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Approaches and advances in transdermal delivery of insulin -A Review

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ABSTRACT

Even today the most preferred delivery of drugs is still through oral route but because of some inherited limitations with this route, various other routes have been explored including transdermal. Delivery and complete absorption of the drugs is the major concern these days due to various reasons including poor solubility and incomplete bioavailability, this could be due to incomplete presystemic absorption or presystemic degradation. Transdermal drug delivery system is the method by which the drug absorption occurs through the skin primarily for its systemic effect. It provides better therapeutic efficacy and safety for the administration of insulin. Most of the oral anti-diabetic drug exhibit low bioavailability and hence a poor patient compliance. Hence, it can be used as better site for delivery of numerous drugs including proteins and peptides such as insulin.

Keywords: Insulin; transdermal delivery; antidiabetic drugs; bioavailability

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INTRODUCTION

Diabetes mellitus is one of the major wide spread disease across the world leading to huge economic loses. Diabetes affects all ages of patients like adolescents and geriatric patients[1]. Type1 diabetes relies on exogenous delivery of insulin because of impaired insulin secretion by beta-cells of pancreas[2]. In traditional practice glycemic control is achieved by sub-cutaneous injections, which are very painful and invasive technique, hence the poor patient compliance[3]. Transdermal method of approach will not only provide convenience and painless administration but also potentially maintain long lasting effect by keeping the plasma drug concentration in the therapeutic range[4].

Transdermal drug delivery system is a self contained system in which the medication is administered topically through the intact skin to deliver the drug to systemic circulation, at a predetermined and controlled rate while maintaining the therapeutic efficacy of drug and with reduced side effects[1]. But the use of method is limited because of the highly selective layer called stratum corneum, which is not sufficiently permeable. But these issues can be easily overcome by use of delivery devices like patches, micro-needle, transfersomel gels, etc. The penetration can also be increased to great extent by the use of penetration enhancers like Dimethyl sulphoxide, propylene glycol, azonoes[5].

Advantages:

It include,

- It avoids first pass metabolism.
- It improves patient compliance, as it is non-invasive and painless.
- Transdermal medication provides a steady infusion of a drug over a prolonged interval of time.
- Therapeutic failure due to intermittent dosing can be avoided.
- There is no interference with the gastric and intestinal fluid.
- Therapeutic value of many drugs is increased as transdermal route avoids problem like gastric irritation, lower absorbance and metabolism.
- It maintains constant and controlled level of drug in body for long time[18].

Disadvantages-

- Drugs having large molecular weight are not suitable for transdermal delivery. Drug below 800 -1000 Dalton are ideal candidate.
- There are chances of local irritation at site of application.

- Hydrophilic drugs are having low penetration through skin.
- Barrier function of skin changes from one site to another or from person with different age.

Figure 1: **Microneedles**

TRANDERMAL DELIVERY THROUGH SKIN

The skin work as a physical barrier and a receiver of external stimuli such as pain. The skin consists of 3 main sections;

- The epidermis,
- Dermis,
- Hypodermis, or subcutaneous tissue

The outer part, epidermis, is approximately 100 µm thick and consists of a main barrier part, stratum corneum, where stacked, dead cells are continuously replaced by outward moving, new cells produced in the more basal layer[3]. This is the most important layer for transdermal delivery as its composition allows it to keep water within the body and foreign substances out[6].

Dermis: The dermis is the inner and larger (90%) skin layer, comprises primarily of connective tissue and provides supports to the epidermis layer of the skin. The boundary between dermis and epidermis layer is called dermal-epidermal junction, which provides a physical barrier for the large molecules of drug and cells. The dermis incorporates blood and lymphatic vesicles and nerve endings[1].

Hypodermis: The hypodermics are the adipose tissue layer, which is found in between of dermis and Apo neurosis and fasciae of the muscles. The subcutaneous adipose tissue is structurally and functionally well integrated with the dermis through the nerve and vascular networks. The hypodermis layer is composed of loose connective tissues and its thickness varies according to the surface of body. The transdermal permeation of insulin extensively investigated and several techniques were explored to reduce the skin barrier properties.

Penetration enhancers act by various mechanisms such as-

- Increased drug solubility (chemical enhancers),
- Optimization of the formulation (chemical modification, encapsulation within carrier systems),
- Increased diffusion coefficients (microdermabrasion, laser ablation, chemical and biochemical enhancers, ultrasound, electroporation, micro needles)
- Provision of additional driving force (ultrasound, iontophoresis, electroporation)[13].

RECENT APPROACHES IN TRANDERMAL DELIVERY OF INSULIN

Most recent approaches towards transdermal insulin delivery include: The conductive polymer nanotube transdermal patch, specifically designed for hydrophilic drugs and insulin[6];

- The iontophoresis treatment with liposomes encapsulating insulin
- The transferosomal (highly deformable vesicles) drug delivery system (gel) that has demonstrated prolonged hypoglycemic effect in alloxan -induced diabetic rats after transdermal administration;
- The dissolving polymer micro needle patches.

MICRONEEDLE PATCHES

This idea of micro needle was first proposed by the Prausnitz Lab at Georgia Institute of Technology in 1998. They reported the use of micro needles that are long enough to cross the stratum corneum, but short enough to not stimulate most nociceptors, which makes the technology minimally invasive and painless. They successfully describe the use of micro fabricated needles to enhance the drug delivery through skin[37]. Microneedle technology is based on combination of multiple needles within a patch to the micron dimensions. When the patch is applied to the skin either manually or using an applicator, microneedles with a length ranging from 100 to 1500 µm, transiently and painlessly perforate the stratum corneum (SC) having a thickness of 10-20 µm and penetrate through the epidermis to a depth of 70 to 200 µm[8,12] as mentioned in figure 2. Micro-channels thus formed are used to deliver the insulin through the skin. Both of the parenteral and micro needles introduced the insulin into the circulation without being passed through the body system but the main advantage of microneedles over the parenteral delivery is painless and fearless administration, enhanced availability and efficacy, avoidance of first pass metabolism[42]. Despite several advantages micro needle have certain disadvantages like dose accuracy because of variable designs and fracture of micro-needles inside the skin may cause toxicity.

Figure2a: Limited permeation due to lipid barrier of skin

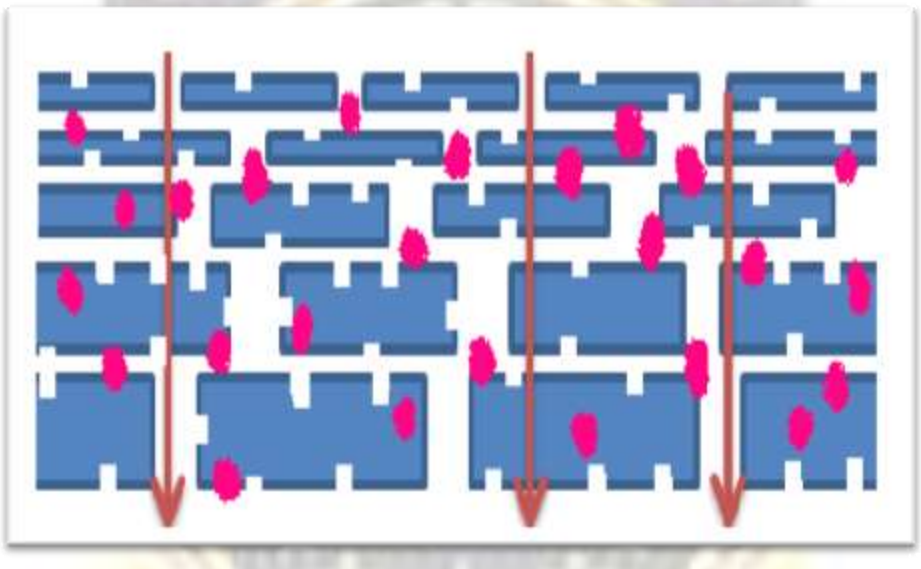

Figure 2b: Enhanced permeation by disruption of lipid barrier and cavitation by use of ultra sound

Aim of drug delivery with microneedles of insulin is through the skin rather than biological circulatory systems such as blood vessels or lymphatic vessels. Accordingly, the micro needle should not cause pain when they penetrate the skin, and should have sufficient length such that they can deliver drugs to the target site. In addition, the microneedles should also have excellent physical hardness so that they can easily penetrate the stratum corneum[39].

There are **four types of micro-needles**

1. Solid Microneedles
2. Hollow Microneedles

3. Coated Microneedles

4. Dissolving Microneedles

Solid microneedles made up silicon wafer were used in first study to demonstrate the micro needle for transdermal delivery. It follows two approaches; first approach is "poke and patch" and "poke and release". In "poke and patch" skin is pretreated with solid microneedles than topical application of drug formulation or patch on microporated skin. In "poke and release" solid microneedle are coated with the drug and inserted into the skin. Solid microneedles are made up of dissolving/biodegradable type encapsulating insulin, kept in mild temperature conditions and use of organic solvents which provide better stability and effective delivery through the skin[42,38].

Hollow microneedles follow the "poke and flow" method to deliver the insulin. They provide faster active delivery of insulin as compare to solid microneedles. In coated microneedles drug to be delivered is coated on the surface of solid microneedle. And in dissolving microneedles the needle is made up of dis-solvable material, which encapsulates the drug[22].

METHOD OF FABRICATING BIODEGRADABLE SOLID MICRO-NEEDLES

It includes the following steps-

1. Coating of substrate surface with a viscous material for formation of biodegradable solid microneedles.
2. Bringing the surface of a frame having pillar patterns formed thereon, into contact with the surface of the coated viscous material.
3. Drawing the coated viscous material using the frame, while solidifying the viscous material.
4. Cutting the drawn material at a given position thereof, thus obtaining biodegradable solid microneedles[38].

In the beginning, microneedles were created using silicon etching technique. The arrays were comprised of needles 150 µm long and tapering from a base of 80 µm to as narrow as 1 µm tip. Due to the brittle nature of silicon, about 5% of microneedles were observed to break and remain in the skin, leading to loss of drug as well as a risk of toxicity or infection. To overcome these problems, small gauge metal and plastic micro devices that could be made into very short, sharp needles for penetration into upper skin layer are being developed for microneedle systems[18,35].

Microneedles Combined with Electrical Driving Forces:

This involves the combination of microneedles with electrical driving forces like electroporation or iontophoresis. This technique creates additional pore in the skin through which current is passed. Firstly the skin is treated with microneedles and than drug is applied by simultaneous iontophoresis for 4-6 hours[1].

ULTRASONIC TRANSDERMAL INSULIN DELIVERY

In earlier times ultrasound used for diagnostic imaging but Francis and William Fry developed the clinical use of ultrasound in 1950. They told that ultrasound could also be used for biological interaction for curative benefits. Their research was used for the development of ultrasound devices for noninvasive surgical treatment. Now ultrasound mediated transdermal drug delivery offers promising potential for noninvasive drug administration. Low frequency ultrasound has capacity to generate micro bubbles as sound energy is transferred into fluid media in tissue. This leads to the formation of negative pressure which is very large due to which bubble gets collapsed causes the

formation of water channels within the lipid by layer which causes the moment of hydrophilic drugs in stratum corneum[49,25] as shown in figure 2.

It is investigated that sonophores is helpful in enhancing the transdermal delivery of drugs using various frequencies in sonicators or therapeutic devices. Transdermal transport of insulin has been observed using 20 kHz commercial sonicators (VCX400, Sonics and Materials, Newtown, CT). For insulin many noninvasive insulin delivery is increasing. In studies 20-105kHz frequency found to enhanced the transport of insulin both in-vitro and in-vivo ultrasonic bath and transducer. The only limitation with ultrasound transdermal delivery of insulin is the large size and poor mobility of the ultrasound devices[31,38].

DESIGN OF A TRANSDUCER

Conventional transducers are piezoelectric and are able to develop same type of waveforms; they are not able to develop alternative waveform effect. When electric signal was given they generate sinusoidal waves,which is avoided in ultrasonic drug delivery. Now in transducers design and material is different as compare to old one, which are able to convert the electrical waveform to sonic waveform at same intensity and frequency in control device. These consist of primary and secondary waveform for insulin delivery to dermis[50,51,52].

ULTRASONIC TRANSDERMAL PATCHES

To make ultrasonic transdermal delivery system portable or wearable these ultrasonic patches come into existence. They are designed specifically for ultrasonic and other electronic delivery as the conventional patches may cause the problem of contamination of drug or denaturing through interaction with adhesive polymer. One of the examples of such ultrasonic patch is Patch-cap as shown in figure 3[50,48,19].

In this an absorbent pad is used to store the drug from ultrasound release from transducer coupler, the drug liberates from the cap into the skin. This cap contains the drug and it is disposable, this

design holds up to 150 units of insulin enough for two day supply for the diabetic patient. This patch cap is replaced in every 24 hours[44,51].

Figure 3: Patch Cap

TRANSFERSOMAL GELS

After many researches to pass the drug from stratum corneum still it become a problem to pass the drug efficiently across barrier function of skin. It leads for the development of one more interesting transdermal drug delivery system in which vesicular system is used. In this system transfersomes used, these are the artificial vesicles, which are more deformable as compare to liposomes. Transfersomes have good permeation because they have the ability to move in inter-cellular lipids of skin. This flexibility of transfersomes help to goes into the skin without any great difficulty of being rupturing the vesicles as shown in figure 4[53].

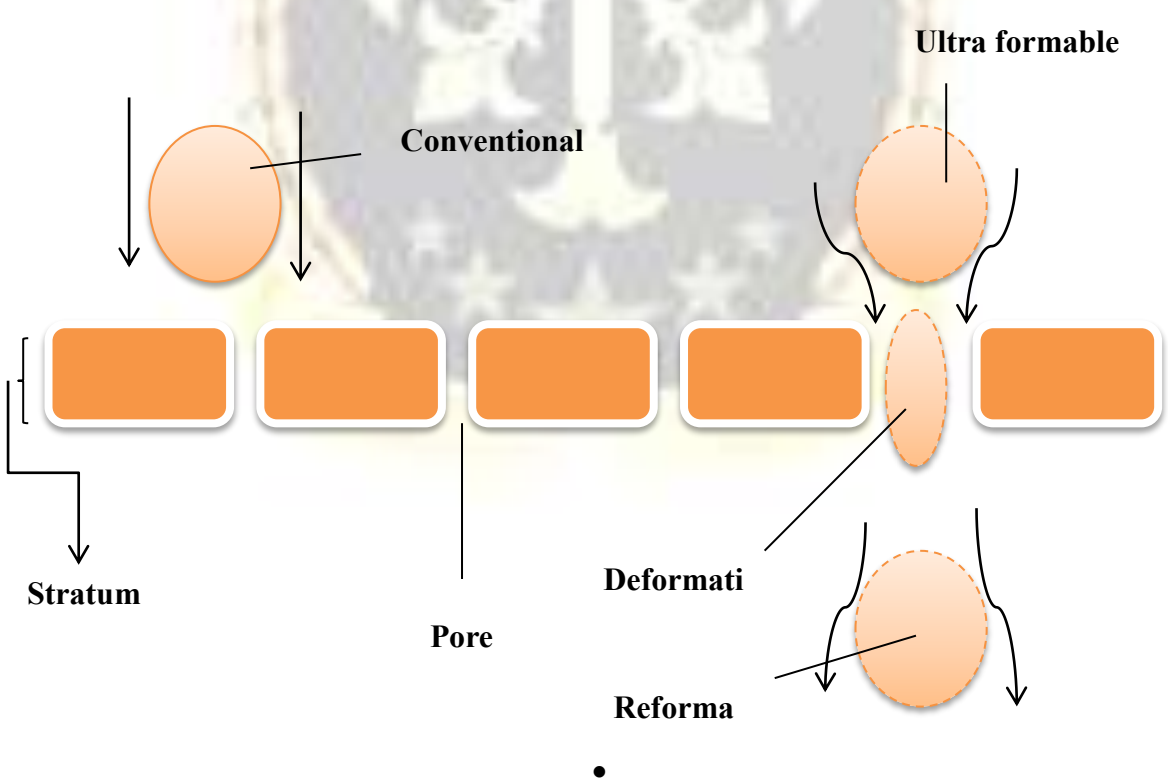

Figure 4: Delivery of vesicles through skin pore

Transfersomes provides different concepts for the delivery of insulin through skin. These transfersomes are metastable because of which the vesicle become flexible so that they cross the pores of stratum corneum easily. Thus, even sizes up to 200–300 nm can penetrate intact skin. This is because of great membrane adaptability that allows the transfersomes to penetrate through the pores. Transferosomal suspensions have low viscosity make it useful for transdermal delivery. Biocompatible gels have weak interaction with the surface-active agents due to which modification in the rheology is important. To improve the rheology the transferosomal suspensions is incorporated into gel matrix, which gives the formation of transfersomal gels, which shows promising results in the transdermal delivery[53,54].

PREPARATION OF TRANSFERSOMES

Reverse phase evaporation is one of the methods for the formation of transformers, which is mentioned in Yang ET AL., 2002. Soya lecithin and cholesterol lipids were taken in a beaker and than Tween 80 was poured into it and this mixture was dissolved in solvent mixture of dieter and chloroform in the ratio 3:1. Beaker was kept for 24 hours at room temperature until the formation of thin film. Than insulin solution of concentration 1.40mg/ml in water was poured onto the thin film. This film was fornicated before for 2 min at frequency of 20Khz. Film was hydrated, sodium deoxycholate in phosphate buffer of pH 7.4 was fornicated for 2min to form the transferal suspension. In each suspension chemical permeation enhancer was added and passed through Hauptmann filter paper and the suspension was transferred to 5% w/v methylcellulose gel and kept in cool and dark place.(as shown in figure 5)

It is difficult in case of insulin like large peptide to improve the permeability by increasing the concentration. Because of cost and physical stability. Stability is one of the difficulties with other conventional insulin therapies so transferal drug delivery system prove to be efficient in treatment of diabetes with maintaining blood glucose level[58,60].

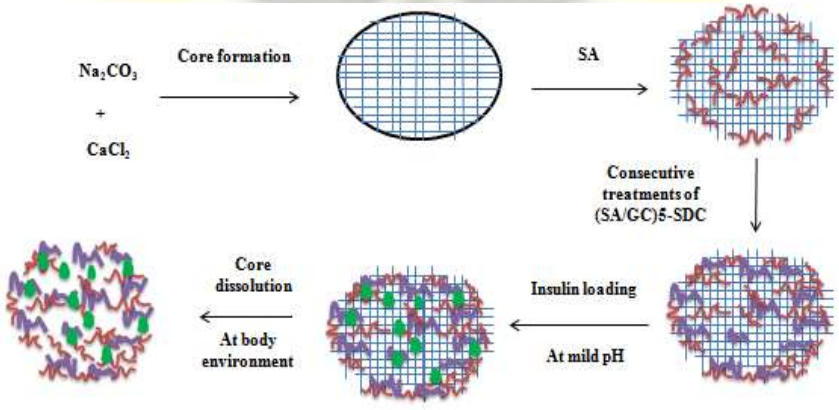

Figure 5: Schematic diagram for preparation of transfersomes

LIPID ENHANCED ELECTROPORATION

In electroporation the permeability of skin is increased by using single or multiple short duration pulses. When potential drop exceeds the membrane breakdown potential due to this pores are formed and get reseal. During this time material can cross through semi-permeable membrane. Through this process only small quantity can cross through skin. Electroporation creates the path directly through subcutaneous layer. It can pass only molecular size limit of <10 kDa. So it is desirable to increase this limit because many drugs including insulin are suitable for this delivery[62].Still work is going on to increase the limit by using keratolytic molecules (e.g., sodium thiosulfate, urea, and heparin)[29,61] simultaneously with electroporation, to enlarge the transport channels.

Table 1: Patents in transdermal delivery of insulin.

Publication number	Publication type	Application Number	Publication Date	Filing Date	Inventors
US6274166 B1	Grant	US 09/424,525	Aug 14, 2001	May 4, 1998	Amnon sintov, Uri wormser
US20120283332 A1	Application	US 13/504,799	Nov 8, 2012	May 12, 2010	Chase A. Scarbrough, Stanley S. Scarbrough, Jay shubrook
US5681580 A	Grant	US 08/448,235	Oct 28, 1997	May 23, 1995	Kwang kyun jang, Young Sig Oh
US20010033858 A1	Application	US 09/796,200	25 Oct 2001	28 Feb 2001	Jie Zhang

Table 2: Summary of technology mentioned in text

Serial no.	Technology mentioned
1	Microneedle technology
2	Ultrasonic transdemal delivery of insulin
3	Transfersomal gels
4	Lipid enhanced electroporation
5	Amidated pectin hydrogel matrix patch

Amidated Pectin Hydrogel Matrix Patch

Amidated pectin hydrogel matrix patches are there with different concentration of insulin. Study was carried out in streptozotocin (STZ)-induced diabetic rats. It is observed that pectin insulin containing patch increases the plasma drug concentration in streptozotocin (STZ)-induced diabetic rats[63].

CONCLUSION

It is evident that this route of delivery has obvious merits over other conventional drug delivery routes, as drugs from various drugs including peptides like insulin can be successfully

administered through this topical route using various techniques. Due to the high patient compliance and its novel approach this delivery system has a lot of potential also this process is scalable and easy to manufacture, hence this will give a boost to the future marketed products. Although still this technique has not been explored to its full potential and we are hoping to see a lot of work being done in the forth-coming years in this field.

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