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RECENT ADVANCEMENTS IN TRANSDERMAL DRUG DELIVERY SYSTEMS – AN OVERVIEW

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ABSTRACT

Great advances have been made on the development of Transdermal drug delivery systems (TDDS) various categories of drugs. Additionally, the system is suitable for drugs having considerable first pass metabolism. Properties of an ideal transdermal drug includes its mass, polarity and degree of lipophilicity. The present review highlights the current status of the developments and the emerging trends of this topical route of delivery. The various generations of this system include lipophilic substances; chemical enhancers and iontophoresis; microneedles, thermal ablation and electroporation. There is a lot of potential in the use of ionic and larger molecules if the stratum corneum becomes easier to penetrate. Microemulsions which are constituted of surfactants, co-surfactants, etc. are used as a vehicle, ensures effective absorption and penetration through the skin. Topical Film Forming Systems are also useful; they provide a transparent film and have an emollient and protective action. Microneedles have marked action for delivery in ocular tissues. Microneedles, by enhancing the skin penetration cause modification in techniques by which formulations are delivered in ocular sites. Powder Injectors, Liquid Jet Injectors and thermal micro ablations also constitute the emerging trends in this aspect. Liquid Jet Injectors remove the use of needles, as a high-speed jet is used to deliver the drug by puncturing the skin. Powder Injectors also uses a needle free powdered device, mainly used for temperature sensitive materials.

KEYWORDS: Stratum Corneum, Powdered Injectors, Liquid Jet Injectors.

INTRODUCTION

Skin

Skin can be regarded as one of the best sites of delivery of drugs. It prevents macromolecular degradation in the alimentary canal, is easily accessible and self administration is possible.

Skin can be considered as an essential route of drug administration for drugs producing systemic effects as well as for those producing local effects. Our skin provides an easy and convenient way for dermal and transdermal drug delivery systems. This is why the drug requires some important features and functions so as to cross the outermost barrier of the skin, which is the corneal layer or *Stratum corneum.*

Properties and Efficacy of Transdermal Drug Delivery

The composition of a drug delivery system includes a core material which contains the drug and a coating to this core made of hydrophobic matrix. The presence of this coating helps to prevent hydration and hence oxidation of the drug, thereby helps mask its original taste. An emulsifying agent, a fatty acid or wax and a glyceride are parts of the coating.

Certain important features which a drug administered transdermally must possess include: The weight of drugs must not exceed 1 kDa; must have high degree of lipophilicity and a definite polarity.

The efficacy of drug administered topically, depends largely on the physicochemical characteristics of drug, ability of patient to adhere to the treatment and the ability of delivery system to stay in contact with the skin, so as to enhance the percolation of drug through layers of skin.

Transdermal Drug Delivery

Transdermal Drug Delivery- Past and Present

The first transdermal drug was approved by the USFDA (US Food and Drug Administration) over 40 years ago. Presently, transdermal drugs are limited in scope to less than twenty clinical indications. Significant performance,

adequate cost issues and drug safety were important regarding transdermal drug products. Today, transdermal drugs have been flooded across the drugs multimillion revenue markets. From 2000 to 2014, around 2.5 new transdermal drugs were approved every year.

Conventional methods of Drug Delivery

The targeting of a drug to a particular body tissue or site of action has become a challenge for the world. This is because it is difficult to act at a target site by free drugs in traditional dosage forms and significant action may not be produced in stipulated time frame. To counter the situation, there was a need to introduce and research on the new drug delivery systems.

In earlier days, the major focus of transdermal drugs was on using the macromolecules, obtained from biological source. But presently, transdermal drugs with lower molecular weights are also permitted for transdermal drug delivery.

Peptides and proteins were not feasible through oral route as they undergo degradation in the gastrointestinal tract. Even passive transdermal drug delivery did not serve the purpose but active transdermal delivery was a promising alternative. These were also replaced due to short half life and hence demand for repeated administration.

Why is advancement required?

There are few drawbacks involved with the use of macromolecules which includes accidental needle sticks, needle phobia and pain. To counter these disadvantages associated with the use of macromolecules, lot of research and development has been done and micro scale devices like liquid jet injectors, powder injectors and micro needles were introduced.

Poor adherence to the skin, poor passage and permeability through skin are few problems related to the use of conventional formulation for dermal and topical preparations.

Emerging Trends

Emerging trends in Transdermal Drug Delivery

Commonly, microemulsions are used as the modern base or carrier for Transdermal drug delivery system. These are composed of appropriate amounts of ingredients which include surface active agents, co-surfactants, hydrophilic and lipophilic agents. Microemulsions are preferred as the vehicles as they can be easily prepared, remain stable for long time. They also have high solubilization capacity. After carrying out a number of studies and research, microemulsions proved to be an effective carrier system as medicaments incorporated in emulsion systems were well absorbed and penetrated through skin.

Another developing drug delivery systems includes topical film forming system, applied topically. These are used to form a thin and transparent layer or film, after getting adhered to the body and thus help deliver the active components to the body cells and tissues. Topical film forming systems have an emollient action. They also have protective action and can be used for penetration of medicament through transdermal route.

Microneedles have been shown to be beneficial for drug delivery in the ocular tissues. Transdermal drug delivery based on Microneedles improves the patient condition and also benefits the industry. The remarkable application of Microneedles is their ability to cause modification in the techniques by which therapeutic character and the formulations are delivered to ocular site.

Transdermal Drug Delivery in children

In the infants, the skin barrier function reduces the loss of water and also entry of chemicals and drugs via percutaneous route. Fentanyl, Clonidine, Scopolamine, oestrogens, nicotine and tulobuterol are few of the transdermal patches used in the children. On the contrary, the immature, less developed and rapidly changing function of skin barrier in infants is a challenge for transdermal drug delivery in children. It is unfortunate that this group of individuals suffer from lack of approved and authentic transdermal drug delivery.

Recent Advancements and Innovation

Various advancements have been made in transdermal drug delivery where skin acts as an excellent site for drug delivery. Drug delivery through skin offers various advantages such as accessibility, possibility of self-medication, immuno-surveillance and avoidance of the degradation of macromolecules in the gastrointestinal tract. Macromolecular drug delivery systems are generally carried out using hypodermic needles but due to their limitations alternatives have been developed which are still under extensive study and research. These include liquid jet injectors, microneedles, powder injectors and thermal microablation. All these microscale devices are the new trends for transdermal drug delivery.

Microneedles

Micron-scale needles are the latest advancements in transdermal drug delivery. The penetration of the drug through the skin is obstructed by the stratum corneum layer. The intended purpose of microneedles is to deliver the drug without stimulating the underlying pain receptors. The success of these needles has been seen especially for the delivery of macromolecules. The inability of most drugs to enter the skin at therapeutically useful amounts was in the past, the main limitation of transdermal drug delivery systems. But now, it is overcome by these needles which enhance the skin permeability to a large extent. Microneedles are available in a variety of shapes, sizes and materials.

Solid microneedles have been largely used which are said to enhance the skin permeability to a broad range of molecules and nanoparticles in vitro. For various studies, needle arrays are used to pierce holes into skin to increase the transport by diffusion or iontophoresis or as drug carriers which then release the drug from the microneedle surface coating into the skin. Hollow microneedles are also designed for the purpose of microinjection. The ratio between microneedle injection force and skin insertion force is optimal for needles with small radius of tip and large thickness of wall.

Delivery of oligonucleotides, glucose level reduction by insulin and induction of immune responses from protein and DNA vaccines are few of the applications.

Clinical use of microneedles constitutes acne vulgaris, acne scars, skin rejuvenation and hair growth. Microneedles are used for influenza vaccination, polio vaccination, and diabetes therapeutically.

Few developments in the research domain include the use of ceramic microneedles (CMs) and hollow microneedles (HMNs) for transdermal drug delivery. Several micro fabrication techniques such as micromolding, microreplication, photopolymerization, etching, modified LIGA, etc are also used to make these microneedle devices. Over the last twenty years, progress has been achieved in the development of porous ceramic microneedles into which medications can be incorporated at room temperature. This is a clinically useful process mainly for thermolabile compounds.

Micro-scale size endows have been introduced due to their various advantages over hypodermic needles, such as painlessness, minimal invasiveness and easier operation, but it may also lead to problem of mechanical failures, which necessitated the use of some other means for transdermal drug delivery, discussed hereunder.

Liquid Jet injectors

These work through a high speed jet of compressed springs or gases which puncture the skin and deliver the drug without any use of needle. They have been used to deliver a number of macromolecules such as vaccines and insulin and small molecules such as antibiotics and anesthetics. But these devices are characterized by bruising and bleeding along with pain which is due to the high and constant jet velocity.

Also they have poor reliability. These limitations can be overcome by the use of the injectors which are capable of controlling the dynamics of the jet velocity during a single injection pulse. The Temporal control of the jet velocity causes the independent control of penetration depth, by time adjustment at huge velocity, and delivered dose, by time adjustment at low velocity, in model materials. This dynamic control is accomplished by a piezoelectric actuator which accelerates a micron scale stream of fluid to velocities sufficient for skin penetration and drug delivery.

The dependence of jet penetration is on parameters such as nozzle diameter, velocity and jet power.

Several drugs such as insulin and growth hormone use the liquid jet injectors for administration.

Though the bioavailability is excellent for many drugs, problems like pain and bruising have reduced the acceptance and use of jet injectors. Thus we need to explore other alternatives.

Splash back phenomenon: It is an undesirable condition in which when the penetration is initiation on the outer skin by the high velocity jet stream causes the jet stream to ricochet backwards leading to the contamination of the nozzle.

Fluid Suck Back: It is a phenomenon according to which the blood, which is there on the nozzle of the jet injector is sucked back in the jet orifice, which contaminates the next dose.

Retrogade Flow: It is an undesirable phenomenon in which after the jet stream penetrates the skin and creates a hole, the pressure of the jet stream causes a backwards flow in which the jet spray, after mixing with tissue fluids and blood, shoots out of the hole, against the incoming jet stream and back into the nozzle orifice.

Powder Injectors

It is a new method for needle-free powdered injections via a bench-top gas-powered device. It is widely used as an alternative method for the delivery of temperature-sensitive materials. The device has interchangeable nozzles to vary orifice geometries and is capable of delivering polymer beads (1-5 µm diameters) into the dermal layer of porcine tissue. The bioavailability is affected by the gas pressure and the drug diameter.

This is extremely useful in patients with needle-phobia. The exact mechanism involved in the action of PIs is based on energy propelled system where a pressure or force is required to aid the penetration of drug across the skin. The energy applied for the drug administration through this route may be in the form of gas/air propelled, Lorentz force or shock waves. Light gas gun has a crucial role in the working of PI in which accelerating piston provides optimum velocity to the particle, after that by the means of a deacceleration pump particle leaves the piston which finally leads to the ejection of particles and administration at the targeted tissue site. The major limitations of this method are the complex procedure and extensive training in the handling of the equipment as well as it is expensive too.

Advantages and Disadvantages of Transdermal Drug Delivery (TDD) System

Advantages

→ This route of administration is convenient for the patients who can't take the drug by enteral route (oral, rectal and sublingual). i.e. those who are suffering from nausea, vomiting, diarrhoea and are feeling giddy or even unconscious. Similarly preferable for the patients who are not even able to take drug by routes other than enteral i.e. parenteral (IV, IM and SQ etc.) such as those who are not able to bear any kind of pain and have phobia of injection. For example: Transdermal patches of fentanyl, an opioid analgesic are available in market and suitable to administer to the cancer patients who have difficulty in swallowing or have some gastrointestinal disorder.

→ This route enhances the delivery of drug, at the location/site where it is needed because of the large skin surface area and at the same time has an additional advantage of maintaining the slow but sustained release of drug for a few days (1-3 days, usually) thus having a prolonged duration of action of administered medicament and thereby reduces the frequency of administering drug and leads to better patient compliance. As in the above given example of fentanyl patches there is no need to administer the drug frequently as the drug maintains a depot within the upper layers of skin before entering in systemic circulation and hence patch is required to be changed after every 72 hours (3 days). Similar results can be seen with transdermal administration of scopolamine which is used to treat the nausea and vomiting due to motion sickness. One patch applied at the mastoid region (skin behind the ear) is able to produce the effect for more than 72 hours. In the same way patients suffering from chronic diseases such as hypertension if use patches of clonidine then it reduce the chance of missing the dose and leads to better management of hypertension. Transdermal patches of nitroglycerin when administered to the patients, it treats the symptoms of angina in an efficient way and the nitroglycerin patches are given on alternate days with identical placebo patches.

→ This route is suitable for drugs which highly undergo the phenomenon of first pass metabolism (degraded in liver by hepatic enzymes and excreted from the body with a very little therapeutic effect) as the drug directly enters into the blood circulation, bypassing the portal circulation. If fentanyl patch is administered to the patient then the required dose of the drug to produce analgesia is comparatively very less than orally given opioid analgesics.e.g. Morphine which has a very high first pass effect. In the same way the patients who have a problem in liver or damaged liver then giving drug by this route will be safer and improve the patient's quality of life. As this can be seen in case of Estradiol patches used in Estrogen Replacement Therapy(ERT) in women suffering from the deficiency of this hormone in their postmenopausal life, who bypasses the portal circulation and reduces the load on liver than orally given drug.

→ Drugs given in the form of transdermal patches are less likely to produce toxic or adverse effects as there is a control release of the drug at the site of application and thus it takes time to drug to cross the plasma peak levels and to show to adverse effects. It also reduces the chances of fluctuations in plasma concentration of drug. Transdermal patches improve the patient's adherence to the drug treatment especially in case when he is under psychiatric treatment and taking psychotropic drugs or agents. For example Rivastigmine patches are available for the treatment of dementia of Alzheimer's type. Usually the patch is applied once in a day and thus improves the patient compliance who is already suffering from cognitive impairment.

→ It is a convenient route as after administration the health care professionals and other hospital staff don't need to visit frequently the patient and reduces the surveillance and thus leads to less costly treatment of the patient.

Disadvantages

→ The skin acts as a mechanical barrier and consists of various layers which have different physiological roles to maintain the homeostasis of the body and to provide physical protection from the outer environment. The stratum corneum which is the outermost layer, itself plays a major role in the passage of drug into the inner layers of the skin. This layer consists of dead cells which are heavily keratinised and hydration of this layer (also called horny layer) is one of the major factor which limits the absorption of drug through it. Thus to enhance the drug absorption an occlusive layer can be formed on skin so as to keep the skin hydrated, for this nonporous patches were developed but they have other demerits. eg. can lead to itching and promote the microbial growth.

→ The extent to which the drug gets absorbed through these patches also depends on various factor such as age, gender, location of the skin, skin temperature and skin lesions etc, and hence can lead to drug toxicity and adverse effects and problems related to therapeutic drug monitoring. For example high skin temperature improves the drug absorption as it increases the fluidity of the lipid content of the horny layer.

→ It has been proven that skin contains various metabolic enzymes which lead to the metabolism of drugs given topically. i.e. transdermally. However this metabolism by the skin enzymes is lesser in comparison to that of liver, it is nearly about 10-12 percent. However, it is not necessary the drug will only be metabolised by the skin enzymes, it can also be metabolized by the microorganisms which are common in case of skin infections. e.g. *Staphylococcus epidermidis occurs in skin boils and Propionibacterium acnes*, the causative agent of skin acne.

→ In case when skin is injured or damaged or a person is suffering from skin diseases. i.e. superficial skin conditions such as dermatitis, eczema, psoriasis then it can cause a reduction in natural physiological barrier of the skin. Similarly inflammation of skin which can be caused by various environmental factors. i.e. due to microbiological, mechanical (thermal or radiation) or chemical can affect the barrier nature of skin and thereby enhance the extent of penetration of drug through skin. Thus in such conditions it is not suitable to administer the drug through these patches as it can cause the over absorption of the drug and can lead to drug toxicity and resultant adverse effects. Hence, it limits the use of transdermal patches.

CONCLUSION

The approach of TDDS not only enhanced the drug's performance in terms of efficacy and safety but also the patient compliance. A significant advantage of this route over others is that it provides controlled release of the medication into the patient which helps in maintaining blood level profile and thus ensuring lesser systemic side effects. An extensive research is going on in the area of TDDS. However, research in this area is still at exploratory stage. Many problems in the research, production and application need to be solved. More attention has to be paid to improve the overall quality of the system and its incorporated agents. Improved delivery of drugs with differing lipophilicity and molecular weight including proteins, peptides and oligonucleotides using various electrical, mechanical and other energy-related techniques have been established. This novel system has potential for improvement considering issues such as device design, ease of handling and cost-effectiveness.

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