FORMULATION, DEVELOPMENT AND EVALUATION OF CONTROLLED DRUG DELIVERY OF ANALGESICS VIA NOVEL ROUTES

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Abstract:

Transdermal drug delivery has made an important contribution to medical practice. It is a medicated patch that delivers a specific amount of medication through the skin into the blood stream. An advantage of a transdermal drug delivery route over other types of medication delivery is that the patch provides a controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive. The present investigation was aimed to formulate transdermal films of non-steroidal anti-inflammatory drug, mercury substrate method and evaluated for physicochemical parameters like thickness, weight variation, moisture uptake, moisture content, folding endurance, and drug content values. The drug enters the bloodstream directly through the skin. Since there is high concentration on the patch and low concentration in the blood, the drug will keep diffusing into the blood for a long period of time, maintaining the constant concentration of drug in the blood flow. Transdermal drug delivery system was introduced to overcome the difficulties of drug delivery through oral route. The conventional oral dosage forms have significant setbacks of poor bioavailability due to hepatic first pass metabolism technique and were evaluated for organoleptic characteristics and other physicochemical properties, such as thickness, weight uniformity, folding endurance, moisture content, drug content, and tolerability and acceptability of patch.

1.0 Introduction:

Optimum therapeutic outcomes require not only proper drug selection but also effective drug delivery. The human skin is a readily accessible surface for drug delivery. Over the past three decades, developing controlled drug delivery has become increasingly important in the pharmaceutical industry Transdermal delivery systems are currently available containing scopolamine (hyoscine) for motion sickness, clonidine and nitroglycerin for cardiovascular disease, fentanyl for chronic pain, nicotine to aid smoking cessation. Transdermal delivery provides controlled, constant administration of the drug and allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation.The TDDS offers several significant advantages such as avoidance of the hepatic-first-pass metabolism, avoidance of gastrointestinal drug absorption difficulty, and noninvasiveness. Pharmaceutically, a transdermal patch is a dosage form that is used for delivery of medication through the skin into the blood stream. Following skin permeation, the drug first reaches the systemic circulation and then is transported to the target site, which could be relatively remote from the site of administration, to produce therapeutic action though the concept of TDDS happens to be a new one and belongs to conventional pharmacology, Umami classical literature has ample evidence of it. There are a number of single and compound Unani formulations exhibiting transdermal activity mentioned in

the celebrated writings of the Unani physicians.

Tran's cellular route: - Drug delivering through this route passes from coenocytes which has highly hydrated keratin creating hydrophilic pathway. Coenocytes are surrounded by lipids connecting these cells. So a drug requires a number of partitioning and diffusion steps. It is the most widely used route by various types of drugs. The highly hydrated keratin provide aqueous pathway to the hydrophilic drugs. A number of partitioning and diffusion steps are needed to pass the drug through the cell matrix.

Intercellular route: - As the name indicates intercellular the drug diffuses through the lipid bilayer between the cells. In this route, the molecule stays in the lipid bilayer and winds around the keratinocytes on its way to the dermis. Although both paths are possible, the most common route of drug penetration is the intercellular route because most drug molecules are more soluble in the lipid environment of the bilayer than in the protein environment of the keratinocytes.

Limitations:

- The drug must have desirable physicochemical properties to penetrate the stratum corneum. Drugs that require high blood levels cannot be administered.
- Skin irritation or contact dermatitis due to use of drugs, excipients, enhancers and adhesives used.
- The adhesives may not adhere well to all types of skin and may be uncomfortable to wear.
- Along with these limitations the high cost of the product is also a major drawback for the wide acceptance of this product.

1.0 Literature review:

[1] WissingSA,Muller R H.(2003) Over the past few decades, the concept of use of bio adhesive polymers to prolong the contact time has gained remarkable attention in trans mucosal drug delivery. Adhesion as a process is simply defined as the "fixing" of two surfaces to one another. Bio adhesion may be defined as the state in which two materials, at least one of which is biological in nature, are held together for extended periods of time by interfacial forces. In the pharmaceutical sciences, when the adhesive attachment is to mucus or a mucous membrane, the phenomenon is referred to as mucoadhesion

[2] Chein YW.(2005) Tran's mucosal routes of drug delivery which comprise of the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity offer excellent opportunities and potential advantages over perioral administration for systemic drug delivery. These advantages include possible bypass of first pass effect, avoidance of presystolic elimination within the GI tract and depending on the particular drug, a better enzymatic flora for drug absorption 3 . The sites of drug administration in the oral cavity include the floor of the mouth (sublingual), the inside of the cheeks (buccal) and the gums (gingival) With the advances and progress in biotechnology, hydrophilic high molecular weight therapeutic agents such as proteins and peptides are readily available for therapeutic use.

[3] Jitendra S, Desai B, Keyur D.(2009) Concluded that the two novel o/w

microemulsions were designed for improving transdermal absorption When microemulsions were gelled, they found to have uniform viscosity, spreadability, elegant appearance and did not produce skin irritation. Drug content at top, middle and bottom of the formulations revealed the percentage of drug close to 100%. The results of physicochemical characteristics are satisfactorily. Both the formulations are superior to marketed formulation in the respect of drug permeation across the membrane

[4]**P. Patel,(2012)**The application of transdermal delivery to a wider range of drugs is limited due to the significant barrier to penetration across the skin which is allied primarily with the outermost stratum conium layer of the epidermis. Formulation on skin can be classified into two categories according to the target site of the action. One has systemic action after drug uptake from the cutaneous micro vascular network and other exhibits local effects in the skin. Transdermal drug delivery can closely mimics the slow intravenous infusion without its potential hazards and also offer another most important advantage in allowing the patient to terminate the drug therapy by simply removing the patch at desired time if toxicity develops

3.0 Methods for enhancing transdermal drug delivery:

The pro drug approach has been used to enhance the dermal and transdermal delivery of drugs with unfavorable partition coefficients the prodrug design involves addition of a pro moiety to increase partition coefficient and also solubility and transport of the parent drug in the stratum conium. For example: The intrinsic poor permeability of the very polar 6-mercaptopurine was increased up to 240times using S6- acyloxymethyl and 9-dialkylaminomethyl promoieties. The prodrug approach has also been investigated for increasing skin permeability of non-steroidal anti-inflammatory drugs, like naltrexone nalbuphinebuprenorphine alpha-blocker and other drugs

Thickness, Weight variation and Drug content:

The thickness of the patch at three different points was determined using thickness gauge and the patches were then weighed individually using digital balance to determine the weight of each patch taken out from the casted film. The patches were subjected to weight variation by individually weighing ten randomly selected patches. Such determinations were carried out for each formulation. Films of specified area were cut and weighed accurately Pieces were taken into a 100 ml volumetric flask containing phosphate buffer (pH 7.4), and the flask was solicited for 8 h A blank was prepared in the same manner using a drug-free placebo patch of same dimensions. The solution was then filtered using a 0.45-µm filter and the concentration is found in respective nm.

Eutectic system: A eutectic system is a mixture of chemical compounds or elements that has a single chemical composition that solidifies at a lower temperature than any other composition. According to regular solution theory, the lower the melting point, the greater the solubility of a material in a given solvent, including skin lipids

Liposomes and vehicles: Liposome is colloidal particles formed as concentric bimolecular layers that are capable of encapsulating drugs. There are many examples of cosmetic products in which the active ingredients are encapsulated in vesicles. These include humectants such as glycerol and urea, unscrewing and tanning agents, enzymes, etc. Phosphatidylcholine from soybean or egg yolk is the most common composition although many other potntial ingredients have been evaluated

Iontophoresis: This method involves permeation of a topically applied therapeutic agent by application of low level electric current either directly to skin or indirectly via dosage form. Parameters that effect design of aionophoretic skin delivery system include electrode type, current intensity and pH of system. Increased drug permeation as a result of this methodology can be attributed to either one or a combination of the following mechanisms: Electrorepulsion (for charged solutes), electro-osmosis (for uncharged solutes) and electro-perturbation (for both charged and uncharged)

Laser radiation and photomechanical waves: Lasers are frequently used for treatment of dermatological conditions like acne and to confer facial rejuvenation. This method involves direct and controlled exposure of a laser to the skin that results in the ablation of the stratum corneum without significantly damaging the underlying epidermis

Radio frequency: It involves the exposure of skin to high frequency alternating current resulting in formation of heat induced micro channels in the membrane. The rate of drug delivery is controlled by number and depth of micro channels formed by device. Treatment duration takes less than a second

Adhesive Dispersion Type Systems: This is a simplified form of the membrane-permeation controlled system. As shown in fig.5, the drug reservoir is formulated by directly dispersing the drug in an adhesive polymer e.g. Poly (isobutylene) or poly (acrylate) adhesive and then 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 the top of the drug reservoir layer, thin layers of non-medicated, ratecontrolling adhesive polymer of a specific permeability and constant thickness are applied to produce an adhesive diffusion – controlled delivery system

Membrane permeation – controlled systems: In this type of system, drug reservoir is encapsulated in a shallow compartment moulded from a drug impermeable metallic plastic laminate and a rate controlling polymeric membrane which may be micro porous or non-porous as shown in fig.4. The drug molecules are permitted to release only through the rate – controlling polymeric membrane. In the drug reservoir compartment, the drug solids are either dispersed homogenously in a solid polymer matrix (e.g. Polyisobutylene adhesive) or suspended in anunble ach able, viscous liquid medium (e.g. Silicon fluids)

to form a paste like suspension.

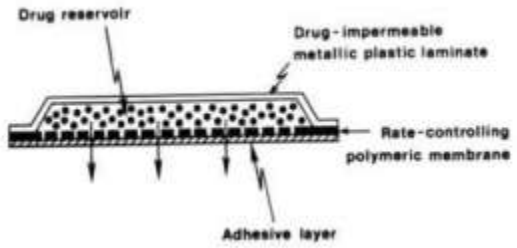

Fig : Membrane permeation controlled system

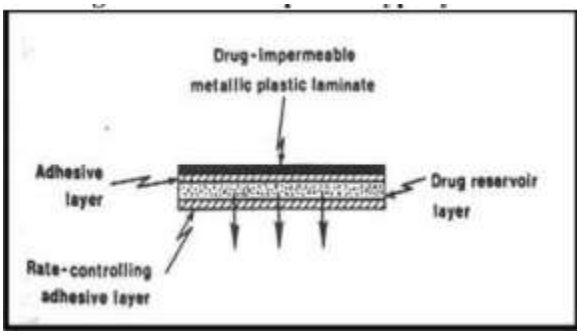

Figure: Adhesive dispersion type system

Vitro Permeation Study of Patch:

The in vitro permeation study of the prepared patch was carried out through egg shell membrane because the egg shell membrane resembles human stratum cornea as it consists mainly of keratin The membrane was accordingly prepared before use The water in the outer jacket of the cell was warmed and set at °C throughout the experiments to provide a skin surface temperature. Phosphate buffer solution of pH 7.4 was used as dissolution medium in the receptor compartment. A 5 × 5 mm^2 piece of patch was taken and applied over the mounted membrane in diffusion cell. After that, the samples were withdrawn from the receptor compartment at regulated intervals. The sampling schedule was at 0, 15, 30, and 60 minutes for the first hour of release and then it was at every hour interval till 6th hour of release. After that the whole system was kept in its normal position overnight and then next day reading was taken at 24th hour. One mL of the receptor solution was collected as sample each time and simultaneously one mL of phosphate buffer solution was added back to the receptor cell for maintaining the same initial volume of the receptor cell solution.

4.0 Formulation methods for transdermal drug delivery:

These system can be multi laminate process e.g. Transdermal Nitro. These products consist of three substrates held together by two layers of drug containing adhesive. First the drug is processed into the physical / chemical form required for incorporation into the product. Then the drug adhesive components and excipients are mixed with a solvent to achieve uniform solution. These adhesive compositions are deposited as a thin film on moving substances rate which are subsequently dried to remove solvent. Then lamination of the dried adhesive film and other layer to form the five layer product consisting of release linear contact adhesive control membrane, drug reservoir and backing substrate. The lamination then printed and die cut into final dosage form. The production is then packed in individual foil pouches. After inspection the products are automatically inserted into a continuously moving web of pouch stock which is sealed around the dosage form

Matrix diffusion controlled system: - The drug is dispersed in an insoluble matrix of rigid non swellable hydrophobic material. Materials used for rigid matrix are insoluble plastics such as PVC and fatty and materials like stearic and beeswax. With the plastic materials the drug is generally kneaded with the solution of Polyvinyl chloride in an

organic solvent and granulated waxy matrix is prepared by dispersing the drug in molten fat followed by congealing. The granules are then compressed into tablets swellable matrix system are popular for sustaining the release of highly water soluble drug. The material for such matrices are generally hydrophilic gums and may be of natural origin (guar gum, tragacanth) semi synthetic (HPMC, CMC) or synthetic (poly cryamides) The drug and the gum are granulated together with a solvent such as alcohol and compressed into tablets. The release of drug from such initially dehydrated hydro gels involves simultaneous absorption of water and desorption of drug via a swelling controlled diffusion mechanism. The gum swells and the drug diffuse out of it the swollen mars devoid of drug appear transport.

Future of Transdermal Drug Delivery System:

Future novel formulation approaches and technologies include liposomes, noisome and micro emulsion. Aim of this strategy is to improve delivery of drug that has low inherent solubility in most of classical formulation excipients. A wide range of potential drugs for delivery like steroids, antifungal, antibacterial, interferon, methotrexate, local anesthetics are formulated. The market for transdermal devices has been estimated to increase in future and has recently experienced annual growth of at rate of 25%. This figure will rise in future as novel devices emerge and list of marketed transdermal drug increases. Transdermal delivery of analgesics is likely to continue to increase in popularity as there are further improvements in design. Research is being performed to increase safety and efficacy. To improve practical matters such as the experience for the wearer of the patch, and also to provide more precise drug delivery associated with increased duration of action. Other potential improvements include improved transdermal technology that utilizes mechanical energy to increase drug flux across the skin either by altering the skin barrier or increasing the energy of the drug molecules. After the successful design of patches using iontophoresis, various modes of 'active' transdermal technologies are being investigated for different drugs. These include electroporation (short electrical pulses of high voltage to create transient aqueous pores in the skin), sonophoresis (uses lowfrequency ultrasonic energy to disrupt the stratum corneum), and thermal energy (uses heat to make the skin more permeable and to increase the energy of drug molecules). Magnetic energy, magnetoapheresis, has been investigated as a means to increase drug flux across the skin

Conclusions:

A lot of progress has been done in the field of Transdermal Patches. Due to large advantages of the Transdermal Drug Delivery System, this system interests a lot of researchers. Many new researches are going on in the present day to incorporate newer drugs via this system. Transdermal dosage forms may provide clinicians an opportunity to offer more therapeutic options to their patients to optimize their care. In recent years the use of a number of biophysical techniques has aided in our understanding of the nature of the stratum conium barrier and the way in which

chemicals interact with and influence this structure. A better understanding of the interaction of enhancers with the stratum conium and the development of structure activity relationships for enhancers will aid in the design of enhancers with optimal characteristics and minimal toxicityTransdermal drug delivery systems represent a beneficial innovation for drug delivery, particularly in patients who cannot swallow or remember to take their medications. Clinicians and other allied health professionals should understand the appropriate administration techniques for transdermal systems to ensure optimal patient outcomes and to ensure the safety of all who encounter patients

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