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ENHANCEMENT OF TRANSDERMAL DELIVERY SYSTEM AND ANTIDIABETIC APPROACH: AN OVERVIEW

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ABSTRACT
The modern era has witnessed development of alternate and successful routes of drug delivery system *i.e.* Transdermal Drug Delivery System (TDDS). In a broad sense, it includes all topically administered drug formulations intended to deliver the active ingredient into the general circulation. Increasing prevalence of diabetes is presently pushing strong demand for novel drug delivery devices. Most of the antidiabetic drugs today are available in injectable form through syringes, pens, pumps and needle-free devices. Today about 74% of drugs are taken orally and are found not to be as effective as desired. Innovations in drug delivery systems have not only enabled the successful implementation of many of these novel pharmaceuticals, but have also permitted the development of new medical treatments with existing drugs. The creation of TDDS has been one of the most important innovations. This article provides an overview on various techniques and new antidiabetic approaches of TDDS.

Keywords: TDDS, Antidiabetic, Pharmaceuticals, Conventional route

INTRODUCTION

Transdermal drug delivery (TDD) is gaining prominence over other forms of drug delivery due to its potential advantages, including reduced systemic side effects, noninvasiveness, increased patient compliance, large area of interface, potential for continuous and controlled delivery[1,2]. Consequently, in recent years, numerous transdermal products have been introduced into the market. Current US market for transdermal patches is over $3 billion[3] and annual sales worldwide are estimated to be $31.5 billion by 2015. Diabetes is a disease in which the pancreas does not produce enough insulin or when the body cannot effectively use the insulin, a hormone that is necessary to convert sugar, starches and other food into energy needed for daily life. It is the most common endocrine disorder affecting around 2-3% of the population worldwide and its incidence is rising. In the year 2000, 150 million people world-wide had diabetes and is expected to double by this year. By 2030, the WHO estimates that the number of people with diabetes will almost double to 366 million[5].

More than 220 million people worldwide have diabetes and almost 80% of diabetes deaths occur in low- and middle-income countries. Currently available antidiabetic agents have relatively short half life, low bioavailability and poor retention, and undesirable side effects. It is a challenge for people with diabetes to keep track of their blood sugar levels and to maintain right amount of insulin throughout the day. However, the basal rate of insulin needed by diabetics is 0.5–1 mg/day. These drawbacks give researchers tremendous opportunities to design and develop novel drug delivery systems to overcome the transport barriers, inherent elimination and metabolism problems associated with these antidiabetic drugs. Therefore, the search for more effective and safer hypoglycaemic agents has

continued to be an important area of active research[6,7,8].

Hence, TDDS are ideally suited for disease that demands chronic treatment. In this review various techniques and strategies are subjected with some anti-diabetic agents of both therapeutic and prophylactic usage.

Historical Perspectives: Transdermal patches were introduced in the late 1970s, starting with a three-day patch to treat motion sickness. In 2001, 51 out of 129 drug delivery products under clinical evaluation in the U.S. were transdermal or dermal systems[5,9]. Still, only few drugs are presently available with transdermal patches **(Table 1.1)**. The fundamental reason why so few drugs are used is that the barrier property of the skin limits the use of patches to therapeutics, where the molecule size is small enough to diffuse through the skin at therapeutic rates.

TRANSDERMAL DELIVERY

Over the past few decades, the skin has generated a great deal of interest as a portal for the systemic delivery of drugs[10]. The potential advantages of this mode of administration have been well documented[11]. The worldwide transdermal market is currently worth more than US$ 4 billion, yet is based on only few drugs (table 1.1). This rather limited number of transdermal drugs is explained by the skin's excellent barrier function, which is accomplished entirely and quite remarkably by the outermost few microns of tissue, the stratum corneum: often referred to as a "brick and mortar" structure[6].

The barrier function of the stratum corneum (SC) is essential to maintaining internal homeostasis; it can be a major impediment to drug penetration. The stratum corneum exhibits low permeability, with a uniform thickness that varies from 8.8-30.9 microns across domestic animal species **(Table 1.2)**[12]. In addition to being pharmacologically potent, a therapeutic agent must possess a balance of physicochemical properties that render it permeable: a relatively low molecular weight (<500Daltons), a moderate octanol-water partition coefficient (10 <Ko/w<1000), reasonable aqueous solubility (>1mg.ml-1) and modest melting point (<200°C)[13].
Before being taken up by blood vessels in the upper papillary dermis and prior to entering the systemic circulation, substances permeating through the skin must cross the stratum corneum and the viable epidermis. There are three possible pathways leading to the capillary network: across the continuous stratum corneum (SC), through hair follicles and their associated sebaceous glands, or via sweat ducts. Although, the diffusion distance across the SC is no more than 10-15µm, the actual pathway of diffusion may be up to 50 fold greater, depending on the route taken **(Fig.1.1)**. While crossing the viable skin layers, drugs can undergo extensive enzymatic degradation[14],[15] numerous proteases (including endopeptidases and exopeptidases) have been detected in the skin, both in the dermis and the epidermis[16],[17].

ENHANCEMENT STRATEGIES FOR TRANSDERMAL DELIVERY

There are two main approaches available to the formulation scientist: (a) the use of chemical enhancers to transiently modify the SC permeability (*i.e.* render the SC more "leaky" towards hydrophilic molecules), and (b) modification of the therapeutic molecule to render it more hydrophobic and therefore "acceptable" to the membrane. The latter strategy involves either chemical derivatization, or encapsulation within a lipophilic core **(Fig 1.2)**.

Chemical penetration enhancers: Different chemical additives have been tested to enhance transdermal penetration. These compounds can increase skin permeability by different mechanisms, including enhancing solubility, increasing partitioning into the SC, fluidizing the crystalline structure of SC and disrupting or altering the ordered lipid structure of the SC. Although exact mechanisms have not been clearly elucidated, it is believed that they will have multiple effects once absorbed into the SC. Different class of penetration enhancers, including surfactants e.g., tween[18], fatty acids/esters e.g., oleic acid[19], terpenes e.g., limonene and solvents e.g., dimethyl sulphoxide, ethanol, urea, unsaturated cyclic ureas, are developed during the past two decades. However, only few chemical enhancers have been shown to induce significant enhancement of drug transport. Our earlier work suggested that formulation of Captopril matrices were found better when it combined with penetration enhancers[20]. With limited success, attempts have made to synthesize novel chemical penetration enhancers e.g. lauracepram (Azone), 2-n-nonyl- 1,3-dioxolane (SEPA) and a silicon-based transdermal penetration enhancer that safely achieve therapeutic transport enhancement and expected to show a low irritation to the skin[21,22].

Chemical modification: Improved intestinal absorption through chemical modification with various fatty acids has been reported, the application of this approach to TDD is quite new. A few

research groups have studied the cutaneous delivery of derivatives of peptides such as the vasoactive intestinal peptide and interferon. The absorption of palmitoyl derivatives of interferon p-IFN into the viable layers of human breast skin was eightfold greater compared to the parent peptide, suggesting that this approach might find an application in topical delivery[23,24].

***Encapsulation technologies*:** Encapsulation consists of the entrapment of drug within delivery systems such as microspheres, liposomes and nanoparticles. Liposomes, typically consisting of phospholipids and cholesterol, are thermodynamically stable vesicles with an aqueous core and at least one surrounding bilayer. Niosomes, analogues of liposomes, are non-phospholipid vesicles formed by the self-assembly of nonionic surfactants in an aqueous dispersion. Niosomes and classical liposomal systems have been found to be effective in forming drug reservoirs in the upper layers of the skin, for local therapy. The controlled topical delivery of cyclosporin A and interferon has been studied[25,26].

ENERGY DRIVEN METHODS

***Iontophoresis*:** This technique developed to deliver charged molecules through the skin at an enhanced rate via application of a small electric current (0.5 mA/cm2). The drug reservoir on the surface of the skin is in contact with an electrode of the same charge as the solute, connected to a grounding electrode and a power supply. In addition to electromigration (direct effect of the applied electric field on the charged species), and current-induced modification of passive skin permeability, positively charged compounds (present in the anodal compartment) benefit from a third transport mechanism called electroosmosis, a convective solvent flow which is a consequence of the skin's net negative charge at physiological pH. This flow also enhances the transport of neutral compounds[27]. Iontophoresis was used to facilitate and regulate the transdermal delivery of insulin in order to control blood glucose levels in diabetic rats. It was found that a considerable reduction in blood glucose levels can be achieved by a lower current intensity and shorter application time, using a pulse current instead of simple direct current[28]. Sibalis and Rosen suggested an apparatus and method for the iontophoretically mediated transdermal delivery of insulin[29]. Henley discloses an ionosonic apparatus suitable for the ultrasonic- iontophoretically mediated transport of therapeutic agents across the skin[30,31]. Brange *et al*, also suggested chemically modifying insulin to produce insulin analogs that resist intermolecular association and enable improved iontophoretic delivery[32]. *In vitro* skin permeation studies in diabetic animals suggested that the systemic bioavailability of peptides and proteins, as well as the pharmacodynamic responses, are dependent upon the electronic variables of the iontophoretic delivery device, e.g. waveform, frequency, on/off ratio and intensity of the current applied, physiochemical parameters, e.g. pH and ionic strength, as well as physiological variables, such as treatment of the stratum corneum[33].

Electroporation: Electroporation involves exposure of the skin to relatively high voltages (approx. 100-1000 V) for short times, typically 1 to several hundred milliseconds, which create intense electric fields across the thin stratum corneum. Molecular transport through transiently permeabilized skin is thought to result from a variety of mechanisms: enhanced diffusion through the aqueous pathways produced in the lipid bilayers, electrophoretic movement (for charged species) and, to a small extent, electroosmosis[34].

The electrotransport device patented by Southam *et al*, utilized a silver foil anodic electrode laminated to one surface of the gel. Using a direct current of 200 mA the flux of fentanyl was observed to increase over the first 8 hr after which it remained constant. Further, the flux decreased if the concentration in the device fell below 6 mg/ml. However, application of 240 mA current density for 10 min was observed to deliver 40 mg dose and 80 such doses could be delivered over 24 hr[35]. The effect of electroporation (EP) on the *in vivo* percutaneous absorption of human insulin was evaluated in rats. Marked decreases in blood glucose levels reflecting the increases in the plasma concentration of insulin was observed after EP treatment[36].

Sonophoresis: Sonophoresis is defined as the movement of drugs through intact skin and into soft tissue under the influence of an ultrasonic perturbation. Low-frequency ultrasound (frequencies below 100 kHz) has been demonstrated to induce the greatest transdermal transport enhancement[37]. Numerous studies have been devoted to understanding the mechanisms of sonophoresis[38,39,40,41]. Tachibana *et al*. reported that application of sonophoresis (48 kHz) enhances transdermal transport of insulin across hairless mouse skin in vivo. They also showed that application of ultrasound enhanced transdermal insulin transport in rabbits[42].

Photomechanical Waves: Photomechanical waves (PW) are broadband compressive waves generated by intense laser radiation[43]. A PW delivery device consists of a drug reservoir backed with a laser target material (e.g., polystyrene). This system is placed on the skin and the laser is applied to the target. The energy of the laser is strongly absorbed by the target, resulting in the formation of photomechanical waves which are hypothesized to transiently permeabilize the stratum corneum. Drug diffuses passively through the channels momentarily created. The mechanism of channel formation remains to be elucidated, but it is known that the effects of PW are due to mechanical forces[44]. The PW delivery of insulin through the skin of diabetic rats was shown to cause reductions in blood glucose of around 80±3%, and was maintained below 200mg/dl for more than 3 hours[45].

HEAT-ASSISTED DRUG DELIVERY

Controlled Heat-Assisted Drug Delivery is the basis of an innovative patch consisting of a layer containing a heat-generating chemical component and a perforated cover membrane. When the package is opened, air flows at a controlled rate through the holes in the cover membrane into the heating mixture and initiates a chemical reaction that spontaneously produces heat. Heat generated within the patch increases skin temperature and thereby drug penetration rates across the skin. According to the manufacturers, the temperature and duration of the reaction can be controlled by the size and number of holes in the cover membrane and the precise composition and quantity of the chemical components[46].

MINIMALLY-INVASIVE SYSTEMS

This technique recently reviewed by Down and Harvey[47] which have been designed, to "by-pass" the skin barrier without blatant SC removal. Microneedles and velocity-based injectors, offer drug delivery platforms that may be suitable for higher MW drugs because of their ability to breach the SC.

Microneedles: These microneedle arrays are applied to the skin surface to pierce the epidermis, creating microscopic holes through which molecules can be transported to reach the upper dermal layers and have been described as painless, inducing neither erythema nor edema[48]. These techniques have been used to deliver insulin *in vivo* in diabetic rats. McAllister *et al*[49] demonstrated a 70% reduction in blood glucose 5 hours after a 30-min microinfusion of insulin at a pressure of 14 psi using this technique.

Velocity-based technologies: This technology offers a high-velocity jet (>100 m/s) that penetrates the skin and delivers drugs into the epidermis, intradermally, subcutaneously, or intramuscularly by means of a compression spring or compressed air[50].

STRATUM CORNEUM ABLATION

The simplest method for overcoming the barrier imposed by the stratum corneum is to remove it. This can be achieved, for instance, by repeated application of adhesive tape to the skin surface. However, for a number of reasons - including those of convenience, reproducibility, and patient compliance, it is difficult to envisage the routine clinical use of such an approach. Laser-assisted ablation and SC ablation by suctioning are perhaps more realistic approaches but are also likely to be associated with patient compliance issues.

Suction ablation: Suction ablation uses a vacuum to produce a small blister (5-6 mm in diameter), the upper surface of which is excised to reveal a portal for entry of drugs into the dermal circulation. However, the vacuum removal of the epithelium caused pronounced hyperaemia in the de-epithelialised dermis and the sites showed slight fading pigmentation even 3 months after treatment, suggesting that this procedure may not be appropriate for the treatment of chronic disease[47].

Laser ablation: In this approach, the high energy of the laser creates pores in the skin that permit the transit of drug through the SC for example, from a topically applied patch or gel. There are two optimal wavelengths at which skin ablation can be achieved: a wavelength absorbed by tissue proteins (2940 nm) and one absorbed by tissue water (mid-infrared; 2790 nm). During laser irradiation, the energy is absorbed by the components of the skin in the form of vibrational heating[47].

Radiofrequency thermal ablation: This technique has only recently been adapted for use as a physical method to enhance drug transport across the skin and well known for electrosurgery and ablation of malignant tissues. A closely spaced array of tiny electrodes is placed against the skin while an alternating current at radio frequency is applied to each of the microelectrodes. This forms microchannels in the outer layer of the skin through the ablation of cells[51].

Microscissioning: Microscissioning entails the use of sharp particles to scize defined areas of the skin. Techniques using a combination of momentum transfer and scizing are well known in cosmetic dermatology. The relatively hard, roughened stratum corneum and epidermis resulting from aging processes can be removed by moderate velocity, sharp particles impinging obliquely against the skin surface[52].

AVAILABLE ANTI- DIABETIC TRANSDERMAL THERAPEUTICS

Drug delivery strategies for diabetes have included a wide range of scientific and engineering approaches, including molecular design, formulation and device design. Passive diffusion through the outer layer of skin has been used successfully for the delivery of low molecular weight lipophilic drugs such as scopolamine, estradiol and nitroglycerine but has been largely unsuccessful for the transdermal delivery of hydrophilic peptides such as insulin due to the low skin permeability of such peptides. Various routes for insulin delivery that have been investigated include intrapulmonary[53,54,] intrauterine[55,56] ora, ocular, nasal, buccaland transdermal systems l[54,56-66]. Insulin has a tendency to form dimers and hexamers in pharmacological compositions, which are considered to be too large for transdermal delivery. Some studies indicated the problems related to poor absorption, high proteolytic degradation, and variable delivery times. Consequently, bioavailability is low, and response times are difficult to predict accurately[54,63,65].

Many oral hypoglycemic agents, such as biguanids and sulfonylureas are also associated with side effects and fail to significantly alter the course of diabetic complications[67,68]. The oral delivery of drug or large biogenic molecules such as peptides or proteins is difficult because they are completely degraded in the GI tract. This leads to increasing demand for non-invasive delivery of antidiabetic drugs with fewer side effects[56] **(Table 1.3)**.

King et al.,[74] employed Biphasix transdermal system successfully delivered insulin transdermally, found significant sustained decrease in blood glucose in diabetic rats with a corresponding increase in serum insulin. Furthermore, Liposomes, transferosomes and ethosomes also have the potential of overcoming the skin barrier and have been reported to enhance permeability of drug through the stratum corneum barrier[75].

Delivery of insulin by transferosomes is the successful means of non invasive therapeutic use of such large molecular weight drugs on the skin[76]. Insulin is generally administered by subcutaneous route that is inconvenient. Encapsulation of insulin into transferosomes (transfersulin) overcomes these entire problems. After transfersulin application on the intact skin, the first sign of systemic hypoglycemia are observed after 90 to 180 min, depending on the specific carrier composition[77,78].

Ethosomes are the ethanolic phospholipid vesicles which are used mainly for transdermal delivery of drugs. Ethosomes have higher penetration rate through the skin as compared to liposomes hence these can be used widely in place of liposomes[79]. The increased permeation of ethosomes is probably due to its ethanolic content. Ethanol increases the cell membrane lipid fluidity which results in increased skin penetrability of the ethosomes. These ethosomes permeates inside the skin and fuse with cell membrane lipids and release the drug. Hot and cold methods are used for formulation of ethosomes. Evaluation parameters include size, shape, drug content, zeta potential etc. Ethosomes have been successfully evaluated for the delivery of many drugs for e.g. Cyclosporine A, insulin, salbutamol etc[80,81].

Trotta et al.[82] reported that solid lipid microparticles also appear to have interesting possibilities as delivery systems for oral administration of insulin. The feasibility of using liposomes as potential oral delivery systems for the systemic delivery of insulin has also been studied. Moufti et al.,[83] were able to produce a 50% reduction in blood glucose levels in normal rats by an insulin-containing liposome. Dobre et al.,[84] also illustrated a lowering of blood glucose levels in normal rats following the oral administration of insulin entrapped in phosphatidylcholine/cholesterol liposomes.

A viable non- injectable insulin delivery route would thus dramatically improve both compliance and quality of life in patients with diabetes. Some recent studies have shown that ultrasound mediated transdermal insulin delivery offers promising potential for noninvasive drug administration[29] (**Table 1.4**).

CONCLUSION

This article provides valuable information regarding the strategies used in transdermal drug delivery systems and antidiabetic approach of this novel drug delivery system. The proliferation of research activity in the field of TDD serves to highlight the pressing need for alternatives to the conventional invasive administration of drugs via needles and syringes.

Noninvasive insulin deliveries are now in development. In the future, patients with diabetes will receive insulin in optimal quantities at optimal times by way of optimal routes into the body because of needle-free routes of administration in order to achieve optimal blood glucose control. These new technologies will facilitate proper treatment of diabetes and improve the lives of diabetic patients. The ultimate goal for the treatment of diabetes remains the development of a fully automated glucose-controlled device. However, regardless of how attractive any new drug delivery concept may appear to be, it must not only deliver therapeutically realistic levels of drug to the target site, but also prove its clinical superiority over conventional injections with respect to long-term safety, patient compliance, ease-of-use, impact on protein quality (physical, chemical and biological stability) and of course, commercial viability (high manufacturing costs would result in a non-viable product). This approach of drug delivery also found more suitable for chronic disease like diabetes by constantly delivering therapeutic amounts of drug for prolonged periods. Furthermore, its evaluation process details as a ready reference for the research scientist who are involved in TDDS. The foregoing shows that TDDS have great potentials, being able to use for both hydrophobic and hydrophilic active substance into promising deliverable drugs. Therefore, this alternative route may be a good choice to deliver the drug directly into systemic circulation through intact skin by bypassing the hepatic first-pass effect to reduce dose frequency by maintaining a prolonged therapeutic blood level of antidiabetic drugs.

Abbreviations

PMM- Polymethyl methacrylate, EC – Ethylcellulose, DBP- Dibutyl phthalate, PEG-Polyethylene glycol, PEG-Polyethylene glycol, PVP-polyvinylpyrrolidone, ERL- Eudragit RL-100, ERS-Eudragit RS-100, DBP- di-n-Butyl phthalate

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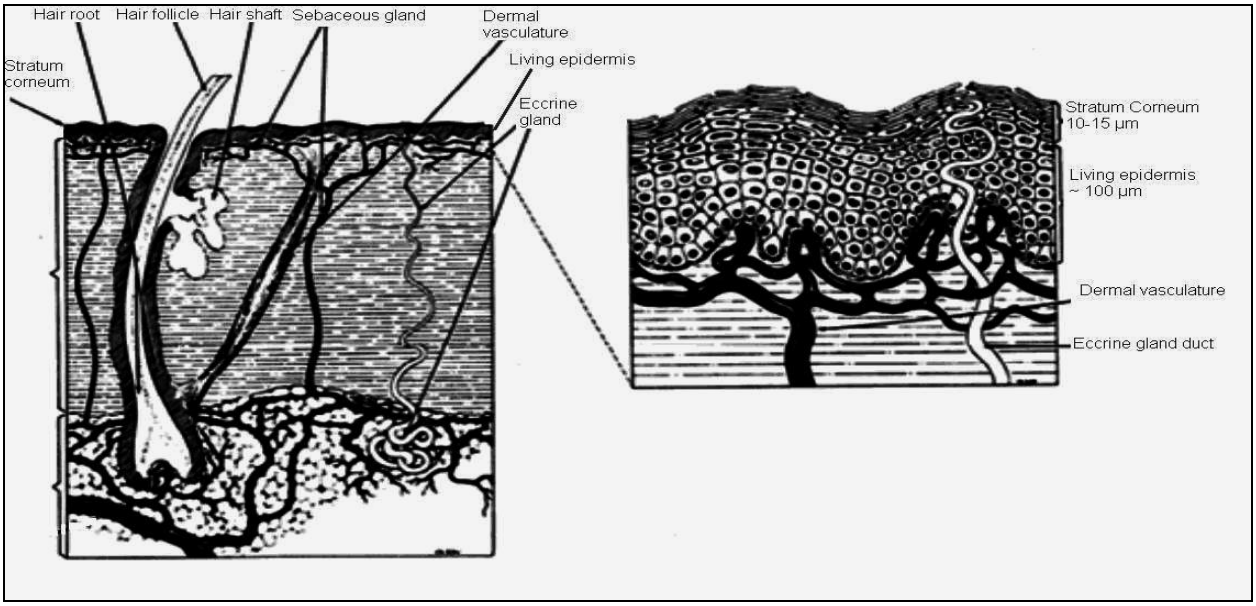

Figure: 1.1 Microscopic structure of skin

Table 1.1: FDA- approved transdermal patches

Drug	Product name	Clinical indication	Manufacturer
Buprenorphine	BuTrans®/ Norspan	Opioid painkiller	Napp Pharmaceuticals
Clonidine	Catapres TTS®[a]	Hypertension	Boehringer Ingelheim
Diclofenac diethylamine/Diclofenac epolamine	NuPatch 100 Fletor®	Anti Inflammatory Analgesia	Zydus Cadila, Inst Biochem
Epinephrine/Lidocaine hydrochloride	Iontociane® Lidosite® Topical System	Analgesia/Dermal analgesia	Iomed Vyteris
Estradiol/ Norethindrone	Alora® straderm®[a] Menostar®, CombiPatch®	Hormone replacement therapy Hypogonadism	Alora, Novartis, Estraderm[a] Menostar
Estrogen/Progesterone	Nuvelle TS/ Fematrix	Hormone replacement therapy/ Postmenstrual syndrome	Ethical Holdings/Schering/ Ethical Holdings/Solvay Healthcare Ltd
Fentanyl/Fentanyl hypochloride	Duragesic® a Ionsys®	Pain relief/Analgesia	Ortho McNeil Alza/Janssen[b]
Granisetron	Sancuso®/ProStrakan	Prevent nausea and vomiting	Aveva Drug Delivery Systems Inc/ ProStrakan Inc
Lidocaine hypochloride	Lidoderm®	Post-shingles pain/Analgesia	Endo, Teikoku Pharma USA
Methylphenidate	Daytrona ®	Attention Deficit Hyperactivity Disorder	Shire
Nicotine	Habitrol® Nicoderm ® [a] Prostep® Nicotrol ®	Smoking cessation	Novartis, GlaxoSmithKline Elan, McNeil [b] Sanofiaventis, Aveva
Nitroglycerine	Minitran ®, Nitro-Dur ® Transderm Nitro ® [a] Nitradisc, Nitroglycerin Generic	Angina	3M, Schering-Plough, Novartis, Rorer
Norelgostromin/ Ethinyl Estradiol	Ortho Evra ™	Postmenstrual syndrome	Ortho- McNeil [b] Janssen
Oxybutynin	Oxytrol ®	Overactive bladder/Incontience	Watson Labs
Rivastigmine	Exelon®	Alzheimer, Antiparkinsonian	Novartis
Rigotine	Neupro ®	Early-stage idiopathic Parkinson's disease	UCB and Schwarz Pharma
Selegiline	Emsam ®	Depression	Somerset
Scopolamine	Transderm Scop ® [a]	Motion sickness	Novartis
Testosterone	Androderm ® Testroderm ® [a]	Hypogonadism	Watson Labs ALZA [b]

Table 1.2: Stratum corneum thickness for several species

Species	Stratum corneum thickness (µm)
Hairless mouse	8.8
Hairless rat	15.4
Guinea pig	18.6
Dog	19.9
Pig	17.5
Human	18.2
Sheep	31.4
Cattle	30.9

Table 1.1: Some Investigational studies on Transdermal patches consisting anti-diabetic activity

Polymers	Drug	Mol. wt	Melt. Point	Solvents	Plasticizer	Penetration Enhancers	Ref.
HPMC: Chitosan: Eudragit RL100	Gliclazide	323.4	181°c	DCM: Ethanol (50:50)	Triethyl citrate	Propylene glycol and Oleic Acid	(Shinde,Shinde, and More, 2010) [69]
Duro-Tak 387-2516: Duro- Tak 87-2852	Rosiglitazone	357.42	123°C	Ethyl acetate : Isopropyl alcohol: Toluene: n- hexane (12:6:1:1)	-	PEG	(Damodharan *et al*, 2010)[70]
HPMC	Glibenclamide	494	172°c	Acetone/ IPA/ Ethanol (50:30:20)	DBP	Isopropyl myristate	(Mishra, Debajyoti, and Bhakti, 2009)[71]
EC:PVP and ERL: ERS	Glibenclamide	494	172°c	chloroform	DBP	Propylene glycol, Transcutol, Tween-20, Polyethylene glycol, N-methyl-2- Pyrrolidinone, Geraniol, Citral, Eugenol,	(Mutalik and Udupa, 2004)[72]
PMM:EC ethylcellulose	Glibenclamide	494	172°c	chloroform	DBP	-	(Sridevi *et al*, 2000)[73]

Table 1.4: A list of transdermally delivered insulin using ultrasound devices

Compound	M.W	Preparation	Frequency	Device	Investigator
Insulin	5807	*In vitro* human, *in vivo* rat	20 kHz	Sonicator[1]	(Mitragotri, Blankschtein and Langer, 1995)[85]
Insulin	5807	*In vivo* rat	20 kHz	Sonicator[1]	(Boucaud *et al*, 2000)[86]
Insulin	5807	*In vivo* rat	48 kHz	LAG-26[2]	(Tachibana and Tachibana, 2001)[87]
Insulin	5807	*In vivo* rabbit	105 kHz	LAG-26[2]	(Tachibana, 1992)[88]
Insulin	5807	*In vivo* rabbit	105 kHz	US tranducer[3]	(Tachibana, 1992)[88]
Insulin	5807	*In vitro* human	20 kHz	Sonicator[4]	(Zhang, Shung, and Edwards, 1996)[89]
Insulin	5807	*In vivo* rat	20 kHz	Sonicator[1]	(Boucaud *et al*, 2002)[90]
Insulin	5807	*In vitro* human	20 kHz	Cymbal TDR	(Smith *et al*, 2003)[91]
Insulin	5807	*In vivo* rat	20 kHz	Cymbal TDR	(Lee, Newnham, and Smith, 2004)[92]
Insulin	5807	*In vivo* rabbit	20 kHz	Cymbal TDR	(Lee *et al*, 2004)[93]

Legend

1. *VCX 400, Sonics and Materials Inc., Newtown, CT*
2. *Leader Electronics Corp., Japan*
3. *Transducer company not indicated*
4. *W-385, Heat Systems Ultrasonics, Inc.*

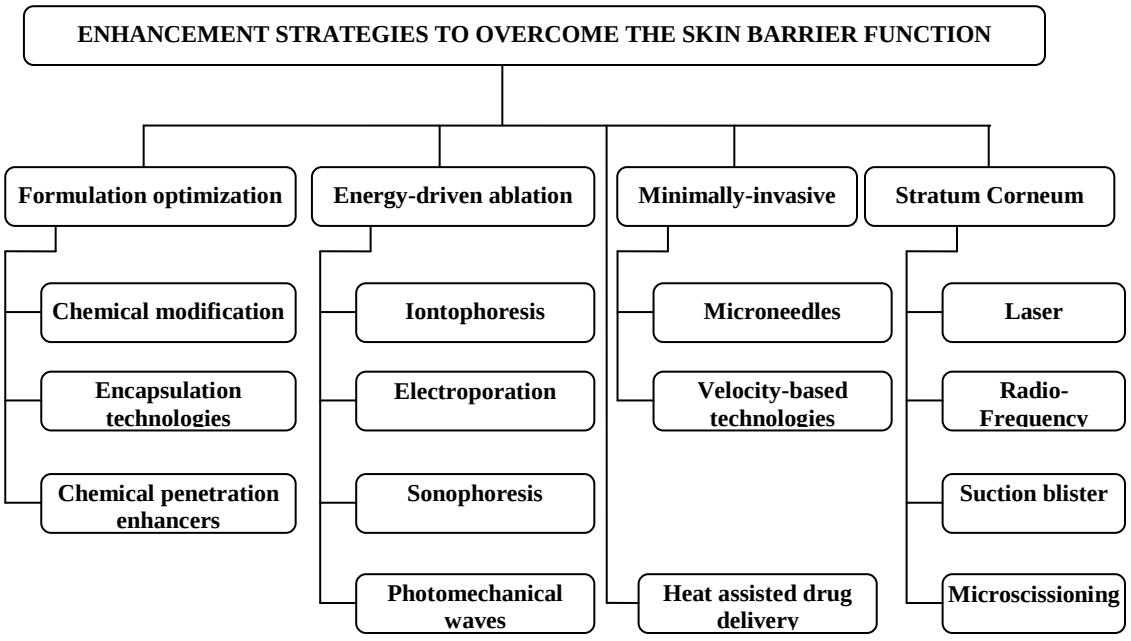

Figure 1.2: Flow chart of current strategies for TDDS

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