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REVIEW ARTICLE

Physical Permeation Enhancers for Transdermal Drug Delivery: A Brief Review

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ABSTRACT

The transdermal route has been recognized as one of the highly potential routes of systemic drug delivery and provides the advantage of avoidance of the first-pass effect, ease of use and withdrawal (in case of side effects) and better patient compliance. However, the major limitation of this route is the difficulty of permeation of drug through the skin. The permeation of drug through skin can be enhanced by both chemical penetration enhancement and physical methods. In this review, we have discussed the physical penetration enhancement technology for transdermal drug delivery as well as the probable mechanisms of action.

Keywords: Percutaneous absorption, Permeation enhancer, Skin, Stratum corneum, Transdermal.

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INTRODUCTION

At present, the most common form of delivery of drugs is the oral route. While this has the notable advantage of easy administration, it also has significant drawbacks; namely poor bioavailability due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high and/or frequent dosing, which can be both cost prohibitive and inconvenient [1].

To get rid of these difficulties there is a need for the development of new drug delivery system; which will improve the therapeutic efficacy and safety of drugs by more precise (i.e. site specific) placement within the body thereby reducing both the size and number of doses. Trans-mucosal (mucosal), trans-alveolar (through the lung tissue), implantable (subcutaneous and deeper implants), injectable (intramuscular or subcutaneous) and transdermal (through intact skin), are such modes of delivery which have been explored extensively over the last 25 years, with varying degrees of commercial and therapeutic success [2].

One of the driving forces for the growth of TDDS is the increasing number of drugs that can be delivered to the systemic circulation, in clinically effective concentration via the skin portal. The delivery of drugs using skin as the port of entry is known as transdermal administration and the drug delivery systems are known as transdermal patches [1].“TDDS are defined as self contained, discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at a controlled rate to the systemic circulation.”The success of this approach is evidenced by the fact that there are currently more than 35 TDD products approved for the treatment of wide variety of conditions including hypertension, angina, motion sickness, female menopause, male hypogonadism, severe pain, local pain control, nicotine dependence, and recently, contraception and urinary incontinence [3].

Transdermal drug delivery is the administration of a therapeutic agent through intact skin for systemic effect. Transdermal drug delivery offers the following advantages over the oral route for controlled drug delivery [4].

- Avoidance of hepatic first pass metabolism.
- Ability to discontinue administration by removal of the system.
- The ability to control drug delivery for a longer time than the usual gastrointestinal transit of oral dosage form.
- The ability to modify the properties of the biological barrier to absorption.

The success of a dermatological drug to be used for systemic drug delivery depends on the ability of the drug to penetrate through skin in sufficient quantities to achieve the desired therapeutic effect [4].

The method employed for modifying the barrier properties of the stratum corneum to enhance drug penetration and absorption through skin may be classified into the following categories [5].

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1. Chemical enhancement (includes use of chemicals that alters barrier function of the skin)
2. Physical enhancement (includes use of physical means like electric current or ultrasound energy to enhance transdermal drug absorption)
3. Bioconvertable prodrugs (use of bioconvertable prodrug forms which after bioconversion gives active drug)

A brief review of skin structure

The skin can be considered to have four distinct layers of tissue [4], as shown in Fig 1.

1. Non-viable epidermis (stratum corneum)
2. Viable epidermis
3. Viable dermis
4. Subcutaneous connective tissue (hypodermis)

1) Non-viable epidermis (stratum corneum)

Stratum corneum is the outer most layer of skin, which is the actual physical barrier to most substance that come in contact with the skin. The stratum corneum is 10 to 20 cell layer thick over most of the body. Each cell is a flat, plate-like structure - 34-44 µm long, 25-36 µm wide, 0.5 to 0.20 µm thick - with a surface area of 750 to 1200 µm2 stocked up to each other in brick like fashion. Stratum corneum consist of lipid (5-15%) including phospholipids, glycosphingolipid, cholesterol sulfate and neutral lipid, protein (75-85%) which is mainly keratin.

2) Viable epidermis

This layer of the skin resides between the stratum corneum and the dermis and has a thickness ranging from 50- 100 µm. The structure of the cells in the viable epidermis are physiochemically similar to other living tissues. Cells are held together by tonofibrils. The density of this region is not much different than water. The water content is about 90%. Dermis Just beneath the viable epidermis is the dermis. It is a structural fibrin and very few cells are like it can be found histologically in normal tissue. Dermis thickness range from2000 to 3000 µm and consists of a matrix of loose connective tissue composed of fibrous protein embedded in an amphorphose ground substance. Subcutaneous connective tissue. The subcutaneous tissue or hypodermis is not actually considered a true part of the structured connective tissue is composed of loose textured, white, fibrous connective tissue containing blood and lymph vessels, secretory pores of the sweat gland and cutaneous nerves. Most investigators consider drug permeating through the skin enter the circulatory system before reaching the hypodermis, although the fatty tissue could serve as a depot of the drug. Pathway of transdermal permeation.

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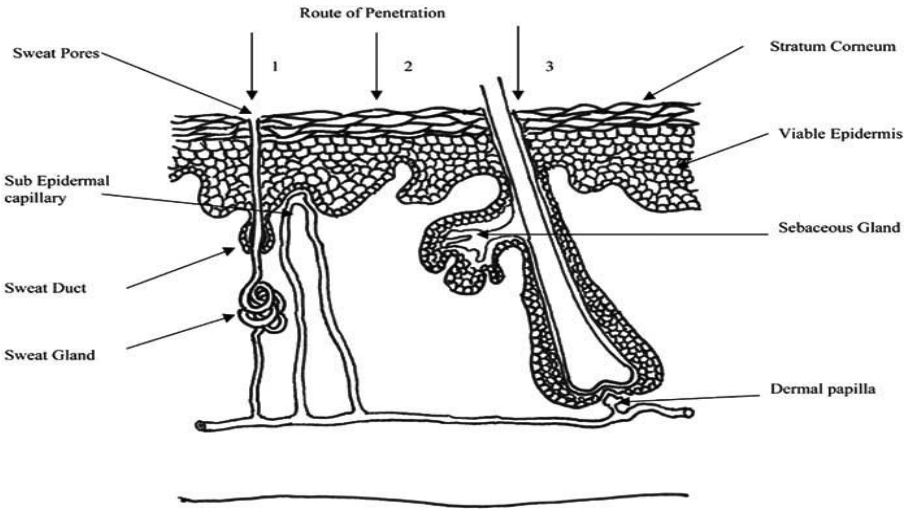

Fig 1. Structure of Human Skin

Permeation can occur by diffusion via [6]:

1. Transdermal permeation, through the stratum corneum.
2. Intercellular permeation, through the stratum corneum.
3. Transappendaged permeation, via the hair follicle, sebaceous and sweat glands.

Most molecules penetrate through skin via intercellular micro-route and therefore many enhancing techniques aim to disrupt or bypass its elegant molecular architecture.

Ideal characteristics of chemical penetration enhancers

Ideally, penetration enhancers reversibly reduce the barrier resistance of the stratum corneum without damaging viable cells [7, 8]. Some of the more desirable properties for penetration enhancers acting within the skin have been given as [9]:

- They should be non-toxic, non-irritating and non-allergenic
- They would ideally work rapidly; the activity and duration of effect should be both predictable and reproducible.
- They should have no pharmacological activity within the body.
- The penetration enhancers should work uni-directionally, i.e., they should allow therapeutic agents into the body whilst preventing the loss of endogenous materials from the body.
- When removed from the skin, barrier properties should return both rapidly and fully to normal.
- They should be cosmetically acceptable with an appropriate skin feel.
  Not surprisingly, no such material that possesses the above ideal properties has yet been discovered although some chemicals demonstrate several of the above attributes.

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PERMEATION ENHANCERS:

Electroporation

The use of electropermeabilization as a method of enhancing diffusion across biological barriers dates back as far as 100 years [10]. Electroporation involves the application of high-voltage pulses to induce skin perturbation. High voltages (≥100 V) and short treatment durations (milliseconds) are most frequently employed. Other electrical parameters that affect delivery include pulse properties such as waveform, rate, and number [11]. The increase in skin permeability is suggested to be caused by the generation of transient pores during electroporation [12]. The technology has been successfully used to enhance the skin permeability of molecules with differing lipophilicity and size (i.e., small molecules, proteins, peptides, and oligonucleotides), including biopharmaceuticals with a molecular weight greater that 7 kDa, the current limit for iontophoresis [13].

Iontophoresis

This method involves enhancing the permeation of a topically applied therapeutic agent by the application of a low-level electric current, either directly to the skin or indirectly via the dosage form [14]. Increase in drug permeation as a result of this methodology can be attributed to either one or a combination of electrorepulsion (for charged solutes), electro-osmosis (for uncharged solutes), and electroperturbation (for both charged and uncharged) mechanisms. Parameters that affect design of an iontophoretic skin delivery system include electrode type, current intensity, pH of the system, competitive ion effect, and permeant type [10]. The launch of commercialised systems of this technology either has occurred or is currently under investigation by various companies. Extensive literature exists on the various types of drugs investigated using iontophoretic delivery. The Phoresor™ device (Iomed Inc., Salt Lake City, UT) was the first iontophoretic system to be approved by the Food and Drug Administration in the late 1970s as a physical medicine therapeutic device. In order to enhance patient compliance, the use of patient-friendly, portable, and efficient iontophoretic systems have been under intense development over the years. Such improved systems include the Vyteris and E-Trans iontophoretic devices. Previous work has also reported that the combined use of iontophoresis and electroporation is much more effective than either technique used alone in the delivery of molecules across the skin [15]. The limitations of iontophoretic systems include the regulatory limits on the amount of current that can be used in humans (currently set at 0.5 mA/cm^2) and the irreversible damage such currents could do to the barrier properties of the skin. In addition, iontophoresis has failed to significantly improve the transdermal delivery of macromolecules of greater than 7,000 Da [16] as shown in Fig 2.

Ultrasound

Ultrasound involves the use of ultrasonic energy to enhance the transdermal delivery of solutes either simultaneously or through pretreatment, and is frequently referred to as sonophoresis. The proposed mechanism behind the increase in skin permeability is attributed

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to the formation of gaseous cavities within the intercellular lipids on exposure to ultrasound, resulting in disruption of the stratum corneum [17]. Ultrasound parameters such as treatment duration, intensity, and frequency are all known to affect percutaneous absorption, with the latter being the most importan [18]. Although frequencies between 20 kHz to 16 MHz have been reported to enhance skin permeation, frequencies at the lower end of this range (<100 kHz) are believed to have a more significant effect on transdermal drug delivery, with the delivery of macromolecules of molecular weight up to 48 kDa being reported [17] as shown in Fig 3.

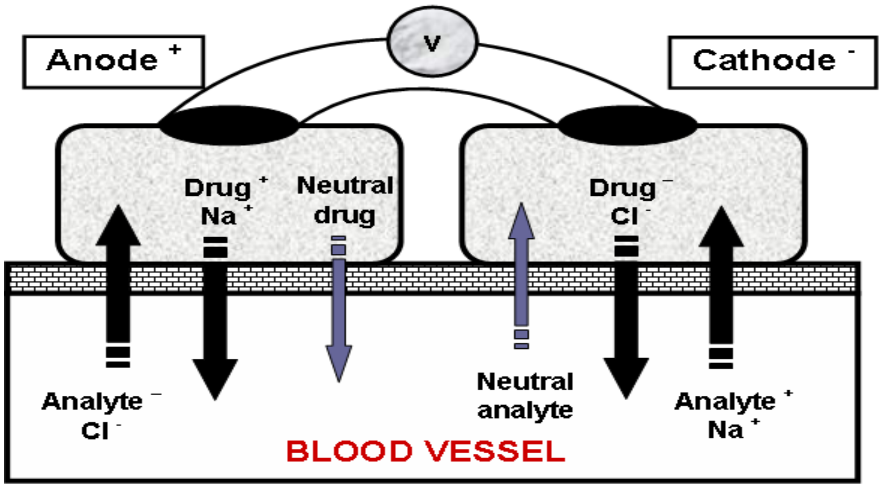

Fig 2. Electrochemistry of Iontophoretic Circuit Electro Repulsion.

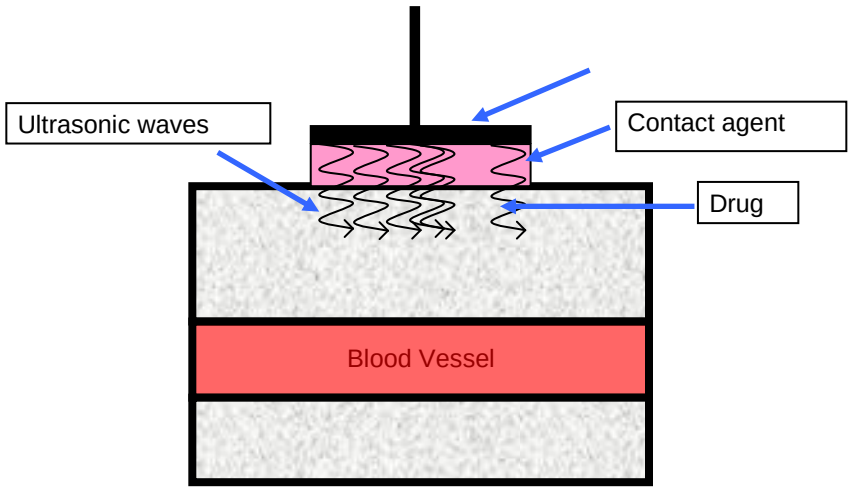

Fig 3. Sonophoretic Delivery

Laser Radiation and Photomechanical Waves

Lasers have been used in clinical therapies for decades, and therefore their effects on biological membranes are well documented. Lasers are frequently used for the treatment of dermatological conditions such as acne and to confer facial rejuvenation, where the laser

radiation destroys the target cells over a short frame of time (~300 ns). Such direct and controlled exposure of the skin to laser radiation results in ablation of the stratum corneum without significant damage to the underlying epidermis. Removal of the stratum corneum by this method has been shown to enhance the delivery of lipophilic and hydrophilic drugs [19]. The extent of barrier disruption by laser radiation is known to be controlled by parameters such wavelength, pulse length, pulse energy, pulse number, and pulse repetition rate. Pressure waves which can be generated by intense laser radiation, without incurring direct ablative effects on the skin, have also been recently found to increase the permeability of the skin [21]. It is thought that pressure waves form a continuous or hydrophilic pathway across the skin due to expansion of the lacunae domains in the stratum corneum. Important parameters affecting delivery such as peak pressure, rise time, and duration have been demonstrated [23]. The use of pressure waves may also serve as a means of avoiding problems associated with direct laser radiation. Permeants that have been successfully delivered *in vivo* include insulin [24], 40 kDa dextran, and 20 nm latex particle [21].

Magnetophoresis

This method involves the application of a magnetic field which acts as an external driving force to enhance the diffusion of a diamagnetic solute across the skin. Skin exposure to a magnetic field might also induce structural alterations that could contribute to an increase in permeability. *In vitro* studies showed a magnetically induced enhancement in benzoic acid flux, which was observed to increase with the strength of the applied magnetic field [25]. Other *in vitro* studies using a magnet attached to transdermal patches containing terbutaline sulphate demonstrated an enhancement in permeant flux which was comparable with that attained when 4% isopropyl myristate was used as a chemical enhancer [26].

Thermophoresis

The skin surface temperature is usually maintained at 32°C in humans by a range of homeostatic controls. The effect of elevated temperature (nonphysiological) on percutaneous absorption was initially reported [27]. Recently, there has been a surge in the interest of using thermoregulation as a means of improving the delivery profile of topical medicaments. Previous *in vitro* studies [28] have demonstrated a 2- to 3-fold increase in flux for every 7 to 8°C rise in skin surface temperature. The increased permeation following heat treatment has been attributed to an increase in drug diffusivity in the vehicle and in the skin because of increased lipid fluidity. [29] Vasodilation of the subcutaneous blood vessels as a homeostatic response to a rise in skin temperature also plays an important role in enhancing the transdermal delivery of topically applied compounds. The *in vivo* delivery of nitroglycerin [30], testosterone, lidocaine, tetracaine, [31] and fentanyl [32] from transdermal patches with attached heating devices was shown to increase as a result of the elevated temperature at the site of delivery. However, the effect of temperature on the delivery of penetrants greater than 500 Da has not been reported.

Microneedle- Devices

One of the first patents ever filed for a drug delivery device for the percutaneous administration of drugs was based on this method [33]. The device as described in the patent consists of a drug reservoir and a plurality of projections extending from the reservoir. These microneedles of length 50 to 110 mm will penetrate the stratum corneum and epidermis to deliver the drug from the reservoir. The reservoir may contain drug, solution of drug, gel, or solid particulates, and the various embodiments of the invention include the use of a membrane to separate the drug from the skin and control release of the drug from its reservoir. As a result of the current advancement in microfabrication technology in the past 10 years, cost-effective means of developing devices in this area are now becoming increasingly common. [34]

Needleless Injections

Needleless injection is reported to involve a pain-free method of administering drugs to the skin. This method therefore avoids the issues of safety, pain, and fear associated with the use of hypodermic needles. Transdermal delivery is achieved by firing the liquid or solid particles at supersonic speeds through the outer layers of the skin by using a suitable energy source. Over the years there have been numerous examples of both liquid (Ped-O-Jet® , Ject® , Biojector2000® , Medi-jector® , and Intraject®) and powder (PMED™ device, formerly known as PowderJect® injector) systems [35]. The latter has been reported to deliver successfully testosterone, lidocaine hydrochloride, and macromolecules such as calcitonin and insulin [36].

Radio Frequency

Radio frequency involves the exposure of skin to high-frequency alternating current (~100 kHz), resulting in the formation of heat-induced microchannels in the membrane in the same way as when laser radiation is employed. The rate of drug delivery is controlled by the number and depth of the microchannels formed by the device, which is dependent on the properties of the microelectrodes used in the device. The Viaderm device (Transpharma Ltd., Lod, Israel) is a hand-held electronic device consisting of a micro-projection array (100 microelectrodes /cm ^{2}) and a drug patch. The microneedle array is attached to the electronic device and placed in contact with the skin to facilitate the formation of the microchannels. Treatment duration takes less than a second, with a feedback mechanism incorporated within the electronic control providing a signal when the microchannels have been created, so as to ensure reproducibility of action. The drug patch is then placed on the treated area. Experiments in rats have shown that the device enhances the delivery of granisetron HCl, with blood plasma levels recorded after 12 hours rising 30 times the levels recorded for untreated skin after 24 hours. [37].

Suction Ablation

Formation of a suction blister involves the application of vacuum [38] or negative pressure to remove the epidermis whilst leaving the basal membrane intact. The cellpatch® (Epiport Pain Relief, Sweden) is a commercially available product based on this mechanism. [39] It comprises of a suction cup, epidermatome (to form a blister), and device (which contains morphine solution) to be attached to the skin. This method which avoids dermal invasivity, thereby avoiding pain and bleeding, is also referred to as skin erosion. Such devices have also been shown to induce hyperaemia in the underlying dermis in *in vivo* studies [40], which was detected by laser Doppler flowmetry and confirmed by microscopy, and is thought to further contribute to the enhancement of dextran and morphine seen with this method.

Skin Abrasion

These techniques, many of which are based on techniques employed by dermatologists in the treatment of acne and skin blemishes, involve the direct removal or disruption of the upper layers of the skin to enhance the permeation of topically applied compounds. The delivery potential of skin abrasion techniques is not restricted by the physicochemical properties of the drug, and previous work has illustrated that such methods enhance and control the delivery of a hydrophilic permeant, vitamin C vaccines [20] and biopharmaceuticals [41]. One current method is performed using a stream of aluminium oxide crystals and motor-driven fraises [20]. Sage and Bock [42] also described a method of pretreating the skin before transdermal drug delivery, which consists of a plurality of microabraders of length 50 to 200 mm. The device is rubbed against the area of interest to abrade the site, in order to enhance delivery or extraction.

CARRIER AND VEHICLES

These are composed of multiple concentric bilayers of surfactant separated by a polar liquid medium, generally water in which the hydrophilic additives can be incorporated. Their lipid core allows encapsulation of lipid additives, and their multilamellar (lipid/water) structure creates good skin affinity leading to cutaneous penetration and good hydration.

Nanoemulsions/Submicron Emulsion

These are oil-in-water emulsions with an average droplet size ranging from 100 to 500 nm. They have very good stability and they do not undergo phase separation during storage. They have a liquid lipophilic core and are appropriate for lipophilic compound transportation. Many studies showed reduced transepidermal water loss, which means support to the barrier function of the skin [43]. Nanoemulsion viscosity is very low, which is interesting because they can be produced as spray.

Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLNs) have recently been investigated as carriers for enhanced skin delivery of sunscreens, vitamins A and E, triptolide, and glucocorticoids [44]. It is thought that their enhanced skin penetrating ability is primarily due to an increase in skin hydration caused by the occlusive film formed on the skin surface by the SLN. A 31% increase in skin hydration has been reported following 4 weeks application of SLN-enriched cream [45].

Multiple Emulsions

These w/o/w emulsions consist in the dispersion of a w/o emulsion in an aqueous phase under several conditions [46]. One can incorporate different water-soluble ingredients (even if they are incompatible) and also oil soluble additives. Like SLNs, these substances will be protected and release sustained by controlling droplet breakdown. These systems can have high oily phase contents (65%, Trixera, Bain emollient, Avθne) and thus present good hydration. Their efficacy has been demonstrated in dermatology to treat stretch marks (Triffadiane, CS Dermatologie).

Micro-emulsions

These formulations have been shown to be superior for cutaneous delivery compared with other conventional vehicles [47]. These systems are identified as transparent mixtures of water, oil, and surfactants. They are thermodynamically stable and optically isotropic. Microemulsions are spontaneously produced in a narrow range of oil-water-surfactant composition, represented on pseudoternary diagram phases. They are dynamic systems with continuously fluctuating interfaces. Their good dermal and transdermal delivery properties could be attributed to their excellent solubilising properties. Their high solubilising properties improve biodispensibility, and thus reduce the efficient dose thereby increasing tolerability. Furthermore, their restructuring effect on skin and hair (because of their high lipid content) make microemulsion formulations adapt to altered skin and hair conditions.

Vesicular Carriers

Liposomes

Liposomes are colloidal particles formed as concentric biomolecular layers that are capable of encapsulating drugs. Their potential for delivering drugs to the skin was first reported by Mezei and Gulasekharam in 1980 who showed that the skin delivery of triamcinolone acetonide was four to five times greater from a liposomal lotion than an ointment containing the same drug concentration [48]. Phosphatidylcholine from soybean or egg yolk is the most common composition, although many other potential ingredients have been evaluated. [49] Cholesterol added to the composition tends to stabilize the structure thereby generating more rigid liposomes. Recent studies have tended to be focused on delivery of macromolecules such as interferon, [50] gene delivery [51], and cutaneous vaccination [52],

in some cases combining the liposomal delivery system with other physical enhancement techniques such as electroporation [53].

Niosomes

Niosomes are vesicles composed of nonionic surfactants that have been evaluated as carriers for a number of drug and cosmetic applications [54]. This area continues to develop with further evaluation of current formulations and reports of other vesicle-forming materials.

Transfersomes

Transfersomes are vesicles composed of phospholipids as their main ingredient with 10 to 25% surfactant (such as sodium cholate) and 3 to 10% ethanol. The surfactant molecules act as 'edge activators,' conferring ultradeformability on the transfersomes, which reportedly allows them to squeeze through channels in the stratum corneum that are less than one-tenth the diameter of the transfersome [55]. According to their inventors, where liposomes are too large to pass through pores of less than 50 nm in size, transfersomes up to 500 nm can squeeze through to penetrate the stratum corneum barrier spontaneously [56].

Ethosomes

These are liposomes with high alcohol content capable of enhancing penetration to deep tissues and the systemic circulation [57]. It is proposed that alcohol fluidises the ethosomal lipids and stratum corneum bilayer lipids thus allowing the soft, malleable ethosomes to penetrate.

Aquasomes

A new class of solid drug carriers, aquasomes, has emerged during the last decade. Aquasomes are three-layered structures (i.e., core, coating, and drug) that are self-assembled through noncovalent bonds, ionic bonds, and Van der Waals forces [58]. They consist of a ceramic core whose surface is noncovalently modified with carbohydrates to obtain a sugar ball, which is then exposed to adsorption of a therapeutic agent. The core provides structural stability to a largely immutable solid [59]. Aquasomes offer an attractive mode of delivery for therapeutic agents belonging to the class of proteins and peptides, because they are able to overcome some inherent problems associated with these molecules. These problems include suitable route of delivery, physical as well as chemical instability, poor bioavailability, and potent side effects. The surface modification with carbohydrates creates a glassy molecular stabilization film that adsorbs therapeutic proteins with minimal structural denaturation. Thus, these particles provide complete protection of an aqueous nature to the adsorbed drugs against the denaturing effects of external pH and temperature, because there are no swelling and porosity changes with change in pH or temperature [60].

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