Journal of Nanomedicine & Biotherapeutic Discovery

Angamuthu and Ainampudi, J Nanomedine Biotherapeutic Discov 2017, 7:2
DOI: 10.4172/2155-983X.1000e146

Editorial Open Access

Role of Physical, Chemical Percutaneous Penetration Enhancement Methods: A Concise Review

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Received date: November 28, 2017; **Accepted date:** November 30, 2017; **Published date:** December 01, 2017

Introduction

Percutaneous delivery of drugs is a viable alternate to oral, intravascular, subcutaneous and transmucosal routes. Potential advantages of percutaneous drug delivery include, but not limited to, elimination of first-pass metabolism, steady-state delivery or blood levels, enhanced patient compliance, minimized systemic toxicity, plausible dose intervention, avoidance of clinically assisted drug administration, prolonged drug delivery, and overall improved therapeutic efficacy. Primitively, transdermal patch products or dosage forms were utilized for percutaneous drug delivery with conceptual simple design. First in this line was transdermal scopolamine patch for drug administration to treat motion sickness. This was huge success which further led to the development of nitroglycerine, fentanyl, estradiol, nicotine and testosterone transdermal systems for patient use. Conception of transdermal patch systems resulted in original medical therapies with existing drugs. Classic example is estradiol patches which is used by millions of patients annually. On contrary to oral route of administration, percutaneous estradiol delivery did not cause liver damage. Another great example is percutaneous nicotine replacement therapy that helped millions of US smokers to quit smoking and increase lifespan [1,2]. However, only fewer more than 35 transdermal patch products have been approved by US Food and Drug Administration for in a wide range of therapeutic areas.

Chemically/Physically Assisted Drug Delivery in Percutaneous Drug Administration

Scientific community hit a major roadblock which limited the delivery of only a handful of active pharmaceutical ingredients or biopharmaceuticals via percutaneous administration. Passive drug delivery via percutaneous route greatly depends on combination of distinctive physicochemical properties of active pharmaceutical ingredients/biopharmaceuticals. Few of several major enabling factors include, low molecular weight (<500 Da), optimal lipophilicity and low therapeutic dose. Dynamic combination of these factors determines percutaneous drug delivery in clinically viable levels to elicit a therapeutic response. Especially, for biopharmaceuticals, including proteins and peptides, molecular size has been a major limiting factor for percutaneous drug absorption. To sum up, percutaneous delivery via passive mode had enabled only fewer active pharmaceutical ingredients/biopharmaceutics to reach systemic circulation in adequate therapeutic levels to elicit a pharmacological response. Although, several biochemical approaches (bioconvertible prodrugs, vasoconstrictors) and chemical permeation enhancers are still being experimented for enhanced percutaneous drug administration. Chemical permeation enhancers (CPEs) can potentially increase skin permeability through one or more following ways including, increased drug partitioning in stratum corneum and breach of bilayer lipid structures in stratum corneum. Increasing aqueous solubility of poorly water soluble drugs have also been proved to be an attractive advantage to enhance percutaneous drug delivery with including oxybutynin, testosterone and estradiol gel systems.

When compared to chemical permeation enhancers, active physical techniques provide superior flexibility in formulation design and ease of administration. Chemical permeation enhancers like surfactants, fatty acids/esters, terpenes and solvent systems were shown to produce significant enhancement towards achieving required therapeutic drug levels in blood. High-throughput methods have made it possible to screen several chemical permeation enhancers within a short span as well as to establish enhancement profiles of binary mixtures of known penetration enhancers. High-throughput concept in percutaneous drug delivery research is an emerging science which boasts testing of few thousand chemicals per day and screening formulations for potency.

Physical techniques in active drug delivery systems were lately included in mainstream percutaneous research to facilitate the delivery of active pharmaceuticals/biopharmaceuticals across skin. Efficiency of these active or assisted enhancement techniques have been proven in several pre-clinical and clinical studies. Few of them are currently under clinical developments that are designed to deliver wide variety of small molecule pharmaceuticals and biologicals.

Most frequently tested 'electrically assisted techniques' in percutaneous drug absorption are iontophoresis and electroporation. These penetration enhancement techniques involve electric current as primary driving force to enhance percutaneous absorption of topically applied drugs. In Iontophoresis, charged drug species are pushed against barrier properties of skin under constant electric current through a phenomenon called electroosmosis and hydrokinesis. Moreover, iontophoresis was proved to be a superior technique to modulate scar skin barrier properties and facilitate percutaneous absorption of drugs [3]. In contrast to iontophoresis, electroporation technique results in reversible aqueous pathways in lipid bilayers when short electric current is pulsed on the skin surface. Appreciable drug fluxes, have been observed for both small and large molecules with minimal lag time when delivered through this technique. Electroporation finds major application in minimally invasive intradermal delivery of biological agents and DNA based vaccines [4,5].

Microneedle approach is yet another technique which actively enhances percutaneous drug absorption in multiple ways. As a drug delivery system, microneedles physically breach structural barrier in stratum corneum resulting in continuous pores/channels for percutaneous absorption. Microneedles technique has been tested as

pretreatment application mode prior to drug administration, leach drugs inside epidermis when pre-coated on needles and also infuse drug when used along with miniature pumps. An alternative approach to microneedle delivery was demonstrated for minimally invasive administration of microspheres (in proximal nail folds) for terbinafine delivery and treatment of onychomycosis (fungal nail infections) [6].

Laser assisted drug delivery in percutaneous absorption involves exposure of skin to low energy levels of laser which effectively alters its barrier properties. Laser leads to rearrangement of lipids and proteins and/or by removal of dead cells in the stratum corneum region in skin. Laser technique was experimented for the delivery of vaccines, vitamins and anti-inflammatory drugs in several pre-clinical and clinical studies.

Hidden Potential

Drug companies are aiming for efficient technologies involving physical and/or chemical enhancement techniques for topical/transdermal drug products especially involving the development of new medical treatments for existing drugs. These initiatives are heavily concentrated on diseases which mandate new drug product development. Need for the existence of new treatment modalities are more prevalent in therapeutic areas like depression, Parkinson's, Alzheimer's, anxiety, urinary incontinence, allergy, obesity, hypertension, pain and epilepsy. Over a decade, more than 25 potential small and large molecule therapeutic agents have been identified for futuristic development into topical/transdermal drug products in aforementioned therapeutic areas. High surge in the global medical needs have already tapped the potentials of physical/chemical enhancement methods for topical/transdermal drug product development. Without slightest speculation, the utility of physical and chemical penetration enhancement techniques warrant multitude growth of topical and transdermal drug delivery systems. Physical/chemical penetration enhancement techniques could catapult exponential growth in topical/transdermal drug product development and has a future all in itself.

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