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Recent Approaches in Transdermal Drug Delivery System

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A recent approach to drug delivery is to deliver the drug into systemic circulation at predetermined rate using skin as a site of application. Transdermal drug delivery is one of the most promising methods for drug application. Increasing numbers of drugs are being added to the list of therapeutic agents that can be delivered to the systemic circulation via skin. The success of Transdermal therapeutic system has created much interest in the pharmaceutical industry and has activated research activities related to it. Transdermal delivery has many advantages over conventional modes of drug administration, it avoids hepatic first pass metabolism, potentially decreases side effects and improves patient compliance. Drug delivery with Transdermal patch systems exhibit slow, controlled drug release and absorption. The plasma drug concentration does not vary significantly over time. Transdermal delivery system is a growing market that is expected to expand in the near future with the discovery of new drug treatment applications and technologies. The biomaterials research field has broadened in the last 3 decades including drug delivery systems, immunological kits and biosensors. Extensive efforts have been focused on placing a drug delivery system in a particular region of the body for maximizing drug availability and minimizing the dose dependent side effects. Apart from the development of oral controlled release formulations, Transdermal drug delivery systems using thin polymeric membranes have been widely studied. Treatment of chronic diseases such as asthma and rheumatoid arthritis by Transdermal route of drug administration might prove to have several advantages over other routes of drug administration. Plasticization of the membranes can be achieved by blending the polymer with another polymer, by crosslinking or by both crosslinking and blending. The advantages of such polymers are not only to create additional free space to accommodate the drug, butalso that these systems are biocompatible.

Keyword: predetermined rate, Transdermal therapeutic system, biosensors.

1. Introduction

Conventional systems of medication which require multidose therapy have numerous problems and complications. The design of conventional dosage form, whether a tablet, an injection or a patch, to deliver the right amount of medicine at the right target site becomes complicated if each medication were to be delivered in an optimal and preferred manner to the individual patient. The impetus for the development of novel drug delivery systems, apart from therapeutic efficacy is cost. Redesigning the modules and means to transport medicine into the body is less demanding and more lucrative task. To address these problems,

controlled release drug delivery system, a novel drug delivery approach evolves, which facilitates the drug release into systemic circulation at a pre-determined rate. Controlled drug release can be achieved by transdermal drug delivery systems (TDDS) which can deliver medicines via the skin portal to systemic circulation at a predetermined rate over a prolonged period of time . TDDS has gained lot of interest during the last decade as it offers many advantages over the conventional dosage forms and oral controlled release delivery systems notably avoidance of hepatic first pass metabolism, less frequency of administration, reduction in gastrointestinal side effects and improves patient compliance . For transdermal products the goal of dosage design is to maximize the flux through the skin into the systemic circulation and simultaneously minimize the retention and metabolism of the drug in the skin. Delivery of drugs into systemic circulation via skin has generated a lot of interest during the last decade as transdermal drug delivery systems (TDDS) offer many advantages over the conventional dosage forms and oral controlled release delivery systems not able to avoidance of hepatic first pass metabolism, decrease infrequency of administration, reduction in gastrointestinal side effects and improves patient compliance.Pharmaceutical science and technology has progressed enormously in the recent years. The advances in therapeutics and the need to optimize drug delivery in the body have increased the value of dosage form in therapy. This increased awareness has resulted in an increased sophistication and level of expertise in the design, development, manufacture, testing and regulation of drugs and dosage forms. Conventional systems of medication usually require multi-dose therapy. There is also fluctuation in peak plasma concentrations and the drugs which undergo hepatic first pass metabolism need a high dose to achieve effective plasma concentration by oral route of administration, so close attention is required to monitor therapy to avoid overdosing. Continuous intravenous infusion is recognized as a superior mode of drug administration which maintains a constant and prolonged drug level in the body and bypass hepatic "first pass metabolism." However such mode of drug administration entails certain risks and therefore necessitates hospitalization of the patient and close medical supervision of administration. It is becoming evident that the benefits of intravenous infusion can be closely duplicated without its hazards, using skin as the port of drug administration by means of transdermal drug delivery system. This is known as transdermal administration and the drug delivery systems are known as transdermal therapeutic systems or popularly as transdermal patches.Transdermal drug delivery offers numerous advantages over other routes of delivery including its accessibility and non-invasiveness allowing for ease and convenience of administration. This approach results in direct entry of bioactive molecules into the systemic circulation, thereby avoiding first-pass metabolism, efflux transporters, as well as metabolizing/digestive enzymes and unfavorable conditions associated with other routes of administration such as oral. Percutaneous absorption is the basis for the development of transdermal drug delivery systems. Fig.1 shows the different steps involved in percutaneous absorption.

2. Desirable Properties for Transdermal Candidate:

2.1 Physicochemical Properties:

1. The drug should have a molecular weight less than 500 daltons.
2. The drug should have affinity for both lipophilic and hydrophilic phases.
3. The drug should have a low melting point.

2.2 Biological properties:

1. The drug should be potent with a daily dose of the order of a few mg/day.
2. The half life (t1/2) of the drug should be short.

3. The drug must not induce a cutaneous irritation or allergic response.
4. Drugs which degrade in the G.I. tract or/are inactivated by hepatic first-pass effect are suitable candidates for transdermal delivery.
5. Tolerance to the drug must not develop under the near zero-order release profile of transdermal delivery.
6. Drugs which have to administered for a long period of time or which cause adverse effects to non-target tissues can also be formulated for transdermal delivery. Although the advantages of transdermal delivery make this route of delivering very desirable, only a selected number of drugs are suitable as candidates for transdermal delivery due to the natural obstacle to drug entry imposed by the skin's barrier function. Significant progress has been made, in the last two decades, in achieving a better control in the delivery through the skin. Research has been directed to find ways of delivering different types of drug molecule with the help of different enhancement techniques.

Polymer Used in Tdds

Polymers are the backbone of TDDS, which control the release of the drug from the device. Polymer matrix can be prepared by dispersion of drug in liquid or solid state synthetic polymer base. Additionally they should provide consistent and effective delivery of a drug throughout the product's intended shelf life and should be of safe status .

Natural Polymers: e.g. cellulose derivatives, gelatin, shellac, waxes, gums, and chitosan etc.

Synthetic Elastomers: e.g. poly butadiene, poly isobutylene, silicon, nitrile, acrylonitrile, neoprene, butyl rubber etc.

Synthetic Polymers: e.g. polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, poly vinyl pyrrolidone, polymethyl methacrylate etc

2.3 Formulation Approachs Used In Development of Tdds:

2.3.1 Membrane Permeation Controlled Systems:

Membrane permeation controlled systems ex. For polymer ethylene vinyl acetate co polymer with a defined drug permeability property. Nitroglycerin- releasing tdds for once a day medication in angina pectoris.

2.3.2 Adhesive Dispersion Type System:

Ex.poly isobutylene or poly acrylate adhesive. Spreading the medicated adhesive by solvent casting or hot melt on to a flat sheet of drug impermeable metallic plastic backing to form a thin drug reservoir layer. On top of the drug reservoir layer thin layers of non medicated rate controlling adhesive polymer of a specific permeability and constant thickness are applied produce an adhesive diffusion controlled drug delivery system.

2.3.3 Matrix Diffusion Controlled Systems:

The drug is prepared by homogeniously dispersing drug particles in a hydrophilic or lipophilic polymer matrix. The resultant medicated polymer is then moulded in to a medicated disc with a defined surface area and controlled thickness. The drug reservoir containing polymer disc is then pasted on to a occlusive base plate in a compartment fabricated from a drug impermeable plastic backing .Ex. Nitroglycerin TDDS for angina pectoris. $Q/t1/2=[(2A-CP)Cp\ Dp\ ]\ 1/2$ A=initial drug loading dose dispersed in the polymer matrix Cp&Dp =solubility and diffusivity of the drug in the polymer respectively Advantage; absence of dose dumping due to polymer cannot rupture.

2.4 Micro Reservoir Type:

The drug reservoir is formed by first suspending the drug solids in an aqeous solutionof a water soluble liquid polymer and then dispersing the drug suspention homogenously in a liphophilic polymer. Depending up on the physico chemical properties of the drug &desired rate of drug

release ,the device can be further coated with a layer of biocompatible polymer to modify the mechanism &rate of drug release. It is produced by positioning the medicated disc at the centre and surrounding it with an adhesive rim. Ex.Nitroglycerin TDDS for angina pectoris.

2.5 Factors Affecting Transdermal Permeability

The principle transport mechanism across mammalian skin is by passive diffusion which is primarily the trans-epidermal route at steady state or through trans-appendage route at initial non-steady state. The factors controlling transdermal permeability can be broadly placed in
following classes.

2.5.1 Partition Coefficient

Drugs possessing both lipid and water solubility are favourably absorbed through the skin. Transdermal permeability coefficient shows a linear dependency on partition coefficient. A lipid/ water partition coefficient of one or greater is generally required for optimal transdermal permeability. The partition coefficient of a drug molecule may be altered by chemical modification of its functional groups, which can be done without affecting the pharmacological activity of the drug. It has been established that membrane partition coefficient increases exponentially as the length of the lipophilic alkyl chain increases. The partition coefficient of a drug molecule may also be altered by varying the vehicle.

2.5.2 PH condition

Application of solution whose pH values are very high or very low can be destructive to the skin. With moderate pH values the flux of ionizable drugs can be affected by changes in pH that alter the ratio of charged and uncharged species and their transdermal permeability.

2.5.3 Penetrant Concentration

Assuming membrane limited transport, increasing the concentration of dissolved drug causes a proportional increase in flux. At concentration higher than the solubility, excess solid drug functions as a reservoir and helps to maintain a constant drug concentration for a prolonged period of time.

2.6 Physico-chemical properties of drug delivery systems

Generally the drug delivery system vehicles do not increase the rate of penetration of a drug into the skin, but serve as carriers for the drug. And mainly depends on the following

2.6.1 Release characteristics

Whether the drug molecules are dissolved or suspended in the delivery system,
The interfacial partition coefficient of the drug from the delivery systems to the
skin tissue and pH of the vehicle

2.6.2 Composition of the drug delivery system

The composition of the drug delivery system not only affects the rate of the drug release but also the permeability of stratum corneum by means of hydration, mixing with skin lipids, or other sorption promoting effects.

2.6.3 Enhancement of transdermal permeation

Majority of drugs will not penetrate skin at rates sufficiently high for therapeutic efficacy. In order to allow clinically useful transdermal permeation of most of the drugs the penetration can be improved by the addition of a sorption or permeation promoter into the drug delivery system.

2.7 Physiological And Pathological Condition of the Skin

2.7.1 Reservoir effect of the horny layer

The horny layer, especially its deeper layer, can sometimes act as a depot and modify the transdermal permeation characteristics of some drugs. The reservoir effect is due to the irreversible binding of a part of the applied drug with skin. This binding can be reduced by the treatment of the skin surface with anionic surfactants.

2.7.2 Lipid Film

The lipid film on the skin surface acts as a protective layer to prevent the removal of moisture from the skin and helps in maintaining the barrier function of the stratum corneum. Defatting of this film has been reported to decrease transdermal absorption.

2.7.3 Skin Hydration

Hydration of the stratum corneum can enhance transdermal permeability, although the degree of penetration enhancement varies from drug to drug. Skin hydration can be achieved simply by covering or occluding the skin with plastic sheeting, leading to the
accumulation of sweat and condensed water vapour. Increased hydration appears to open up dense, closely packed cells of the skin and increase its porosity.

2.7.4 Skin Temperature

Raising skin temperature results in an increase in the rate of skin permeation due to6
Increased diffusivity due to enhanced thermal energy. Altered solubility of drug in skin tissues Increased vasodilatation of skin vessels.

- **Skin age:** The young skin is more permeable than aged skin. Children are more sensitive for skin absorption of toxins. Thus, skin age is one of the factors affecting penetration of drug.

- **Blood supply:** Change in peripheral circulation can affect transdermal absorption.
- Capillaries and blood vessels present beneath the stratum corneum take up drug permeated through the skin. Injury or skin disease can change peripheral blood circulation.
- **Regional skin site:** Thickness of skin, nature of stratum corneum, and density of appendages vary site to site. These factors affect penetration significantly. There are differences in structure and chemistry of human stratum corneum from one region of the body to another. Despite greater thickness, plantar and palmer are not good diffusion barrier. Thus, stratum corneum shows some regional variation, which affect skin permeability (Table1) show regional variation of stratum corneum with respect of thickness.

Table 1: Regional variation of stratum corneum

Sl.No.	Skin region	Thickness (µm)
1	Abdomen	15.0
2	Volar forearm	16.0
3	Back	10.5
4	Forehead	13.0
5	Scrotum	5.0
6	Back of hand	49.0
7	Palm	400.0
8	Plantar	600.0

Skin metabolism: skin metabolizes steroid, hormones chemical carcinogens and some drugs. So skin metabolism determine efficacy of drug permeated through the skin.

2.8 Transdermal Applications:

Examples of Transdermal Applications Membrane-controlled transdermal system Adhesive Diffusion-Contrilled System Matrix Dispersion-Type System Microreservior System

2.8.1 Membrane-controlled transdermal system:

Membrane-controlled transdermal system Reservoir encapsuleted in shallow campartment molded from drug impermiable metallic plastic laminate & rate cantroling polimeric membrane. Drug solid or dispers in solid polymer matrix or suspended in an viscous liquid medium (silicon fluid) Rate cantroling membrane- EVAC Adhesive polymer-silicon or polyacrylate

2.8.2 Adhesive Diffusion-Contrilled System:

Adhesive Diffusion-Contrilled System Version of membrane moderate system. Reservoir directly dispers in adhesive polymer. Solvent costing on to impermiable metallic plastic backing. At the end rate controling adhesive layer.

2.9 Matrix Dispersion-Type System:

Matrix Dispersion-Type System Drug solid in hydrophilic or lipophilic polymer matrix, then molded in disc. Disc glue onti impermible membrane. Strip of adhesive polymer around the disc.

2.10 Microreservior System:

Microreservior System Combination of reservoir & matrix dispersion system. Drug in aq solution of water soluble polymer then dispers in lipophilic polymer. Gel like structure

2.11 Active Methods for Enhancing Transdermal Drug Delivery:

Recent progress in active transdermal drug delivery technologies has occurred as a result of advances in precision engineering (bioengineering), computing, chemical engineering and material sciences, which have all helped to achieve the creation of miniature, powerful devices that can facilitate the generation of drug-delivery profile required clinical response. The various classes of active systems under development include: A) Chemical methods:

2.12 Permeation Enhancers:

These are compounds which promote skin permeability by altering the skin as a barrier to the flux of a desired penetrant. Permeation enhancers are hypothesized to affect one or more of these layers of skin to achieve penetration enhancement of drugs. A large number of compounds have been investigated for their ability to enhance stratum corneum permeability. These may be conveniently classified under the following main headings:

- **Solvents:** Water, alcohols (methanol and ethanol), alkyl methyl sulfoxides-(dimethyl sulfoxide), dimethyl acetamide and dimethyl formamide, miscellaneous solvents (propylene-glycol, glycerol, isopropyl-palmitate)etc.
  Surfactants: Commonly used surfactants are: Anionic-surfactants (Dioctyl-sulphosuccinate, Sodium-laurylsulphate,Decodecyl-methyl-sulphoxide), nonionic-surfactants (Pluronic F127,Pluronic F68).
- **Bile salts**: Sodium taurocholate, Sodium deoxycholate, Sodium tauroglycocholate.
- **Binary systems:** Eg. Propylene glycol-oleic acid and 1,4-butane diol-linoleic acid.
- **Miscellaneouschemicals**: Eg. Urea, N,N-dimethyl-m-toluamide, Calcium thioglycolate, Anticholinergic agents.

2.13 Prodrug Approach:

The structural modification of active moieties get a better permeability is also a useful approach. It involves the chemical modification of a known pharmacologically active compound into a bioreversible derivative with the aim of changing it pharmaceutical and/or pharmacokinetic character and thereby enhancing its delivery, efficacy and therapeutic value. The skin is a highly active metabolic organ. The capacity of skin is utilized by the prodrug to revert back the active parent drug, once they are in the viable layers of the skin. Usually hydrophilic drug diffuse poorly through the skin. Development of derivatives with higher lipophillicity usually helps in the permeation. Historically prodrug approach was used to develop derivatives resistant to hepatic metabolism, but recently approach has been attempted to develop moieties of higher skin permeability. The important parameters, which influence the activity of prodrugs, are physicochemical, biopharmaceutics and pharmacokinetic properties, as well as the toxicity and bioactivity. The skin is a highly active metabolic organ. It contains a multitude of different enzymes that may metabolize a wide range of synthetic and naturally occurring xenobiotics. This capacity of skin is utilized by the prodrugs to revert back the active parent drug, once they are in the viable layers of the skin. Usually hydrophilic drugs diffuse poorly through the skin. Development of derivatives with higher lipophilicity usually helps in the permeation. Prodrugs approach can be used in topical formulation (corticosteroids) as well as in the

transdermal formulation, where the objective is the systemic transport of drugs (antihypertensive agents). Good aqueous solubility is a primary requirement of the prodrugs. On the other hand, high lipid solubility i.e., higher octanol-water partition coefficients, favors the passage through the SC. The recent investigation has shown, shapes of the molecules also play a role. Studies on cis- and trans- isomers of 11-octadecenoic acid had shown that the cis-form was able to enhance significantly the flux of salicylic acid across porcine epidermis whereas trans-isomers .

2.14 Recent Technology Used in Transdermal Drug Delivery System

2.14.1 Iontophoresis:

This method involves the application of a low level electric current either directly to the skin or indirectly via the dosage form in order to enhance permeation of a topically applied therapeutic agent19, 20. Increased drug permeation as a result of this methodology can be attributed to either one or a combination of the following mechanisms: Electro-repulsion (for charged solutes), electro-osmosis (for uncharged solutes) and electro-pertubation (for both charged and uncharged). Several iontophoretic systems are currently under commercial development including the Phoresor device developed by Iomed Inc. and the Vyteris and E-TRANS devices developed by Alza Corp.

2.14.2 Electroporation:

This method involves the application of high voltage pulses to the skin which has been suggested to induce the formation of transient pores. High voltages (100 V) and short treatment durations (milliseconds) are most frequently employed. Other electrical parameters that affect permeation rate include pulse properties such as waveform, rate and number. The technology has been successfully used to enhance the skin permeability of molecules with differing lipophilicity and size (i.e. small molecules, proteins, peptides and oligonucleotides) including biopharmaceuticals with molecular weights greater than 7kDA.23

2.14.3 Microneedle-based Devices:

The very first microneedle systems, described in 1976, consisted of a drug reservoir and a plurality of projections (microneedles 50 to 100 mm long) extending from the reservoir, which penetrated the stratum corneum and epidermis to deliver the drug. The ALZA Corp. has recently commercialized a microneedle technology named Macroflux which can either be used in combination with a drug reservoir or by dry coating the drug on the microprojection array24, the latter being better for intracutaneous immunization.

2.14.4 Abrasion:

The abrasion technique involves the direct removal or disruption of the upper layers of the skin to facilitate the permeation of topically applied medicaments. Some of these devices are based on techniques employed by dermatologists for superficial skin resurfacing (e.g. microdermabrasion) which are used in the treatment of acne, scars, hyperpigmentaion and other skin blemishes.

2.14.5 Needle-less Injection:

This is reported to involve a pain-free method of administering drugs to the skin. Over the years, there have been numerous examples of both liquid (Ped-O-Jet, Iject, Biojector2000, Medi-jector and Intraject) and powder (PMED device formerly known as Powderject injector) systems. The latter device has been reported to successfully deliver testosterone, lidocaine hydrochloride and macromolecules such as calcitonin and insulin. of ultrasonic energy to enhance the transdermal delivery of solutes either simultaneously or via pre-treatment and is frequently referred to as sonophoresis or phonophoresis. The SonoPrep device (Sontra Medical Corp.) uses low frequency ultrasound (55 kHz) for an average duration of 15 seconds to enhance skin permeability. This battery-operated, handheld device consists of a control unit, ultrasonic horn with control panel, a disposable coupling medium cartridge, and a return electrod.

2.14.6 Laser Radiation

This method involves direct and controlled exposure of a laser to the skin which results in the ablation of the stratum corneum without significantly damaging the underlying epidermis. Removal of the stratum corneum using this method has been shown to enhance the delivery of lipophilic and hydrophilic drugs.

2.15 Iontophoretic Drug Delivery System:

"Iontophoresis can be defined as the permeation of ionized drug molecules across biological membranes under the influence of electrical current." Iontophoresis implies the use of small amount of physiologically acceptable electric current to drive ionic (charged) drugs into body by using an electrode of the same polarity as the charge on the drug; the drug is driven into the skin mainly by electrostatic repulsion. The technique has been observed to enhance the transdermal permeation of ionic drugs several folds and this proposed to expand the horizon of transdermal control drug delivery for systemic medication. Beside the usual benefit of transdermal drug delivery, iontophoresis present a unique opportunity to provide programmed drug delivery. This is because the permeation rate is proportional to the current density, which can be readily adjusted. Such dependence on current may also make drug absorption via iontophoresis less dependent on biological variables.

2.15.1 Microporation

Microporation involves the use of microneedles that are applied to the skin so that they pierce only the stratum corneum and increase skin permeability. Microneedles are needles that are 10 to 200 µm in height and 10 to 50 µm in width. Microneedles do not stimulate the nerves, so the patient does not experience pain or discomfort. They are usually drug coated projections of solid silicon or hollow, drug filled metal needles.

2.15.2 Needleless injection

Needleless injection involves a pain-free method of administration of drugs to the skin. This technique involves firing the liquid or solid particles at supersonic speeds through the stratum corneum. Problems with this technique include the high developmental cost for both the device and dosage form and the inability to program or control drug delivery to compensate for intersubject differences in skin permeability.Needleless injection - Mechanism The mechanism involves forcing compressed gas such as helium or nitrogen through the nozzle with the resultant drug particles entrained within the jet flow, reportedly traveling at sufficient velocity for skin penetration.

2.16 Four Major Transdermal System:

Four major transdermal system

1. Polymer Membrane Permeation Controlled TDDS.
2. Polymer Matrix Diffusion Controlled TDDS.
3. Drug Reservoir Gradient Controlled TDDS/ Adhesive Dispersion Type System.
4. Microreservoir Dissolution Controlled TDDS.

2.16.1 Polymer Membrane Permeation Controlled TDDS. Drug Reservoir:

Dispersed on solid polymer matrix e.g polyisobutylene . Suspended in unleachable viscous liquid medium eg . Silicone fluid. Dissolved in solvent. Rate controlling Membrane: Microporous , Nonporous. Eg . Ethylene-Vinyl acetate copolymer. Adhesive Layer: Thin layer, adhesive, drug compatible, hypoallergic , eg . Silicone adhesive. e.g. Estradiol releasing transdermal system Colinidine releasing transdermal .

2.16.2 Polymer Membrane Permeation Controlled TDDS:

Polymer Membrane Permeation Controlled TDDS Intrinsic rate of drug release is given by :- dQ / dt - rate of drug release Cr - Drug concentration in reservior . Dm & Da - Diffusion coefficient in rate controling membrane and adhesive layer. hm & ha - Thickness of membrane and adhesive layer. K m/r & K a/m - Partition coefficient for the interfacial partioning

of drug from reservior to membrane and from membrane to adhesive respctively .

2.16.3 Polymer Matrix Diffusion Controlled TDDS:

Polymer Matrix Diffusion Controlled TDDS Drug reservior : - Drug dispersed homogenously in a hydrophillic or lipophillic polymeric matrix. e.g. silicone elastomers,Polyurethanes , polyviny alcohols etc. Homogenously mixing drug with liquid polymer and higly viscous polymer followed by Crosslinking . At elevated temp. drug is homegenously blend with rubbery polymer. Occulusive base plate : -drug reservior containig polymer disc is pasted in it. Impermeable plastic backing Adhevise polymer : - is spread along the circumference to form a strip of adhesive rim around medicated disc. e.g. nitroglycerin release transdermal (Nitro dur).

2.16.4 Drug reservoir gradient controlled tdds/ adhesive dispersion type system:

Drug Reservoir Gradient Controlled TDDS/ Adhesive Dispersion Type System Simplified form of membrane permeation contolled system. Drug reservior : - Drug dispersed in adhesive polymer e.g. polyisobutylene , polyacrylate . Drug reservior layer :- medicated adhesive spread over a flat sheet impermeable metallic plastic backing, by solvent casting or hot melt. Rate contolling adhesive : - thin layer, non medicated, specific permeability and constant thickness applied on top of drug reservior layer to produce diffusion contolled delivery system. e.g. Isosorbide dinitrate and verapamil can be administrated by controlled manner in this adhesive dispersion type system.

3. Conclusion

The Transdermal drug delivery system has gained importance in recent years. The Transdermal route is an extremely attractive option for the drug with appropriate pharmacology and physical chemistry. The Transdermal drug delivery system has potential advantages of avoiding hepatic first pass metabolism, maintaining constant blood level for longer period of time resulting in a reduction of dosing frequency, improved bioavailability, decreased gastrointestinal irritation that occur due to local contact with gastric mucosa and improved patient compliance.[16] Recently ,it is becoming evident that the benefits of intravenous drug infusion can be closely duplicated , without its hazards by using the skin as a part of drug administration to provide continuous Transdermal drug infusion through intact skin.

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