TRANSDERMAL DRUG DELIVERY BASED ON DISRUPTION OF THE BARRIER PROPERTIES OF THE STRATUM CORNEUM

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Abstract

The conventional oral dosage forms has significant drawbacks of poor bioavailability due to hepatic first pass metabolism and 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. The skin offers an accessible and convenient site for the administration of medications. To this end, the field of transdermal drug delivery, aimed at developing safe and efficacious means of delivering medications across the skin, has in the past and continues to garner much time and investment with the continuous advancement of new and innovative approaches. This article details the progress and current status of the transdermal drug delivery field and describes numerous pharmaceutical developments which have been employed to overcome limitations associated with skin delivery systems. Advantages and disadvantages of the various approaches are detailed, commercially marketed products are highlighted and particular attention is paid to the emerging field of microneedle technologies.

Keywords:- *Transdermal; drug delivery; velocity based device; ultrasound; thermal ablation; microneedle.*

Introduction

Transdermal drug delivery systems (TDDS), also known as "patches," are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin[1]. Conventional systems of medication which require multi dose therapy have numerous problems and complications. The design of conventional dosage form, whether a tablet, an injection or a patch, to deliver the right amount of medicine at the right target site becomes complicated if each medication were to be delivered in an optimal and preferred manner to the individual patient[2]. The impetus for the development of novel drug delivery systems, apart from therapeutic efficacy is cost. Redesigning the modules and means to transport medicine into the body is less demanding and more lucrative task. To address these problems, controlled release drug delivery system, a novel drug delivery approach evolves, which facilitates the drug release into systemic circulation at a pre-determined rates. Controlled drug release can be achieved by transdermal drug delivery systems (TDDS) which can deliver medicines via the skin portal to systemic circulation at a predetermined rate over a prolonged period of time[3].For transdermal products the goal of dosage design is to maximize the flux through the skin into the systemic circulation and simultaneously minimize the retention and metabolism of the drug in the skin. Transdermal drug delivery systems (TDDS) are defined as self-contained, discrete dosage forms which, when applied to intact skin, deliver the drug(s), through the skin, at a controlled rate to systemic circulation. The transdermal route of administration is recognized as one of the potential route for the local and systemic delivery of drugs[4].The most common routes of drug delivery are the oral and parenteral routes with the majority of small molecule drugs

conventionally delivered orally[5]. The oral route has the advantage of pre-determined doses, portability and patient self-administration. For these reasons, the oral route remains the most convenient means of delivering medications[6]. However, most therapeutic peptides or proteins are not delivered by the oral route, due to rapid degradation in the stomach and size-limited transport across the epithelium[7]. The primary mode of administering macromolecules is therefore via injection which is not without limitations, such as the invasive nature of injections eliciting pain and lower acceptance/compliance by patients, in addition to the requirement for administration by a trained administrator[8]. Rationally, the conventional routes of medication delivery have many inherent limitations which could potentially be overcome by advanced drug delivery methodologies such as transdermal drug delivery (TDD).

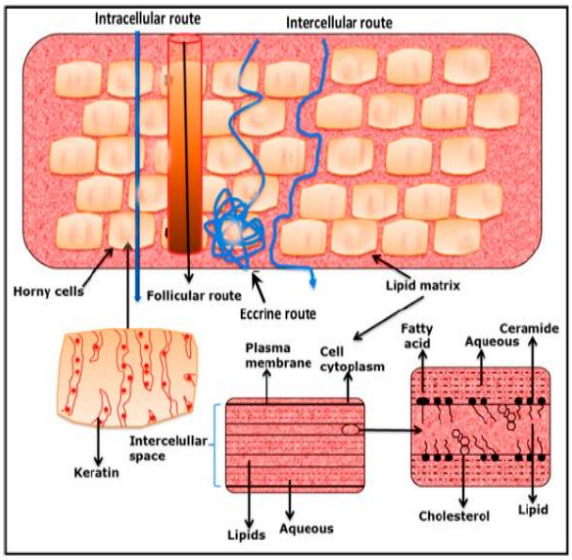

Figure-1: Possible drug penetration routes across human skin

Transdermal Drug Delivery (TDD)

TDD is a painless method of delivering drugs systemically by applying a drug formulation onto intact and healthy skin. The drug initially penetrates through the stratum corneum and then passes through the deeper epidermis and dermis without drug accumulation in the dermal layer. When drug reaches the dermal layer, it becomes available for systemic absorption via the dermal microcirculation[9]. TDD has many advantages over other conventional routes of drug delivery[10,11]. It can provide a non-invasive alternative to parenteral routes, thus circumventing issues such as needle phobia. A large surface area of skin and ease of access allows many placement options on the skin for transdermal absorption. TDD avoids pre-systemic metabolism, thus improving bioavailability. With reference to the use of the skin as a novel site for vaccination strategies, this organ is known to be replete with dendritic cells in both the epidermal and dermal layers which play a central role in immune responses making TDD an attractive vaccination route for therapeutic proteins and peptides[6]. The requirement for an inexpensive and non-invasive means of vaccination, especially in the developing world[12], has given rise to substantial research focused on the development of simple, needle-free systems such as TDD for vaccination purposes.

Drug Penetration Routes

There are two possible routes of drug penetration across the intact skin, namely the transepidermal and transappendegeal pathways, which have been diagrammatically presented in Figure-1. The transepidermal pathway involves the passage of molecules through the stratum corneum, an architecturally diverse, multi-layered and multi-cellular barrier. Transepidermal penetration can be termed intra- or inter-cellular[13]. The intra-cellular route through corneocytes, terminally differentiated keratinocytes, allows the

transport of hydrophilic or polar solutes. Transport via inter-cellular spaces allows diffusion of lipophilic or non-polar solutes through the continuous lipid matrix. The transappendegeal route involves the passage of molecules through sweat glands and across the hair follicles[14].

Techniques for Enhancement of Skin Permeabilisation

Technologies used to modify the barrier properties of the stratum corneum can be divided into passive/chemical or active/physical methodologies. Passive methods include the influencing of drug and vehicle interactions and optimization of formulation, in order to modify the stratum corneum structure[13]. Passive methods are relatively easy to incorporate into transdermal patches such as chemical enhancers and emulsions[15]. However, the main drawback of passive methods may be a lag time in drug release incurred with obvious negative influence on rapid onset drugs, such as insulin.One of the most widely used passive approaches is the use of chemical penetration enhancers which facilitate drug permeation across the skin by increasing drug partitioning into the barrier domain of the stratum corneum, without long-term damage to the skin[10]. Several types of penetration enhancers are known and they can be divided into several groups based on their chemical structure, rather than their mechanism of action[16]. Most of these have mixed modes of action so it is difficult to classify them according to this characteristic. Examples of commonly investigated penetration enhancers are alcohols, sulphoxides, azone, pyrrolidones, essential oil, terpenes and terpenoids, fatty acids, water and urea[16]. However, the major limitation for penetration enhancers is that their efficacy is often closely correlated with the occurrence of skin irritation[17]. Gels have been used in TDD and recent developments in the technology have introduced new variations of semisolid vehicles such as proniosomes and microemulsion gels into the field of penetration enhancers[15]. Proniosomes are non-ionic based surfactant vesicles, they are known as ‘‘dry niosomes’’ because they may require hydration before drug release and permeation through the skin. Upon hydration proniosomesare converted into niosomes which are capable of diffusing across the stratum corneum and then adhere to the cell surface which causes a high thermodynamic activity gradient of the drug at the vesicle/stratum corneum surface, thus acting as the driving force for the penetration of lipophilic drugs across the skin. Some of the limitations associated with penetration enhancers are poor efficacy and safety. They do not achieve the desired skin disruption and their ability to increase transport across the skin is low and variable[18].The active methods for skin permeabilisation include ultrasound, electrically assisted methods (electroporation and iontophoresis), velocity based devices (powder injection, jet injectors), thermal approaches (lasers and radio-frequency heating) and mechanical methodologies such as microneedles (MN) and tape stripping[19]. These approaches allow a broader class of drugs to be delivered into the skin. Active methods involve the use of external energy to act as a driving force for drug transport across the skin or by physically disrupting the stratum corneum. In addition, active methods also offer more reproducible control over the delivery profiles of the medications, thus overcoming lag times

between the application and the drug reaching the systemic circulation when compared to passive methods[10]. Some of these active methodologies will be described in detail below.

Ultrasound Devices

Ultrasound is an oscillating sound pressure wave that has long been used for many research areas including physics, chemistry, biology, engineering and others in a wide range of frequencies. Ultrasound, sonophoresis, or phonophoresis can be defined as the transport of drugs across the skin by application of ultrasound perturbation at frequencies of 20 kHz–16 MHz which has a sufficient intensity to reduce the resistance of skin[7]. The proposed mechanisms by which ultrasound effects tissues and cells include thermal effects and cavitation effects caused by collapse and acoustic streaming which can be explained as oscillation of cavitation bubbles in the ultrasound field[7]. Ultrasound can increase the temperature of the insonated medium (the skin) by the absorption of the sound waves with a frequency greater than the upper limit of the human hearing range. Obviously, the higher the medium's absorption coefficient, the higher the increase in temperature and thus the greater the thermal effect[20]. All recent studies point out that cavitation is believed to be the predominant mechanism in the enhancement of TDD via ultrasound treatment[20].

Electrical Techniques

Electroporation

The two major means of electrically-facilitated TDD are iontophoresis and electroporation[5]. In electroporation, cells are temporarily exposed to high intensities of electric pulses that lead to the formation of aqueous pores in the lipid bilayers of the stratum corneum, thus allowing the diffusion of drugs across skin[7]. Usage of high voltage pulses (50–500 V) for short times of only one second have been shown to increase transport across the skin for different molecular weight drugs ranging from small e.g., fentanyl, timolol[21], orcalcein[22], to high molecular weight drugs such as LHRH, calcitonin, heparin or FITC–dextran with molecular weights up to 40 kDa. However, the main drawbacks are the lack of quantitative delivery, cell death with high fields and potential damage to labile drugs, e.g., those of protein origin.

Iontophoresis

Iontophoresis involves the application of physiologically acceptable electrical currents (0.1–1.0 mA/cm^2) to drive charged permeants into the skin through electrostatic effects and make ionic drugs pass through the skin into the body by its potential gradient[7]. Unlike other transdermal enhancement methodologies, it acts mainly by involving a second driving force, the electrical potential gradient as companion to the concentration gradient across the skin since uncharged species can also be delivered through electroosmosis.

Several factors affect iontophoretic TDD, including pH of the donor solution, electrode type, buffer concentration, current strength and the type of current employed[23]. A plethora of studies correlating flux as a function of molecular weight have been conducted and it was found that the transport of compounds decreased with increase in molecular weight (chloride > amino acid > nucleotide > tripeptide > insulin)[23]. There is a linear relationship between the current and drug flux across the skin but the current is limited to 1 mA in order to facilitate patient comfort and consider safety concerns as

with increasing current, the risk of nonspecific vascular reactions (vasodilatation) also increases[23]. The use of continuous direct current (DC) can decrease the drugs flux due to its polarization effect on the skin. The most common electrodes that are used in iontophoresis are aluminum foil, platinum and silver/silver chloride electrodes. However, the preferred one is Ag/AgCl since it resists the changes in pH. In addition, the electrode materials used for iontophoretic delivery should be harmless to the body and flexible so as to be applied closely to the body surface[24]. However, it was found that a small protein, cytochrome c (12.4 kDa) was delivered non-invasively across intact skin[25]. Afterwards, ribonuclease A, with isoelectric point of 8.64 (13.6 kDa), was successfully delivered across porcine and human skin. More recently, it was shown that transdermal iontophoresis was also able to deliver biologically active human basic fibroblast growth factor (hbFGF; 17.4 kDa) in therapeutically relevant amounts corresponding to those used in clinical trials and animal studies[26].

Velocity Based Devices

Velocity based devices, either powder or liquid jet injections, employ a high-velocity jet with velocities ranging from 100 to 200 m/s to puncture the skin and deliver drugs using a power source (compressed gas or a spring)[27]. Since then, interest in this method of drug delivery has expanded significantly and two types of liquid jet injectors have been developed; single-dose jet injectors and multi-use-nozzle jet injectors (MUNJIs)[27]. Jet injections have been used for more than 50 years for parenteral delivery of vaccines, as well as small molecules, such as anesthetics and antibiotics. A jet injector is a needle free device capable of delivering electronically controlled doses of medication which result in improved consistency of delivery and reduced pain for the patient.

Thermal Approaches (Lasers and Radio-Frequency Heating):-Thermal ablation is a method used to deliver drugs systemically through the skin by heating the surface of the skin, which depletes the stratum corneum selectively at that site of heating only, without damaging deeper tissues[28]. Many methods could be used to cause thermal ablation such as laser, radiofrequency, in addition to electrical heating elements. In order to generate the high temperatures needed to ablate the stratum corneum without damaging the underlined epidermis, the thermal exposure should be short, so the temperature gradient across the stratum corneum can be high enough to keep the skin surface extremely hot but the temperature of the viable epidermis does not experience a significant temperature rise[28].

Mechanical Approaches to Mediate Skin Permeation

The use of hypodermic needles, often associated with phobia, pain and the risk of needle-stick injuries have been used to overcome some of the delivery limitations often experienced when delivering macromolecular compounds[29]. Some innovative methodologies have been explored to overcome these issues and include the use of MN and tape stripping.

Conclusion:-In conclusion, the TDD sector continues to grow and develop with rapid expansion in fundamental knowledge feeding industrial development. In time, it is hoped that technological advancements in TDD will lead to enhanced disease prevention, diagnosis and control, with

concomitant improvement in health-related quality of life for patients worldwide. To this end, this article has charted the development of numerous novel TDD methodologies. Due to the exponential growth in investment and interest in MN technologies and the numerous associated advantages of this approach, particular attention was paid to this TDD system.

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