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Monthly Focus: Pulmonary-Allergy, Dermatological, Gastrointestinal & Arthritis

Therapeutic patents for topical and transdermal drug delivery systems

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For more than 30 years techniques of delivering drugs through skin have been elaborated as clinically relevant methods to administer therapeutic agents. The great contributions of transdermal and topical administrations on clinical therapeutics are firmly based on their distinctive properties. Progress in new technologies and compound is continuously stimulating the growth and revolution of topical and transdermal administration. This review summarises recent developments in the design of formulations and the patent literature in the area of topical and transdermal drug delivery systems.

Keywords: *absorption enhancer, delivery system, formulation, patch formulation, transdermal formulation*

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1. Introduction

Advances in drug delivery into and through the skin have established a unique and useful method among the various routes of drug administration in recent decades. Applying medication to the skin is an instinctive method that has played a significant role in the history of primitive remedies without clear exploration. The nature and essence of this simple-looking, but rather complicated, delivery method should be further clarified into transdermal delivery and topical administration. Absorption of medications by skin occurs in both delivery systems, but permeation into blood vessels only occurs in the transdermal delivery system. Molecules delivered through topical application remain on skin or tissues to attain local therapeutic actions; whereas those administered through a transdermal delivery system reach the blood circulation and accomplish their effects systemically. The use of a transdermal drug delivery system can avoid first pass hepatic or intestinal metabolism and yield sustained plasma concentration with minimal fluctuations. It overcomes the problems of low bioavailability associated with oral administration. Its convenient method of administration fortifies patient compliance and clinician acceptance compared to iv. or im. administrations. Academic interest in dermatological products has therefore paralleled marketing interests due to the potential and considerable profits.

A limited number of drugs can be formulated as transdermal delivery products due to the functions of the stratum corneum, which provides the principal barrier to skin permeation. The molecular weight of medication administered by transdermal delivery should always be < 500 Da and the

daily dose of the drug should not exceed 20 mg [1,2]. Marketed products include nitroglycerine, nicotine, clonidine, oestradiol, scopolamine and fentanyl [3,4]. The feature of formulation retains the inimitable therapeutic uses of these products in clinical settings.

The FDA recently issued guidance covering assessment of *in vitro* testing and *in vivo* bioequivalence methods of dermatological-dosage products [5,6]. Steps that must be taken by a company were outlined to maintain certification of its dermatological products after any changes have been made in their formulations. The approaches and principles of dermato-pharmacokinetics (DPK) in topical drug products were also discussed.

The aim of this article is to review the transdermal drug patents approved from 1997 to 1999. Patents approved during this period of time have been researched using the following keywords: transdermal; topical or dermatological dosages/formulations. Literature related to these patents is also briefly discussed. These patents were divided into two groups according to the nature of their applications: 1) new methods to enhance transdermal delivery; 2) new formulae of pharmacological agents. The impact and originality of the patents is highlighted in the discussion of individual patents. New trends, interests and difficulties in transdermal drug delivery are also discussed and compared.

2. New methods to enhance transdermal delivery

2.1 Penetration enhancers

Macrochem has claimed the use of 1,3-dioxolanes or 1,3-dioxanes to increase transdermal absorption of six NSAIDs in neutral compositions. The claimed formulations comprise 2 - 10% NSAID, 5 - 10% 1,3-dioxolanes or 1,3-dioxanes as enhancer, 1 - 15% propylene glycol, 55 - 70% ethanol, water and a gelling agent. The fluxes of skin penetration were measured by HPLC in human or porcine skin. Propylene glycol did not enhance skin penetration whereas 2-nonyl-1,3-dioxolane dose-dependently increased skin penetration of the NSAIDs [101].

Alza has claimed a dual skin permeation enhancer comprising glyceryl monolaurate and lauryl acetate for enhancing the transdermal delivery of active agents. This dual enhancer may be used to deliver a

large number of active agents for the treatment of a wide variety of disorders such as fungal infections, migraine and parasitic infections. The transdermal fluxes of alprazolam, oxybutynin, or testosterone were measured with various enhancers, including ethylene vinyl acetate, glyceryl monolaurate, glyceryl monooleate, lauryl acetate, lauryl lactate and myristyl lactate. The highest rate among these enhancers was that of the dual system including glyceryl monolaurate/lauryl acetate [102].

Minnesota Mining & Manufacturing has claimed a device for transdermal delivery of testosterone consisting of a terpene and a fatty acid derivative as enhancing adjuvants to treat testosterone deficiency, including male hypogonadism and wasting conditions associated with AIDS and cancer. The skin penetration profile was measured by using hairless mouse skin or human cadaver skin. The effects of varying the nature and the amount of enhancing adjuvants and preparation method of an isooctyl acrylate/acrylamide/vinyl acetate 73/7/20 co-polymer were described [103].

2.2 New adjuvant for transcutaneous immunisation

The US Army has claimed a formulation for transcutaneous immunisation comprising an antigen and an adjuvant to induce the immune response specific to the antigen. Application of the formulation to intact skin did not perforate the skin. It was stated that cholera toxin, the B subunit of cholera toxin, *E. coli* heat labile enterotoxin and pertussis toxin were all potent adjuvants for transcutaneous immunisation. The formulations of transcutaneous immunisation induced high levels of IgG antibodies but not IgE antibodies [104].

2.3 Topical application of macromolecules from thermoreversible gel

Crandall has claimed the preparation of pluronic and lecithin pluronic organogels to facilitate the transdermal transport of macromolecules through the stratum corneum into the dermis, the hypodermis or adjacent connective tissue or joints. Pluronic gel is a non-toxic, di-block co-polymer of polyoxyethelene and polyexypropylene [7]. It is an aqueous solution of thermoreversible gelation, being liquid when the temperature is below 15°C and a robust gel when the temperature is above 15°C. The specified compound, bromelain, is a protease macromolecule isolated from pineapple which has demonstrated various

pharmacological effects, including antitumour, antiplatelet, anticoagulation, cAMP elevation and downregulation of IL-1, PG and IL-8 [8-10]. The claimed formulation included bromelain powder (7.5 g), capsaicin (25 mg), honey almond oil (2 ml), lecithin-isopropyl palmitate (20 ml) and 20% pluronic mixture (80 ml). It was tested for its ability to denature copperhead snake venom (id.) to reduce necrotic regions in mice and relieve pain of interphalangeal joint inflammation in human subjects. Claims also included methotrexate formulations, and other macromolecules, to treat rheumatoid arthritis and psoriasis [105].

2.4 Controlling release of desired enantiomers

Chiroscience has claimed the administration and separation of the enantiomers of verapamil for different indications to obviate undesirable side effects from the unwanted isomer. The (*S*)-enantiomer is used as a calcium channel blocker for the treatment of hypertension, while the (*R*)-enantiomer is a multi-drug resistance inhibitor. Due to the different metabolic clearance rates of the two isomers, their ratio can change over time in oral, rectal, transdermal, nasal or ophthalmic administrations. Controlling the release rates of the two enantiomers from a skin patch or pellets can provide a desired constant ratio of enantiomers throughout the dosing period [106].

3. New formulae of pharmacological agents

25 Patents were categorised into nine therapeutic/pharmacological classes.

Transdermal or topical formulations in some of the following have been developed historically, such as agents for skin disorders or antimicrobials. Whereas, the design of dermatological dosage forms for some of the therapeutic/pharmacological classes are extremely original, showing good prospects for newly marketed medications.

3.1 Agents for skin disorders

Avon has claimed active exfoliators at neutral pH comprising an N-acyl-N,N',N'-ethylenediaminetriacetic acid derivative to treat abnormal keratinisation, hyperkeratinisation, xerosis, dandruff and ichthyosis. The monosodium salt of ethylenediaminetriacetic acid proved to be superior to both the vehicle and glycolic acid on 20 patients. No discomfort was observed with the specified compound

(solution pH 7.0), but with glycolic acid (solution pH 3.8) sensory discomfort and mild skin reddening were noted [107].

Estée Lauder has claimed the synthesis and application of novel steroid esters, including dehydroepiandrosteryl salicylate, to treat dry skin, dandruff, acne, keratoses, psoriasis, eczema, pruritis, age spots, hyperpigmented skin, age-related skin changes, hyperkeratotic skin, inflammatory dermatoses, skin in need of cleansers and skin atrophy. Efficacy and safety of the compounds were examined by Stratum corneum samples and human volunteers [108].

Incyte Pharmaceuticals, Inc. claimed human kallikrein (HKALL), amino acids encoding the protein, DNA constructs, expression vectors and transformed cells as well as antibodies against the protein. They are all potentially useful for treating skin disorders. The diverse pharmacological properties and biochemical characteristics of kallikrein-kininogen-kinin systems raised widespread academic and commercial interest, including the applications in autocrine and paracrine signalling for skeletal and cardiac muscle energy metabolism, availability of better kallikrein inhibitors, specific kinin receptor antagonists and techniques of genetic manipulation [11,12]. In this patent, HKALL was identified by computer-assisted database searching by its significant homology to human stratum corneum chymotryptic enzyme. Assays such as ELISA, RIA and FACS can be used as diagnostic probes against HKALL antibodies to measure HKALL in patients with skin disorders [109].

Schering AG has claimed a gel with enhanced penetration properties, comprised of benzoic acid and EDTA in 60 to 70 parts water, triglyceride (1 part), polysorbate 80 (1.5 parts), lecithin (1 part), propylene glycol (12 parts), polyacrylic acid (1 part) azelaic acid (15 parts) and sufficient sodium hydroxide solution. Compared to the traditional cream of azelaic acid, which is more lipophilic than the gel formulation, this new formulation increased concentrations in the stratum corneum and reduced amounts remaining on the surface [110].

Heng claimed the use of curcumin with or without either vitamin D₃, etritinate, diltiazem or anthralin in the treatment of wounds, burns, eczema, acne, exposure to sunlight, damage from nicotine or tobacco and premature ageing and inflammation. Curcumin, extracted from *Curcuma longa* L, is used in the treatment skin disorders in the practice of Chinese

herbal medicine. Other applications of curcumin have been extensively studied recently including its effect on arresting cell proliferation and inducing cell apoptosis [13-18]. Significant improvement on wound healing and reduction of phosphorylase kinase activity were observed in patients treated with 1% curcumin gel for 2 - 3 weeks [111].

3.2 Antimicrobial agents

Bristol-Myers Squibb has claimed topical administration of lipid formulations to prevent skin adherence of micro-organisms, including *Candida albicans*, *Staphylococcus* spp. and other bacteria. These formulations further reduce the amount of antimicrobial agents required and replenish skin lipids. Several formulations have been discussed and the preferred choice contained 0.1 - 0.5% of the specified compound, 5 - 10% alcohol and/or 6 - 99% component co-polymer. One of the three specified compounds claimed was palmitoleic acid [112].

Ganeden Biotech has claimed topical administration of a formulation containing a fructo-oligosaccharide (FOS) and the spores or viable dry cell mass of *Bacillus* spp. to prevent or treat infections of the skin or mucous membranes, including *Pseudomonas* and *Staphylococcus B. coagulans*. These formulations may be applied as a cream, lotion, gel, ointment etc., or be impregnated into a diaper, skin-wipe, dermal patch, or tampon. Formulations containing 100 - 500 mg/g FOS with viable bacteria or spores of either *Bacillus coagulans*, *B. subtilis*, *B. laterosporus* or *B. laevolacticus* were specifically claimed [113].

Salafsky *et al.* have claimed a liposomal formulation comprising the mixture of 7.5% N,N-diethyl-m-toluamide (DEET) with one or more glycerophospholipids for topical administration to prevent parasitic diseases caused by skin-penetrating parasites, especially schistosomes such as *Schistosoma mansoni*. A polyol prepolymer carrier and liposomal carrier were also claimed. DEET, one of the most widely used insect repellents, is a near odourless liquid which is soluble in alcohol and benzene and insoluble in water. After topical application, 6 - 8% percent of DEET is absorbed systemically [19]; this has been associated with toxic encephalopathy in children [20]. Application of high-concentration DEET to the skin is not advised so as to minimise the possibility of adverse reactions. This claimed liposomal formulation is stated to fuse with lipids in the stratum corneum, but not to penetrate deeply into

the skin, thus minimising systemic absorption of the active agents. Safety of the specified formulation was tested on the ears of male New Zealand white rabbits [114].

3.3 Steroids and hormones

Rotta Res. BV has claimed transdermal patches and the preparation process for oestradiol and norethisterone acetate in management of hormone replacement therapy (HRT). The patches are stated to force diffusion of the active agents at high concentrations in the absence of a permeability enhancer. They comprise the impermeable backing foil, pressure-sensitive adhesive matrix and removable protective liner. The backing foil is composed of polyester lacquered with epoxy resin, polyaminoamide resin and precipitated calcium carbonate. The main matrix of the patch is made of silicone-coated paper or silicone-coated polyester, which is coated with a dried adhesive matrix. The ingredients of the adhesive matrix include a co-polymer of 2-ethylhexyl acrylate, vinyl acetate, 2-hydroxyethyl acrylate, glycidyl methacrylate, oestradiol, octyldodecanol, norethisterone acetate, aluminium acetylacetonate, ethyl acetate and methyl ethyl ketone. One of the claimed formulations comprised 1.3% oestradiol and 8.5% norethisterone acetate (w/w in the matrix), in a matrix comprising 65% 2-ethylhexyl acrylate, 4.5% 2-hydroxyethyl acrylate, 24% vinyl acetate, 0.1% glycidyl methacrylate, 2% octyldodecanol and 0.5% aluminium acetylacetonate [115].

Rutgers University has claimed a transdermal contraceptive delivery system (TCDS) for controlling fertility in women. This TCDS constitutes a backing layer, an adhesive polymer matrix containing oestrogen and progestin, and skin permeation enhancers. The preferred adhesive polymer matrix contained a 2-ethylhexyl acrylate monomer and 50 - 60% w/w vinyl acetate as a co-monomer. The preferred ingredients included a skin permeation enhancer (dimethylsulphoxide, lauryl lactate and ethyl lactate at a ratio of 4:1:1), oestrogen (17 β -oestradiol), progestin (levonorgestrel) and a humectant/plasticiser (polyethylene glycol). One of the oestrogens formulated in the TCD was 17 β -oestradiol with daily delivery rates from 42.1 - 110.4 μ g/day; progestin was levonorgestrel with rates of 51.0 - 163.7 μ g/day. Contraceptive efficacies achieved in a Phase I trial carried out on 48 fertile Chinese women and a phase II study on 150 Chinese women (of unspecified fertility) were 100% and 96%,

respectively. Mild to moderate skin irritation of the TCDS was seen when assessed on rabbits [116].

Schering Ag has claimed a delivery system to improve the perfusion rate for transdermal controlled release of second and third generation gestagens, including levonorgestrel, norgestimate and cypoterone. The system contains an N-vinyl lactam/vinyl ester or amide co-polymer. It is stated that when used for the delivery of gestagens, optionally in combination with an oestrogen, a greater time period before the onset of crystallisation is observed as compared with existing systems. The perfusion rates of levonorgestrel through excised hairless mouse skin from patches containing levonorgestrel (0.5 - 2%) and oestradiol (1 - 4%) measured by Franz diffusion cells were 50 - 237 ng/cm²/h [117].

Schwarz Pharma AG has claimed a high release rate transdermal therapeutic system (TTS) for sexual hormones, including oestrogens, androgens and gestagens. The TTS consists of a matrix layer, containing acrylate co-polymers with ammonium moieties, a softener, polyethylene glycol and at least 2% of every active substance and a covering layer. The TTS contained no organic solvents and sustained a long release period for up to seven days. During production of the system, thermal exposure is kept to a minimum to prevent decomposition and disintegration. In an open, four-fold cross-over clinical study, the bioavailability of oestradiol administered by this method was compared with previous transdermal delivery systems. Each formulation was administered to eight postmenopausal women, followed by a wash out period of at least one week. Oestradiol plasma levels were significantly higher for six days using the new formulations, with AUC values at least two-fold higher than those for the two control formulations. The preparation of two oestradiol formulations and one oestradiol/norethisterone acetate formulation is described [118].

Rosenbaum has claimed transdermal patch formulations and methods for the use of dehydro-epiandrosterone (DHEA) with phospholipid as a skin penetration enhancer to treat malignancy, systemic lupus erythematosus, rheumatoid arthritis, hair loss, wrinkles, atherosclerosis and erectile dysfunction. The incorporation of phospholipids was stated to elevate plasma DHEA-sulphate above 4 µg/ml in some cases. The preparation of 15 cream, lotion and gel formulations of DHEA and phosphatidylcholine are exemplified [119].

Res Triangle Inst. Has claimed a group of novel androgen agonists, 7 α ,11 β -disubstituted steroidal compounds, for use in HRT and male contraception. One of seven specifically claimed is 7 α ,11 β -dimethyl-19-nortestosterone. These new compounds are more potent and last longer than testosterone or dihydrotestosterone (DHT) and therefore require smaller skin patches. Compared to DHT and testosterone, the specified compound showed relatively high androgenic potency but very weak oestrogenic activity in castrated male rats. The syntheses and IR, ¹H-NMR and MS data of 12 compounds were also discussed. These new compounds may be combined with other agents such as a progestin or a gonadotrophin releasing hormone (GnRH) analogue for clinical uses. This is an area with high potential for the development of a transdermal drug delivery system [120].

3.4 Analgesics and anti-inflammatory agents

Russinsky has claimed the esters of cyclooxygenase (COX) inhibitors and terpene derivatives to treat inflammation, including the specified compound, (-)-menthyl 4,5-diphenyl-2-oxazolepropanoate. These compounds are stated to have increased lipophilicity and are easily cleaved by hydrolases after penetration through the skin. Analysis with melting point, IR, ¹H-NMR, a process for manufacture and a transdermal patch including the compound were also claimed [121].

Minnesota Mining & Manufacturing has claimed an adhesive transdermal delivery device for the transdermal application of flurbiprofen. Topical use of flurbiprofen, a potent NSAID, has been applied for the treatment of gingivitis or inhibition of mitosis during cataract [21-22]. This device comprises a backing and an adhesive layer containing 1 - 25% of (S)-flurbiprofen, isopropyl myristate, polyvinylpyrrolidone and co-polymers of N-vinyl-2-pyrrolidone and vinyl acetate plus acrylate and acrylamide. The device was found to demonstrate good skin adhesion and to penetrate effectively as determined in mouse, or human skin [122].

Alza Corp. Has claimed a transdermal patch device for administration of the κ -opioid agonist asimadoline for the treatment of chronic pain. The patch comprised multiple layers including reservoirs, rate controlling membranes, 5 - 50% asimadoline HCl, 5 - 40% monoglyceride and a C10 - C20 fatty acid ester. It

caused a flux in the range of 1.5 - 11.5 $\mu\text{g}/\text{cm}^2/\text{h}$ compared to 0.6 $\mu\text{g}/\text{cm}^2/\text{h}$ for controls [123].

3.5 Mucolytic and antitussive agents

Pharmacia & Upjohn AB has claimed a transdermal delivery device to administer N-acetylcysteine at concentrations between 1 and 4 mg/cm^2 with β -cyclodextrin for mucolytic use. Previously approved transdermal delivery of N-acetylcysteine [124,125] has been suggested to be ineffective for mucolytic use. The diffusion of N-acetylcysteine through pig skin or artificial membranes was measured using Franz cells. Several delivery devices comprising different drug-inadhesive and multi-laminate types were also claimed. They were stated to be suitable for drug delivery over periods of 8, 12 and 24 h [126].

Pharmacia & Upjohn AB has also claimed a transdermal delivery device used to administer 0.5 - 2 mg/cm^2 dextromethorphan with β -cyclodextrin for antitussive use. Topical administration of this medication has been claimed [127] for other indications. Through bypassing the cytochrome P450 2D6 enzyme, transdermal administration of dextromethorphan reduces the degree of hepatic metabolism. The diffusion of dextromethorphan through pig skin or artificial membranes was measured using Franz cells [128].

3.6 α -Adrenergic antagonists

Flora has claimed transdermal patch and permeation enhancers for seven α -adrenoreceptor blocking agents for the treatment of benign prostatic hyperplasia, frost bite, phoebitis, acute arterial occlusion, Raynauds disease, shock and hypertension. The highest flux across hairless mouse skin *in vitro* among 28 different enhancer systems was achieved by a 50:50 ratio of N-methylpyrrolidone to oleyl alcohol, which gave a flux value of 59.10 $\mu\text{g}/\text{cm}^2/\text{h}$. The patch size to deliver a compound at a minimum daily dose of 0.75 mg for a patient weight of 75 kg was 5 - 40 cm^2 . One of the specified compounds is 2-cyclohexyl-8-[3-[4-[2-methoxy-phenyl]-1-piperazinyl]propylcarbamoyl]-3-methyl-4-oxo-2-phenyl-4H-1-benzopyran [129].

Cygnus has claimed the first transdermal delivery system of tamsulosin to treat benign prostatic hypertrophy (BPH), prostatitis or prostatic cancer. The system had a backing layer impermeable to tamsulosin, a polymer reservoir to hold the drug and a

skin permeation enhancer. Skin flux profiles were measured using human cadaver skin for up to 160 h with various enhancers, including long chain fatty acids, hydrophilic compounds such as butyrolactone, and lipophilic compounds such as long chain esters [130].

3.7 Agents for neurologic/psychologic diseases

SmithKline Beecham has claimed transdermal delivery formulations of the centrally acting dopamine D_2 agonist ropinirole, in a free base form, to treat Parkinson's disease. The use of ropinirole in free base form improved skin penetration by 20- to 40-fold more than hydrochloride, with a target skin flux of 5 - 25 $\mu\text{g}/\text{cm}^2/\text{h}$ [131].

Alza has claimed the delivery of pergolide or its pharmaceutically acceptable salt, such as pergolide mesylate, through a body surface or membrane at a therapeutically effective rate to treat Parkinson's disease. This method allows virtually constant blood plasma levels of pergolide to be maintained in an individual over extended periods of time. The average baseline skin flux of the pergolide base and mesylate through human cadaver epidermis was approximately 0.3 and 1.1 $\mu\text{g}/\text{cm}^2/\text{h}$ over a 52 h period, individually. The most preferred device for the transdermal administration of pergolide comprises a reservoir consisting of pergolide mesylate, glycerol monolaurate, methyl laurate, mineral oil and ethylene vinyl acetate [132].

Britannia Pharm. has claimed a new method to treat attention deficit hyperactivity disorder (ADHD), which involves the administration of lofexidine or a salt with or without clonidine or guanfacine. The medicament may be formulated as a controlled release preparation, skin patch, syrup, nasal spray or suppository. Lofexidine is an analogue of clonidine that possesses a central α -adrenergic agonist currently approved for hypertension or opiate withdrawal. Oral administration of lofexidine has been shown to be less potent than clonidine in treating hypertension. With regard to the use of lofexidine in ADHD, it was stated that lofexidine improved attention span by up to 60% in aged monkeys and 20% in young monkeys with no apparent sedation or alteration in blood pressure [133].

3.8 Immunosuppressants

Fujisawa Pharm. has claimed aqueous-based emulsified tacrolimus (FK506) for the treatment of

inflammatory, hyperproliferative and immunologically mediated skin diseases. Tacrolimus is a macrolide immunosuppressant used to prevent allograft rejection in solid organ transplantation by oral administration. Topical use of tacrolimus has recently been discussed for the treatment of atopic dermatitis [23-25]. Due to its high lipophilicity, the claimed formulations incorporate a hydrophilic substance, preferably a carboxyvinyl polymer, an oily substance, isopropyl myristate or diethyl sebacate, a surfactant and optionally a pH control agent. These formulations showed good absorption without irritability in shaved rats after application of 50 mg of the active drug. Plasma concentrations were assayed over a 24 h period and all of the tested formulations provided AUC values > 30 ng/ml/h [134].

4. Expert opinion

Interesting trends in dermatological formulations can be clearly observed from this review. Topical or transdermal application as a new route for the administration of some medications or chemicals, such as bromelain, dehydroepiandrosterone, ropinirole and tacrolimus, may lead to a new era in therapeutics. Efforts to formulate new medications into transdermal or topical applications are always valuable and intelligent practice. Novel dermatological formulations of medications that have been used for years may reveal their new therapeutic uses or indications. Despite the attraction of topical or transdermal drug delivery, thorough evaluation of the pharmacokinetic profiles and side effects of the drug are essential to avoid unnecessary expenditure.

Clinical significance is also focused on the improvement of transdermal delivery devices or techniques, such as patch and hydrogel comprising polymers and co-polymers (as mentioned above). Adjuvants incorporated into the delivery devices to enhance permeability or solubility effectively increase the absorption of drugs. An electrically assisted transdermal delivery system is largely discussed to enhance permeation for either molecules or macromolecules such as peptides, insulin and calcein [26]. Both iontophoresis (low current density) and electroporation (high voltage) can significantly enhance and control drug delivery across the skin [27]. The use of novel vehicles is currently being studied in the academic area as a new approach to advance transdermal administration. Liposomes and phospholipids are used as drug carriers for topical

delivery for either local or systemic purpose [28]. A number of patents and commercial products concerned with liposomes have become more significant in the last three years both in therapeutic and cosmetic areas. Microemulsions are useful as drug carriers due to their special manufacturing technique [29]. Multi-block co-polymers and microspheres are also attractive drug carriers for topical application. A prodrug strategy offers a possibility to give more favourable pharmacokinetic profiles of product [30]. Since poor topical absorption of some drugs can be attributed to their physicochemical properties, adequate lipid and water solubility is important criteria for predicting the optimal topical delivery of drugs. A lipophilic prodrug improves the permeability across skin and then converts to its parent compound into the skin.

Progress in the academic field may be modified to become the commercial patents and products of the future. Although the advanced attempts are successfully applicable in the laboratory, many problems need to be overcome before they can be commercialised. The high cost of ingredients or adjuvants always hinders the emergence of products for industry. The key question to be solved is how to change or modify the preparation procedure from laboratory scale to mass producing scale. Patient compliance to the products of dermatological dosage form should also be considered. For patients living in tropical and subtropical regions, sweating and skin irritation by occlusive dressing may cause difficulty of adhesion. Resolving these realistic difficulties is the challenge and mission for the development of new patents and products of topical or transdermal application in the future.

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