5): 235-246.

[55] Curdy C, Naik A, Kalia YN, Alberti I, Guy RH (2004) 'Non-invasive assessment of the effect of formulation excipients on stratum corneum barrier function in vivo'. Int. J. Pharm. 271(1-2): 251-256.

[56] Honeywell-Nguyen PL, Gooris GS, Bouwstra JA (2004) 'Quantitative assessment of the transport of elastic and rigid vesicle components and a model drug from these vesicle formulations into human skin in vivo'. J. Investig. Dermatol. 123(5): 902-910.

[57] Jadoul A, Doucet J, Durand D, Preat V (1996) 'Modifications induced on stratum corneum structure after *in vitro* iontophoresis: ATR-FTIR and X-ray scattering studies'. J. Control. Rel. 42(2):165-173.

[58] Attama AA, Müller-Goymann CC (2006) A critical study of novel physically structured lipid matrices composed of a homolipid from *Capra hircus* and theobroma oil. Int. J. Pharm. 322, 67-78.

[59] Brinkmann I, Müller-Goymann CC (2005) An attempt to clarify the influence of glycerol, propylene glycol, isopropyl myristate and a combination of propylene glycol and isopropyl myristate on human stratum corneum. Pharmazie. 60: 215-220.

[60] Oilman MR (1982). Skin and Eye Testing in Animals. Principles and Methods of Toxicology; Hayes, A.W., Ed.; Raven Press: New York. 209–222p.

[61] Garg A, Aggarwal D, Garg S, Singla AK (2002). Spreading of Semisolid Formulations An Update. Pharmaceutical Technology, Sept.

[62] Idson B, Lazarus J.J (1987) Semisolids. In The Theory and Practice of Industrial Pharmacy, L. Lachman, H.A. Lieberman, and J.L. Kanigs, Eds. Lea and Febiger, Philadelphia, PA, 2d ed. pp. 215–244.

[63] Duggin G (1996) Softening skin with emollient ingredients. Manufacturing Chemist 67 (6): 27–31.

[64] Barry BW, Grace AJ (1972) Sensory testing of spreadability: Investigation of rheological conditions operative during application of topical preparations," J. Pharm. Sci. 61(3): 335–341.

[65] Rance RW (1973) Studies of the factors controlling the action of hair sprays. Part I: The spreading of hair spray resin solutions on hair. J. Soc. Cosm. Chem. 24 (7): 501–522.

[66] Islam MT, Rodríguez-Hornedo N, Ciotti S, Ackermann C (2004) Rheological characterization of topical Carbomer gels neutralized to different pH. Pharm. Res. 21(7): 1192-1199.

[67] Lawrence MJ, Rees GD (2000) Microemulsion-based media as novel drug delivery systems. Adv Drug Deliv Rev. 45: 89-121.

[68] Kreilgaard M (2002) Influence of microemulsions on cutaneous drug delivery. Adv Drug Deliv Rev. 54: S77-S98.

[69] He W, Tan Y, Tian Z, *et al.,* (2011). Food protein-stabilized nanoemulsions as potential delivery systems for poorly water-soluble drugs: preparation, *in vitro* characterization and pharmacokinetics in rats. Int J Nanomedicine. 6: 521-533.

[70] Heuschkel S, Goebel A, Neubert RHH (2008) Microemulsions —modern colloidal carrier for dermal and transdermal drug delivery. J Pharm Sci. 97: 603-631.

[71] Zhao X, Liu J, Zhang X, *et al*., (2006) Enhancement of transdermal delivery of theophylline using microemulsion vehicle. Int. J. Pharm. 327: 58-64.

[72] Neubert RHH (2011) Potentials of new nanocarriers for dermal and transdermal drug delivery. Eur J Pharm Biopharm. 77: 1-2.

[73] Grampurohit N, Ravikumar P, Mallya R (2011) Microemulsions for topical use–a review. Ind J Pharm Edu Res. 45: 100-107.

[74] Valenta C, Schultz K (2004) Influence of carrageenan on the rheology and skin permeation of microemulsion formulations. J. Control. Rel. 95: 257-265.

[75] Sonneville-Aubrun O., Simonnet J.T., L'Alloret F (2004) Nanoemulsions: a new vehicle for skincare products. Adv Colloid Interface Sci. 108–109:145–149.

[76] Seiden MV, Muggia F, Astrow A, *et al* (2004) A phase II study of liposomal lurtotecan (OSI-211) in patients with topotecan resistant ovarian cancer. Gynecol Oncol. 93: 229–232.

[77] Kuo F, Subramanian B, Kotyla T, Wilson TA, Yoganathan S, Nicolosi RJ (2008) Nanoemulsions of an anti-oxidant synergy formulation containing gamma tocopherol have enhanced bioavailability and anti-inflammatory properties. Int. J. Pharm. 363:206–213.

[78] Wu H, Ramachandran C, Bielinska AU, et al (2001) Topical transfection using plasmid DNA in a water-in-oil nanoemulsion. Int. J. Pharm. 221:23–34.

[79] Subramanian B, Kuo F, Ada E, et al (2008) Enhancement of anti-inflammatory property of aspirin in mice by a nano-emulsion preparation. Int. Immunopharmacol. 2008;8:1533–1539.

[80] Mou D, Chen H, Du D, et al (2008) Hydrogel-thickened nanoemulsion system for topical delivery of lipophilic drugs. Int. J. Pharm. 353: 270–276.

[81] Wu H, Ramachandran C, Weiner ND, Roessler BJ (2001) Topical transport of hydrophilic compounds using water-in-oil nanoemulsions. Int. J. Pharm. 220: 63–75.

[82] Alves MP, Scarrone AL, Santos M, Pohlmann AR, Guterres SS (2007) Human skin penetration and distribution of nimesulide from hydrophilic gels containing nanocarriers. Int. J. Pharm. 341: 215–220.

[83] Kumar VS, Asha K (2011) Herbosome a Novel carrier for herbal drug delivery. Int. J Current Pharm. Res. 3(3): 36-41.

[84] Jung S, Otberg N, Thiede G, Richter H, Sterry W, Panzner S, Lademann J (2006) Innovative liposomes as a transfollicular drug delivery system: penetration into porcine hair follicles. J. Invest. Dermatol. 126: 1728–1732.

[85] Honeywell-Nguyen PL, Wouter Groenink HW, de Graaff AM, Bouwstra JA (2003) The in vivo transport of elastic vesicles into human skin: effects of occlusion, volume and duration of application. J Control. Rel. 90: 243–255.

[86] Honeywell-Nguyen PL, de Graaff AM, Groenink HW, Bouwstra JA (2002) The in vivo and *in vitro* interactions of elastic and rigid vesicles with human skin. Biochim. Biophys. Acta. 1573: 130–140.

[87] Verma DD, Verma S, Blume G, Fahr A (2003) Liposomes increase skin penetration of entrapped and non-entrapped hydrophilic substances into human skin: a skin penetration and confocal laser scanning microscopy study. Eur. J. Pharm. Biopharm. 55: 271–277.

[88] Cui Z, Han S, Padinjarae D, Huang L (2005) Immunostimulation mechanism of LPD nanoparticles as a vaccine carrier. Mol. Pharm. 2: 22–28.

[89] Herffernan M, Murthy N (2005) Polyketal nanoparticles: a new pH-sensitive biodegradable drug delivery vehicle. Bioconjug. Chem. 16: 1340–1342.

[90] Dubey V, Mishra D, Dutta T, Nahar M, Saraf DK, Jain NK (2007) Dermal and transdermal delivery of an anti-psoriatic agent via ethanolic liposomes. J. Control. Rel. 123: 148–154.

[91] Manosroi A, Kongkaneramit L, Manosroi J (2004) Stability and transdermal absorption of topical amphotericin B liposome formulations. Int. J. Pharm. 270: 279–286.

[92] Maestrelli F, González-Rodríguez ML, Rabasco AM, Mura P (2005) Preparation and characterisation of liposomes encapsulating ketoprofen–cyclodextrin complexes for transdermal drug delivery. Int. J. Pharm. 298: 55–67.

[93] Essa EA, Bonner MC, Barry BW (2004) Electrically assisted skin delivery of liposomal estradiol; phospholipid as damage retardant. J. Control. Rel. 95: 535–546.

[94] Sharma BB, Jain SK, Vyas SP (1994) Topical liposome system bearing local anaesthetic lignocaine: preparation and evaluation. J. Microencapsul. 11: 279–286.

[95] Uchegbu IF, Florence AT (1995) Non-ionic surfactant vesicles (niosomes): physical and pharmaceutical chemistry. Adv. Colloid Interface Sci. 58: 1-55.

[96] Vora B, Khopade AJ, Jain NK (1998) Proniosome based transdermal delivery of levonorgestrel for effective contraception. J. Control. Rel. 54: 149-165.

[97] Alsarra IA, Bosela AA, Ahmed SM, Mahrous GM (2005) Proniosomes as a drug carrier for transdermal delivery of ketorolac. Eur. J. Pharm. Biopharm. 59: 485–490.

[98] Muzzalupo R, Tavano L, Cassano R, Trombino S, Ferrarelli T, Picci N (2011) A new approach for the evaluation of niosomes as effective transdermal drug delivery systems. Eur. J. Pharm. Biopharm. 79: 28–35.

[99] Manconi M, Caddeo C, Sinico C, et al (2011) Ex vivo skin delivery of diclofenac by transcutol containing liposomes and suggested mechanism of vesicle–skin interaction. Eur. J. Pharm. Biopharm. 78: 27–35.

[100] Mura S, Manconi M, Sinico C, Valenti D, Fadda AM (2009) Penetration enhancer containing vesicles (PEVs) as carriers for cutaneous delivery of minoxidil. Int. J. Pharm. 380: 72–79.

[101] Guinedi AS, Mortada ND, Mansour S, Hathout RM (2005). Preparation and evaluation of reverse-phase evaporation and multilamellar niosomes as ophthalmic carriers of acetazolamide. Int. J. Pharm. 306: 71–82.

[102] Balakrishnana P, Shanmugama S, Lee WS, et al (2009) Formulation and in vitro assessment of minoxidil niosomes for enhanced skin delivery. Int. J. Pharm. 377: 1–8.

[103] Junyaprasert VB, Singhsa P, Suksiriworapong J, Chantasart D (2012) Physicochemical properties and skin permeation of Span 60/Tween 60 niosomes of ellagic acid. Int. J. Pharm. 423: 303–311.

[104] Jain S, Jain P, Umamaheshwari RB, Jain NK (2003) Transfersomes—A Novel Vesicular Carrier for Enhanced Transdermal Delivery: Development, Characterization, and Performance Evaluation. Drug Dev. Ind. Pharm. 29 (9): 1013-1026.

[105] Planas ME, Gonzalez P, Rodriguez S, Sanchez G, Cevc G (1992) Non-invasive percutaneous induction of topical analgesia by a new type of drug carrier and prolongation of the local pain intensity by liposomes. Anesth. Analge. 95: 615–621.

[106] Cevc G, Schatzlein A, Blume G (1995) Transdermal drug carrier basic properties, optimization and transfer efficiency in the case of epicutaneously applied peptides. J. Control. Rel. 36: 3–16.

[107] Paul A, Cevc G, Bachhawat BK (1998). Transdermal immunization with an integral membrane component gap junction protein, by means of ultradeformable drug carriers, transfersomes. Vaccine 16: 188–195.

[108] Mbah CC, Builders PF, Attama AA (2014). Nanovesicular carriers as alternative drug delivery systems: ethosomes in focus Expert Opin. Drug Deliv. 11(1):1-15.

[109] Touitou E (1996). Composition of applying active substances to or through the skin. US5716638.

[110] Jain S, Tiwary AK, Sapra B, Jain NK (2007). Formulaion and evaluation of thosomes for transdermal delivery of lamivudine. AAPS PharmSciTech. 8(4): Article 111.

[111] Coderch L., Fonollosa J., De Pera M., et al (2000) Influence of cholesterol on liposome fluidity by EPR: relationship with percutaneous absorption. J Control. Rel. 68: 85-95.

[112] Serikawa T, Kikuchi A, Sugaya S, *et al*., (2006) *In vitro* and *in vivo* evaluation of novel cationic liposomes utilized for cancer gene therapy. J. Control. Rel. 113(3): 255-260.

[113] Barry BW (2004) Breaching the skin' barrier to drugs. Nat. Biotechnol. 22: 165-167.

[114] Honeywell-Nguyen PL, Bouwstra JA (2005) Vesicles as a tool for transdermal and dermal delivery. Drug Discov. Today. 2: 67-74.

[115] Elsayed MMA, Abdallah OY, Naggar VF, *et al.,* (2007a). Lipid vesicles for skin delivery of drugs: reviewing three decades of research. Int. J. Pharm. 332: 1-16.

[116] Ainbinder D, Touitou E (2005) Testosterone ethosomes for enhanced transdermal delivery. Drug Deliv. 12: 297-303.

[117] Paolino D, Lucania G, Mardente D, *et al*., (2005) Ethosomes for skin delivery of ammonium glycyrrhizinate: in vitro percutaneous permeation through human skin and in vivo anti-inflammatory activity on human volunteers. J. Control. Rel. 106: 99-110.

[118] Dayan N, Touitou E (2000) Carriers for skin delivery of trihexyphenidyl HCl: ethosomes vs. liposomes. Biomaterials. 21: 1879-85.

[119] Elsayed MM, Abdallah OY, Naggar VF, *et al.,* (2007b) Deformable liposomes and ethosomes as carriers for skin delivery of ketotifen. Pharmazie 62: 133-137

[120] Li G, Fan Y, Fan C, et al. (2012) Tacrolimus-loaded ethosomes: physicochemical characterization and in vivo evaluation. Eur. J. Pharm. Biopharm. In press 2012.

[121] Chourasia MK, Kang L, Chan SY (2011) Nanosized ethosomes bearing ketoprofen for improved transdermal delivery. Results Pharm Sci. 1: 60–67.

[122] Fang YP, Huang YB, Wua PC, Tsai YH (2009) Topical delivery of 5-aminolevulinic acid-encapsulated ethosomes in a hyperproliferative skin animal model using the CLSM technique to evaluate the penetration behavior. Eur J Pharm Biopharm. 73: 391–398.

[123] Paolino D, Lucania G, Mardente D, Alhaique F, Fresta M (2005) Ethosomes for skin delivery of ammonium glycyrrhizinate: in vitro percutaneous permeation through human skin and in vivo anti-inflammatory activity on human volunteers. J Control. Rel. 106: 99–110.

[124] Touitou E, Dayan N, Bergelson L, Godina B, Eliaz M (2000) Ethosomes – novel vesicular carriers for enhanced delivery: characterization and skin penetration properties. J Control. Rel. 65: 403–418.

[125] Maheshwari RGS, Tekade RK, Sharma PA, et al (2012) Ethosomes and ultradeformable liposomes for transdermal delivery of clotrimazole: a comparative assessment. Saudi Pharm J. 20: 161–170.

[126] Dayan N, Touitou E (2000) Carriers for skin delivery of trihexyphenidyl HCl: ethosomes vs liposomes. Biomaterials. 21: 1879–1885.

[127] Parekh HS (2007) The advance of dendrimers– a versatile targeting platform for gene/drug delivery. Curr. Pharm Des. 13, 2837–2850.

[128] Esfand R, Tomalia DA (2001) Poly(amidoamine) (PAMAM) dendrimer: from biomimicry to drug delivery and biomedical applications. Drug Discov. Today 6:427–436.

[129] D'Emanuele A, Attwood D (2005) Dendrimer-drug interactions. Adv. Drug Deliv. Rev. 57: 2147–2162.

[130] Wang Z, Itoh Z, Hosaka Y, et al (2003) Novel transdermal drug delivery system with polyhydroxyalkanoate and starburst polyamidoamine dendrimer. J Biosci Bioeng. 95: 541–543.

[131] Chauhan AS, Sridevi S, Chalasani KB, et al (2003) Dendrimer-mediated transdermal delivery: enhanced bioavailability of indomethacin. J. Control. Rel. 90: 335–343.

[132] Yiyun C, Na M, Tongwen X, et al (2007). Transdermal delivery of nonsteroidal anti-inflammatory drugs mediated by polyamidoamine (PAMAM) dendrimer. J. Pharm. Sci. 96: 595–602.

[133] Venuganti VVK, Perumal OP (2008) Effect of poly(amidoamine) (PAMAM) dendrimer on skin permeation of 5-fluorouracil. Int. J. Pharm. 361: 230–238.

[134] Niederhafner P, Šebestík J, Ježek J (2005) Peptide dendrimers. J. Peptide Sci. 11: 757–788.

[135] Mehnert W, Mäder K (2001) Solid lipid nanoparticles. Production, characterization and applications. Adv Drug Del Rev. 47: 165–96.

[136] Müller RH, Keck CM (2004) Challenges and solutions for the delivery of biotech drugs – a review of drug nanocrystal technology and lipid nanoparticles. J Biotech. 113: 151–70.

[137] Castelli F, Puglia C, Sarpietro MG, et al (2005) Characterization of indomethacin-loaded lipid nanoparticles by differential scanning calorimetry. Int. J. Pharm. 304: 231–238.

[138] Siekmann B, Westesen K (1992) Submicron-sized parenteral carrier systems based on solid lipids. Pharm. Pharmacol. Lett. 1: 123–126.

[139] Manjunath K, Venkateswarlu V (2005) Pharmacokinetics, tissue distribution and bioavailability of clozapine solid lipid nanoparticles after intravenous and intraduodenal administration. J. Control. Rel. 107: 215–28.

[140] Müller RH, Souto EB, Radtke M (2000) PCT application PCT/EP00/04111.

[141] Attama AA, Momoh MA and Builders PF. Lipid Nanoparticulate Drug Delivery Systems: A Revolution in Dosage Form Design and Development. InTech. 2012:1-34. http://www.intechopen.com/subjects/pharmacology-toxicology-and-pharmaceutical-science.

[142] Wissing SA, Müller RH (2002) The influence of the crystallinity of lipid nanoparticles on their occlusive properties. Int. J. Pharm. 242(1-2): 377-379.

[143] Jenning V, Thünemann AF, Gohla SH (2000) Characterisation of a Novel Solid Lipid Nanoparticle Carrier System Based on Binary Mixtures of Liquid and Solid Lipids. Int. J. Pharm. 199(2): 167–177.

[144] Villalobos-Hernandez JR, Müller-Goymann CC (2006) Sun protection enhancement of titanium dioxide crystals by the use of carnauba wax nanoparticles: The synergistic interaction between organic and inorganic sunscreens at nanoscale. Int. J. Pharm. 322(1-2): 161-170.

[145] Guterres SS, Alves MP and Adriana R (2007) Pohlmann.Polymeric nanoparticles, nanospheres and nanocapsules, for cutaneous application. Drug Target Insights. 2: 147–157.

[146] Xu ZP (2006) Inorganic nanoparticles as carriers for efficient cellular delivery. Chem. Eng. Sci. 61: 1027–40.

[147] Scheindlin S (2004) Transdermal drug delivery: past, present, future. Mol. Interv. 4(6): 308–312.

[148] Micromedex 1.0 (Healthcare Series) Thomson Reuters. [Accessed 27 December, 2013]. www.thomsonhc.com/home.

[149] Yarosh DB (1992) Liposome-encapsulated enzymes for DNA repair. In: Braun-Falco O, Korting HC, Maibach H, editors. Liposome dermatics. Springer-Verlag; Heidelberg. pp. 258-69.

[150] Barry BW (2001) Novel mechanisms and devices to enable successful transdermal drug delivery. Eur. J. Pharm. Sci. 14(2):101-14

[151] Al-Obaidi H, Nasseri B, Florence AT (2010) Dynamics of lipid microparticles inside lipid vesicles: movement in confined spaces. J. Drug Target. 18(10): 821-830.

[152] Chiranjib C, Souman P, George PDC, Zhi-Hong W, Chan-Shing L (2013) Nanoparticle as smart pharmaceutical delivery. Frontiers in Bioscience (Landmark Ed) 18: 1030-1050.

[153] International Conference on Harmonisation Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals. Federal Register 1997; 62 (227): 62922–62925.

[154] Makena H and Uday B. Kompella (2006) Nanotechnology and Nanoparticles: Clinical, Ethical, and Regulatory Issues. In Nanoparticle nanotechnology for drug delivery. vol. 159. Ed by Ram B Gupta AND Uday Kompella. pp. 381-393.

[155] Florence AT, Attwood D (2009) Physicochemical principles of Pharmacy. 4th Ed. Pharmaceutical Press, UK. 329-390p.

[156] Wertz PW, Miethke MC, Long SA, Strauss JS, Downing DT (1985) The composition of ceramides from human stratum corneum and from comedones.Journal of Investigative Dermatology 84: 410–12.

[157] Devi VK, Nimisha J, Valli SK (2010) The importance of novel drug delivery systems in herbal medicines. Pharmacognosy Review. 4(7): 27-31.

[158] Verma M, Gupta PK, Varsha BP, Purohit AP (2007) Development of transdermal drug dosage formulation for the anti-rheumatic ayurvedic medicinal plants. Ancient Sci. Life. 11: 66-69.

[159] Kidd PM (2011) Phytosome: A technical revolution in phytomedicine. Available from: www.indena.com [Last accessed 10 September 2011].

[160] Ajazuddin SS (2010) Applications of novel drug delivery system for herbal formulations. Fitoterapia. 81: 680-9.

[161] Goyal A, Kumar S, Nagpal M, *et al*., (2011) Potential of novel drug delivery systems for herbal drugs. Ind. J. Pharm. Edu. Res. 45(3): 225-235.

IntechOpen