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Recent Trends In Transdermal Patches - A Review

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ABSTRACT :- Transdermal drug delivery system is the system in which the delivery of the active ingredients of the drug occurs by means of skin. Transdermal distribution establishes the most important channels for a revolutionary medication delivery method. Basically, the Transdermal drug delivery system is a non-invasive method of drug administration. The drug delivery method will incorporate the drug to be delivered into polymeric membranes, which then diffuse the drug into skin at planned and controlled rate. The various advantages of drug the patch containing a medicinal substance onto the skin, which is both convenient and painless, as well as therapeutic first-pass metabolism. From throughout the body, an adhesive patch is designed to deliver a specific dose of medication into the bloodstream and through the skin. The Transdermal drug delivery has several advantages over other routes of administration, and for some instance, its less invasive, patient-friendly, and it is able to do the bypass of first-pass metabolism and the destructive acidic environment of the stomach that will occurs upon the oral ingestion of drugs. For decades, the transdermal patches were used to deliver drugs such as nicotine, nitroglycerin, fentanyl and clonidine to treat various diseases or conditions. The goal of this review is to know the history and origination of the transdermal patches, the design and usage of medical patches in transdermal drug delivery, with a focus on the recent advances in the innovation and technology that led to the emergence of smart, dissolvable/biodegradable, high-loading/release, as well as 3D-printed patches.

Key words :- Transdermal, non-invasive, adhesive patch, first pass metabolism, nicotine, fentanyl, nitroglycerin, clonidine, smart patches, high loading release, 3D printed patches.

1. INTRODUCTION :-

The skin is the largest organ in the human body by mass, with an area of between 1.5 and 2.0 meters in adults. Drugs have been applied on the skin for the treatment of the superficial disorders, and also the transdermal administration of therapeutics will manage its systemic ailments and also cosmetics, which are dating back to its old existing medical records of the man. The usuage of salves, ointments, and patches, which are consisting of a plant or animal or mineral extracts, was already became popular in the ancient Egypt and the medicine of Babylonian (around 3000 BC) (Magner, 2005; Geller, 2010). However, the routine usage of the transdermal delivery systems will became a common practice to the latter third of the 20th century, which are enable to precise, when the delivery technology was developed and reproducible administration through the skin for systemic effects. For the commercial use, the Transdermal patches have been developed for the distribution of nitroglycerin, nicotine, testosterone, fentanyl, lidocaine, scopolamine, oxybutynin, estradiol, ketoprofen, tacrine, L-DOPA, and for hormonal replacement and contraceptives (Prausnitz et al., 2004). One of the first transdermal patches developed was the nitroglycerin patch in the year 1985. The patch was developed by Gale and Berggren (1985) and also it utilizes the drug ethylene vinyl acetate, a rate-controlling membrane and also Perhaps the most common and well known transdermal patch is the nicotine patch which is used to aid the cessation of the smoking. The detailed rich history of topical and transdermal delivery that has evolved over thousands of years, focusing particularly on the evolution and current use of transdermal patches. In the blood, these drug concentrations are, in turn, it will defined by the amount of drug which is released into the body from the delivery system and also the are which is applicated. Transdermal delivery is also used to produce clinical effects, such as local anaesthesia and anti-inflammatory activity, deep within or beneath the skin. In contrast, the topical delivery used to treat the superficial, although at times there are very serious, and the skin problems will relatively leads to a local action.

1.1 HISTORY AND ORIGINATION OF TRANSDERMAL PATCHES :-

In 1980, a US patent disclosed a transdermal patch for hypertension therapy. The drug delivery system contained a gel mineral oil–polyisobutene–clonidine reservoir and its contact with the adhesive layer which has a microporous membrane in-between the drug release at a controlled rate (Chandrasekaran et al., 1980).

The Early use of topical therapy **(Pre-20th century)**	Topical remedies anointed, bandaged, rubbed or applied to the skin (Figure 1) are likely to have been used since the origin of man, with the practices becoming evident with the appearance of the records which was written, such as the clay tablets which are used by the Sumerians (Kramer, 1963). Indeed, the given suggestion that a liquefied ochre-rich mixture, which was made some 1,00,000 years ago and it was found at a Blombos Cave, which is located on South Africa, and it may have been used as a purpose of decoration and also as a protection to the skin (Henshilwood et al., 2011). Ancient Egyptians used oil (example - castor, olive and sesame), fats (mainly animals), perfumes (examples - bitter almond, peppermint and rosemary) and other ingredients to make their cosmetic

and dermatological products (such as; unguents, creams, pomades, rouges, powders, and eye and nail paints) (Forbes, 1955). The mineral ores of copper (malachite: green) and lead (galena: dark grey) were used to prepare a kohl, a paste which is used as a paint to the eyes. The Red ochre, which was used as a lip or face paint, and a mixture which contains a powdered lime and oil was used as a cleansing cream (Lucas and Harris, 1962). The ancient lead-based products, which were applied by both of its basic appearance and, also the religious beliefs, for the protection which are against to the eye diseases (Tapsoba et al., 2010). However, these effects may have been real as the recent studies which are involving the incubation of low lead ion concentrations with skin cells (Tapsoba et al., 2010), which is known to defence against the infection (Coleman, 2001). From the negative side, it could be asked, if these lead products which will causes toxicity, and noting down the high blood levels of lead and it have been reported in modern kohl users (Hallmann, 2009). The Papyrus Ebers (1550 BC) which are well known, and it describes more than 800 prescriptions and also about 700 drugs, appears to be the best pharmaceutical record from the ancient times (LaWall, 1927). It contains so many recipes for the treatment of skin conditions, which was including burns, wounds, blisters and exudation. The Other remedies are used to preserve the hair, to make the hair grow, and to improve the skin and it also beautifies the body. A poultice (with 35 ingredients) which is reported for the weakness of the male member and the Other remedies are the first transdermal delivery of drugs for its systemic effects, such as the topical application of frankincense to expel pain from the head and a product which is applied on the belly region to a woman or a man to expel pains caused by the tapeworm (Bryan, 1930; Ebbell, 1937). From the basis of the emphasis on the topical treatments which was happened at that time is evident by the portrayal of an ointment workroom in an Egyptian tomb painting from 1400 BC (Kremers, 1976).

A millennium and a half later, A greek physician named Galen (AD 129–199), who introduced the compounding of herbal drugs and other excipients into a dosage forms. He is widely considered as the 'Father of Pharmacy' and his practices are known as the 'Galenic pharmacy'. The Galen's Cerate (Cérat de Galien), a cold cream (Figure 1B), which is certainly the most renowned formula of galen, and composition which was relatively similar to the one is being used on today times (Bender and Thom, 1966). The Medicated plasters **(**emplastra**)**, which were generally applied on the skin for local conditions, it can be traced back to Ancient China (around 2000 BC) , which are the early predecessors of today's transdermal patches *(*emplastra transcutanea*)*. These early plasters are generally contained a lot of multiple ingredients for the herbal drugs, which was dispersed into an adhesive natural gum rubber base and applied to a backing support made of fabric or paper (Chien, 1987). Nicotine, which is known as a new-world transdermal agent, was already being used as a plaster (Emplastrum opodeldoch) and

	during the time of Paracelsus (1493–1541) (Aiache, 1984). Unlike the medicated plasters which was originated in China, the Western-type medicated plasters were much simpler formulations , and a single active ingredient is only required. And the Examples of the plasters were listed in the United States Pharmacopoeia (USP) almost 70 years ago and also some of them are included such as; belladonna (used as a local analgesic), mustard (as an effective local irritant) and salicylic acid (as a keratolytic agent) (Pfister, 1997). The little concept about a certain drugs which are cross to the skin and it will appeared and it have been applied by Ibn Sina (AD 980–1037), a Persian physician best known as Avicenna within the Western World. In The Canon of Medicine, he proposed that the topical drugs have two spirits or states: which are soft and hard. So, He suggested that, when the topical products are applied to the skin, the soft part penetrates on the skin surface and whereas the hard part does not penetrate. And he further proposed that the dermally applied drugs are not only have local effects, but also it will affect the tissues immediately beneath the skin including the joints (regional effects) as well as systemic effects in remote areas. One of his topical formulations acting systematically and for some conditions, where drugs could not be taken as orally. One of the regional therapies of Avicenna, the usage of plaster-like formulation, sulphur was mixed with the tar and it will applied on the skin with a piece of paper and applied as a backing to keep the formulation in its place. This product was used for the treatment sciatica, ie, pain arising from the compression of the sciatic nerve felt in the back, hip and outer side of the leg (Moghimi et al., 2011). The modern transdermal medications includes; the mercurial ointments (Unguentum Hydrargyri*)* used for the treatment of syphilis, (late 15 century) (Figure 1) (Cole et al., 1930). The Unguentum Hydrargyri Fortius L. (stronger mercurial ointment), made up as a purified mercury, lard and suet (Castle, 1828; Coxe, 1830; Pereira, 1839), these are became examples for these preparations.
A phase of 'non-belief' in transdermal products **(19th century)**	In the year 1872, the German pharmacopoeia produced a compilation in Latin language, listed 28 Emplastra formulae. And These are included as the adhesive products (e.g. Emplastrum adhaesivum, which contained oleic acid, lead oxide and colophony, and the Emplastrum adhaesivum anglicum, a hydrophilic formula); products meant to produce systemic effects [e.g. Emplastrum aromaticum, which contained peppermint and other aromatic oils targeted for the treatment of the stomach; Emplastrum belladonnae (Figure 1), from Atropa belladonna *leaves*, which was meant for the treatment of tuberculosis and tumours; Emplastrum opiatum*, which* was used to reduce the stomach movement and it is associates pain*;* Emplastrum conii containing Conium maculatum (poison hemlock, by Socrates), it was thought to be useful for the treatment to the tuberculosis and tumours; and the products for will be used for topical purpose (example; Emplastrum hydrargyri a pure quicksilver, which is used for trating the topical

	swellings and infections, Emplastrum cantharidum ordinarium, a vesicant, Emplastrum picis irritans *and* Emplastrum fuscum for dealing with topical infections). Nevertheless, on the year 1877, one review suggests that the intact to the human skin which was totally impermeable to all the substances (Fleischer, 1877) – and in several cases of systemic poisoning, it will applied externally application of belladonna (example - plaster, liniment and lotion), these are reported in the British Medical Journal during the year 1860–1870s (Morgan, 1866; Harrison, 1872).
Development of topical products (20th century)	In the year 1940, a scientist named Schwenkenbecker generalized that - skin is permeable to lipid-soluble substances but not permeable to the water and electrolytes. Mostly in children, Various poison cases were reported in the early 1900s in the city France after the nitrobenzene or aniline dyes are topically applied in dyed clothing or shoes (The Lancet annotations, 1902; White, 1909; Muehlberger, 1925), and further supports its notion of topical product of potential systemic absorption . The death arising from the systemic absorption of phenol from a large body surface in a young man after the accidental spillage of a bottle of phenol over himself (Johnstone, in the year 1948) it emphasizes the lethal potential consequences which are associated with accidental 'overexposure' to the drugs which is applied on the skin. So, However the lethality was being promoted on the range of higher concentrations by its corrosive nature of the phenol , and it can cause a substantial enhancement towards the skin penetration (*Roberts* et al., 1977) and also the saturation of the pathways like sulphate and glucuronidation present in body for identify its detoxification (Mellick and Roberts, 1999). In recent series of reports, it is described as the potential toxicity of lethal is arising from the exposure to the drug hexachlorophene after it is applied to the babies (Martin-Bouyer et al., 1982). The beginning of the 20th century, the various in vivo studies demonstrated its systemic absorption after its topically applied by estimating its drug levels in the blood, urine and faeces (Malkinson and Rothman, 1963). In the Initial analytical methods, which were strictly qualitative and also the substances were detected on the blood or urine by looking at the change into its measured sample with regards to its colour, acidity or density related to the standard sample (Scheuplein and Blank, 1971). Mercury, it is one of the first therapeutic compounds which are used for the detection and then it will quantified in excretion of human, and it was initially detected in urine following its treatment of syphilis by using such amalgamation methods (i.e. Reinsch test) (Wile and Elliott, 1917). Later more accurate analytical methods (e.g. using a calibrated capillary tube) enabled the quantitative determination of 5 mg of mercury in 1 L of solution (Cole et al., 1926). Colorimetric methods were commonly used. p-chloro-m-xylenol (basically a halogenated phenol) in the biological materials (such as; urine, blood and minced tissues), the concentration of these phenol was

determined by using the Millon's reagent (an aqueous solution used in the mercury and nitric acid). The dirty red compound which was formed and then it will be extracted by ether to give a clear yellow solution which was suitable for its photometric measurements (Zondek et al., 1943). The absorption of the drug methyl salicylate from the various vehicles of 10 male subjects was studied via excretion in the urine of its salicylate metabolite by using a colorimetric titration with the ferric alum (Brown and Scott, 1934). And the absorption of the free iodine, through its unbroken dog skin, which was investigated by a redox titration of the iodine and it will eliminated in the urine with sodium thiosulphate (Nyiri and Jannitti, 1932). So, in vivo humans, The penetration-promoting effect of the polyethylene glycol ointment was investigated and by determining its excretion from the phenolsulfonphthalein, drug concentration, so it will used as a tracer dye for the use of a photoelectric colorimeter (Nadkarni et al., 1951). In the other early studies, the characteristic pharmacological or physiological end points were used as a proof to the absorption of its compounds into its systemic circulation (Gemmell and Morrison, 1957). The sex hormones are widely investigated on experimental animals such as; rats, mice, dog, frog by using them as a subjects. The hormone testosterone will propionatly applied as an ointment on the skin of castrated male guinea pigs are shown and it is readily absorbed under the accessory reproductive organs which remained functional (Moore et al., 1938). So, similarly, the oestrogen application on the shaven back skin of female mice which is ovariectomized , by using vehicles containing ethanol and/or benzol, led to oestrus (Zondek, 1938). The convulsions in mice, rats and guinea pigs are convulsions and it was applied externally and also it contains highly toxic strychnine alkaloids (Macht, 1938).

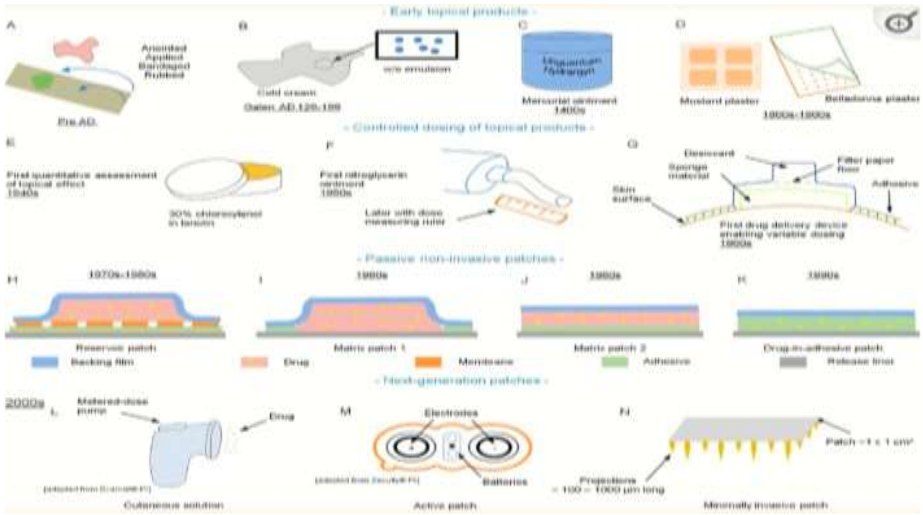


Fig (01) ;- the historical development of the transdermal patches. Early topical products ; (a)products from ancient times, (b) Galen's cold cream, (c) Mercurial Oientment, (d) Mustard and belladonna plasters ; controlled dosing of topical products, (e) first quantitave systemic delivery [zondek system}, (f) individualized delivery system ; nitroglycerin ointment, (g) topical delivery device (wruster and kramer system}, passive non invasive patches , (h) first patch system ; the reservior introdcued for scopalamine, nitroglycerine, clonidol. Osterodial (i,j,k) other types of patches – matrix and drug-in-adhesive {fentanyl and nicotine patches} , next generation patches (l) cutaneous solutions{examples – patchless patch and evamist}, active patches {examples – iontophorosis, zecuity} (n) minimally invasive patches [examples – microneedles and nanopatch} .

2. Development of topical products with systemic effects :-

The clinically managing of this 1st quantitative report, a systemic condition which is topically applied and it will appears as the work of Zondek, from now, around 70 years ago. Zondek reported that an external disinfectant (chloroxylenol), is still present in today's most of the antiseptic soaps and solutions (Dettol®; Reckitt Benckiser, Slough, Berkshire, UK), and it could be effective, when it is topically applied as a 30% lanolin ointment for the treatment of urogenital infections (Figure 1E) (Zondek, 1942a,b). Interestingly, the potential percutaneous absorption of the drugs are now found in many of our current transdermal products which has been demonstrated so much earlier through this inadvertent toxicity after the topical exposure during on its manufacturing, consumer use of the products and also it will be used in farming too. So, for instance, nitroglycerin permeation across the human skin, and now it is used transdermally to prevent and for the treatment of angina, first came on light in the early 1900s as a side effect –'nitroglycerin head' – it's a severe headache experienced by the people who are working in the manufacturing of explosives or otherwise handling nitroglycerin-containing materials (Laws, 1898; 1910; Evans, 1912). And Experimentally, 1 and 10% alcoholic nitroglycerin solutions are applied topically to the forearm of healthy humans which leads to its prolonged systemic effects (such as; headache, changes in BP and pulse rate), and with volunteers it eventually showing an acquired tolerance to the headache effects after an average of 38 hours (Crandall et al., 1931). However, it was not last until the year 1948 that a nitroglycerin, an ointment was successfully applied for the treatment of Raynaud's disease (Fox and Leslie, 1948; Lund, 1948). This work led to a 2% nitroglycerin ointment (Nitrol®; Kremers Urban Company, Seymour, IN, USA) being used to treat angina pectoris in the 1950s. a wooden applicator, which was used to measure its dose of nitroglycerin was applied on chest (Davis and Wiesel, 1955). In the year 1974, a clinical trail demonstrates a sustained prophylactic efficacy lasting for up to 5 hours (Reichek et al., 1974). However, the ointment was messy and needed to be applied several times a day. Therefore, the Concerns are remained about the exact amount of drug which is being applied on each time (No authors listed, 1976). And also another example, the systemic adverse effects of nicotine, the transdermal smoking cessation drug, it becomes apparent after it is topically contacted and also it is associated with the usage of a topical insecticide (Wilson, 1930; Faulkner, 1933; Lockhart, 1933). In addition, of the nicotine absorption was noted among workers who are harvesting tobacco leaves in the form of the green tobacco sickness (Gehlbach et al., 1974; 1975,). The

percutaneous absorption of oestrogens were discovered in the year 1940s, when men are working in stilboestrol plants which will be notices its enlargement of their breasts (Scarff and Smith, 1942; Fitzsimons, 1944). Major barrier layer of the skin, the stratum corneum, Which consists of an interstitial lipid pathway and a proteinaceous cellular compartment. These drug molecules can penetrate into the skin primarily through the tortuous and continuous intercellular path. The Transport of topical drugs, especially with the aid of its solvents and enhancers are used in the formulation, and may also occur through a transcellular route, the hair follicles, or sweat ducts. Only the drug on the molecular state can penetrate through the skin. The Occluded skin, for example- the application of the ointment on skin, it may retain a significant amounts of the transepidermal water and it will facilitate the drug transport through the hydrated skin.

From looking it into the drug delivery perspective ; the concentration gradient between the formulation and site of action provides the driving force for penetration of drug through the skin. Thus the saturation of drug in the vehicle having a thermodynamic activity of unity will provides a larger driving force for transporting through skin than a formulation at a lower fraction of the saturation (example - highly solubilized system). The Super-saturated conditions having its thermodynamic activity greater than its unity, so it can further enhance the drug delivery through the skin. The drug in a super-saturated solution is in a metastable state and, hence, it may convert back to its stable form, from changing its flux of the drug through the skin.

2.1 The development of adhesive transdermal delivery devices

The simplest form of the adhesive system is the membrane permeation control system. In this system, the adhesive system contains a lot of drugs and serves to glue on different layers together. Then the drug mixture will be sandwiched between its layers of liner and backing. Dale Wurster's contribution to the early understanding of the transdermal drug delivery is acknowledged (Roberts, 2013). So many Important components of that work, which are often associated with the transdermal delivery, and the defined delivery system in the dose, area, the vehicle and the device; the quantification of the time course of its absorption into urine; and the application of pharmacokinetic principles to quantify the resulting drug delivery kinetics. The first set of transdermal studies in wurster, his student whose name was Sherman Kramer, glued a diffusion cell containing at a defined dose of the salicylate esters to the forearm of his human volunteers and then he measured their systemic absorption by the excretion of salicylates in the urine. The extent of absorption could be modified by varying the diffusion area of the cell and by changing the level of the skin hydration (Wurster and Kramer, 1961). The primitive diffusion cell was designed (Figure 1G) and it is used in a study appears very much to be the forerunner of cells which are currently used on transdermal research and could even be more considered as a first prototype on the today's commercial transdermal devices in that. In vivo diffusion cell will permits a precise which are according to its area-dependent dosing of a topically applied drug (Roberts, 2013). There are a number of salicylate esters and other non-steroidal anti-inflammatory products on the market for the local pain relief. The Skin biopsies and also the microdialysis

have been used to show their selective targeting to the deeper tissues in preference to its systemic blood supply (Cross et al., 1998; Roberts and Cross, 1999). Recently, the dermal vasculature is a major conduit to deeper tissues for highly bound anti-inflammatory drugs based upon the analysis of the available microdialysis data (Dancik et al., 2012) and for corticosteroids by biopsy (Anissimov and Roberts, 2011).Ten years after Kramer's studies, the first patent using a rate-controlling membrane to control the rate of transdermal delivery from a bandage for the continuous delivery through the skin of drugs into the systemic circulation was filled by the biochemist and entrepreneur Alejandro Zaffaroni (1923–2014) (Zaffaroni, 1971). The drugs which are studied, such as; scopolamine, nitroglycerin, oestradiol and fentanyl all drugs are developed into marketed transdermal systems. So, it can be considered as the history associated with the patch development of each of these drugs.

2.2 Nitroglycerin for angina pectoris: from the ointment to the transdermal patches ;-

To the treatment for angina and anal fissures, the nitroglycerin will be used as a medication. It works by promoting blood flow. For the transdermal patches, the marketing of the transdermal scopolamine patch, a nitroglycerin ointment was the only transdermal product on the market. Whereas the nitroglycerin ointment led to more sustained serum levels than sublingual and parenteral oral sustained release capsule dose forms (Maier-Lenz et al., 1980), the plasma levels were dependent at a given dose of ointment was applied on the surface area (Sved et al., 1981). However, applying a precise dose to a stratified area is difficult. (For example, the dosages of Nitro-Bid® the nitroglycerin ointment, which USP around 2%; Fougera, Melville, NY, USA), and also it is used in clinical trials to define the length of ointment it was determined by using a ruler. The ribbon will be ejected from the ointment tube (Figure 1F) and its ranges around 1.3 cm (1/2 in.; 7.5 mg) to 5.1 cm (2 in.; 30 mg), typically it is applied to be 232 cm^2 (36 $in.^2$) on skin located on the trunk of the body. An additional limitation of these semi-solids is the need for the frequent dosing, example - every 8 hours for the Nitro-Bid, to achieve a therapeutic effect, which is likely to lead to a greater patient non-compliance than once daily dosing possible with the patches. However, the nitroglycerin volatilization are appeared to not as a issue (Cossum and Roberts, 1981). But in contrast, some unintentional transfer through the interpersonal contact was a problem, as evidenced by the report of spousal headache after intercourse with partner who had rubbed a nitroglycerin patch on his penis for the treatment for erectile dysfunction (Talley and Crawley, 1985).

In the year 1973, Alza Corporation filed an additional US patent based upon its topical rate-controlling membrane, a medicated adhesive bandage concept for the controlled systemic administration of vasodilators , such as nitroglycerin. The patent embodiment is shows that the drug within the reservoir could be mixed with a transporting agent to assist the drug delivery. At the beginning of the year 1980s, Key Pharmaceuticals and Searle Laboratories disclosed two different nitroglycerin transdermal system designs: one will be a water-soluble polymeric diffusion matrix containing nitroglycerin and second one is a microsealed pad with a polymer matrix containing nitroglycerin within a hydrophobic solvent to enhance nitroglycerin transport

and diffusion is Associated with these patents, three nitroglycerin transdermal patches varying in structure and dosages which were introduced on the US market in the year 1981 for prevention and treatment to the angina pectoris: Transderm-Nitro® (Ciba Pharmaceuticals Company), Nitro-Dur® (Key Pharmaceuticals) and Nitrodisc ® (Searle Laboratories). Since it had been learnt in some clinical studies that nitroglycerin inactivated itself upon from the sustained delivery, in each marketed patch was to be applied once daily with an approximately 12 hours consists of the 'rest period' between the wear times. A subsequent patent claimed that addition of ethanol as a permeation enhancer to the transdermal nitroglycerin system enabled nitroglycerin skin fluxes of atleast 40 $\mu g \cdot cm^{-2} \cdot h^{-1}$ (preferably in the range of 50–150 $\mu g \cdot cm^{-2} \cdot h^{-1}$) greater than the prior art. In the country United States, the Key Pharmaceuticals eventually developed a patch at which the drug was contained solely as a adhesive, the first successful commercial patch of this kind and this patch was captured a greatest share in the nitroglycerin market. The patch was later marketed as Nitro-Dur II® and described in a US patent.

2.3 Transdermal clonidine for the treatment of hypertension ;-

The Transdermal clonidine is used alone or in combination with other medications to treat high blood pressure. Clonidine is in a class of medications called centrally acting alpha-agonist hypotensive agents. By decreasing your heart rate and relaxing the blood vessels it will work and so that the blood can flow more easily through the whole body. The Clonidine was approved by the US Food and Drug Administration (FDA) in 1984 for up to 1 week transdermal delivery to manage mild-to-moderate hypertension (Sica and Grubbs, 2005), it is applied on the facial skin as a form of shaving lotion, a soap (or) a cream and also for its pilomotor effect (Zeile et al., 1965), in which its stimulation of the arrector pili muscle of the skin causes goose bumps so that hairs are raised away from the skin. In the year around 1960s, hypotensive effect on drug clonidine was discovered by an accident, when a drug solution was introduced into the nose of a woman suffering from cold to test the nasal decongestive properties of the clonidine. But Surprisingly, until the next day the woman fell into a deep sleep, and when she woke up, while performing the controlled tests shows a significant drop in BP and heart rate (Stähle, 2000). Transdermal clonidine was developed to reduce drug side effects (mainly drowsiness and dry mouth) and to improve patient compliance (Shaw et al., 1983), which was estimated to be no more than 50% with parenteral oral hypertensive therapy (Haynes et al., 1978). In a patent, the drug release rate will be claimed of a clonidine transdermal system could be modulated from 1.6 to 2.4 $\mu g \cdot cm^{-2} \cdot h^{-1}$ by modifies the polyisobutylene (PIB)/mineral oil ratios on the drug reservoir. First clinical trials showed that the clonidine transdermal patch was an effective alternative to parenteral oral administration in decreasing BP in healthy volunteers (Arndts and Arndts, 1984) and in patients with essential hypertension (Popli et al., 1983; Weber et al., 1984). The clonidine patches have been associated with a high rate of the dermatological adverse reactions (example - allergic contract dermatitis), leads to the treatment for discontinuation (Boekhorst, 1983; Groth et al., 1983; Holdiness, 1989).

2.4 Transdermal oestradiol for female hormone replacement therapy :-

Cutaneous application of follicular hormone (follicle-stimulating hormone), oestrone, for amenorrhoea was introduced by Zondek (1938). In 1960, 2 g of an ointment containing both radiolabelled oestradiol-17β and progesterone was applied to human subjects. Between 16.5 and 44% of the radioactivity appeared in the urine within 72 h (Goldzieher and Baker, 1960). The Oestradiol drug was first applied transdermally for the treatment purpose of the post-menopausal replacement therapy as a hydroalcoholic gel (Oestrogel®; Benins-Iscovesco) (Holst et al., 1982; Holst, 1983). This dosage form was messy and dosage control was so difficult. In the year 1983, a united states (US) patent discloses a bandage which is applied on the skin for its administration of the drug oestradiol within a vehicle it is so rich in ethanol, and latter it will be used as a enhancer for the percutaneous absorption (Campbell and Chandrasekaran, 1983). A microporous polymer film membrane was used to maintain the fluxes of oestradiol and ethanol in the vicinity of 0.1 and 400 $\mu g \cdot cm^{-2} \cdot h^{-1}$ respectively. The plasma levels of oestradiol which are sustained and also obtained with the device overcame the key peak and through profile limitation and then the marketed oestradiol drug ointment (Strecker et al., 1979). In the year 1984, the transdermal oestradiol system is the first system which is reached in the United states (US) market. The application oestradiol plasma levels results are being circulated as (40–60 $pg \cdot mL^{-1}$) and also it is so sufficient to meet the early follicular phase of the hormone levels (Good et al., 1985). A number of clinical trials demonstrated the efficacy of Alza's transdermal device in reducing hot flushes and showed the advantages of transdermal delivery as compared to conventional parenteral oral. oestrogen treatment (i.e. reduction in daily dose required, limited effects on liver function) (Laufer et al., 1983; Powers et al., 1985). Eventually, the patches with oestradiol are exclusively in the form of adhesive and were developed and these are assumed under strong market positions. Today, an alternative approach is to use metered-dose applicators, exemplified by Elestrin® (oestradiol 0.06% in a hydroalcoholic gel base; Meda Pharmaceuticals, Somerset, NJ, USA) packed as 100 doses each of 0.87 g gel and Divigel® (Orion Corporation Pharm, Turku, Finland) packed as single use gel-filled sachets (0.25, 0.5 and 1.0 g gel-filled foil packets containing 0.25, 0.5 and 1 mg of oestradiol respectively).

2.5 Transdermal fentanyl for the treatment of pain :-

For the treatment of pain, the Alza fentanyl patch, marketed by Johnson & Johnson (J&J) as Duragesic®, has dominated the transdermal market with peak sales of greater than $2 billion in 2004. Michaels et al. (1975) showed its potential as a transdermal candidate by reporting maximum fluxes through human thigh skin of 0.8–3.8 $\mu g \cdot cm^{-2} \cdot h^{-1}$ (average, 2 $\mu g \cdot cm^{-2} \cdot h^{-1}$) at 30°C. A 1986 US patent, disclosing various transdermal system designs with different sizes (5–100 cm^2) for the delivery of the free base of the narcotic fentanyl, observed that *in vitro* skin penetration rates of 0.5–10 $\mu g \cdot cm^{-2} \cdot h^{-1}$ could be maintained for at least 12 h and for up to 7 days (Gale et al., 1986). The in vivo delivery of fentanyl citrate of this system and also its base (and sufentanil citrate and base) was demonstrated through the skin by applying 50 μg of the drug in water to the forearm skin of five volunteers (six volunteers for sufentanil) under an occlusive dressing,

showing that about 20% of the absorbed do se was recovered in urine after 24 h (Sebel et al., 1987). The first clinical studies evaluating Alza's TTS-fentanyl patch, a standard Zaffaroni system with the drug in the pouch of a form-fill-seal design, were conducted in patients in the late 1980s (Duthie et al., 1988; Holley and van Steennis, 1988; Caplan et al., 1989). On studies, by comparing the permeation of fentanyl and sufentanil drugs across human skin in vitro, the relationship of the physicochemical properties and its suitability for the transdermal delivery (Roy and Flynn, 1989; 1990,), Roy et al. (1996) shows that optimum flux of fentanyl through human skin from various adhesive patches was achieved when its activity thermodynamic and in the patch it was maximal. The Alza patch can ran into difficulties in the year 2006, when its patent was expired and it was found that the drug fentanyl could leak out from the patch reservoir (Watkinson, 2012). while the United states (US) FDA approved the Mylan fentanyl matrix [drug-in-adhesive (DIA)] patch, described in a US patent (Miller et al., 2009), in the month January, year 2005 and another from Lavipharm in August 2006, J&J had sales of more than $1.2 billion in 2006 and $900 million in 2009, mainly due to J&J's assertive marketing and patent protection (Watkinson, 2012). Although the Noven received approval for its new generic patch in the year 2009, and its initial application in September year 2005, because of its patch it was failed and contains a much more fentanyl than that in Duragesic. So, Ultimately these matrix designs, are together with Activis (2007), Watson (2007) and Teva (2008), dominated the whole market (Watkinson, 2012).

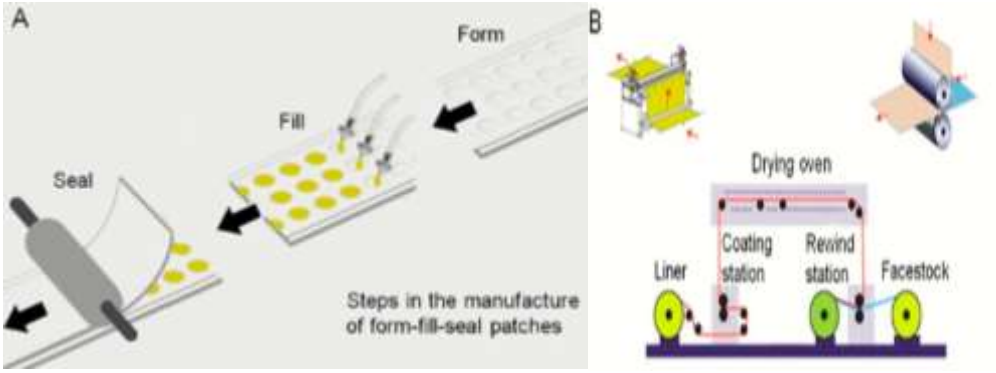
2.6 Nicotine patches for smoking cessation aid: the first transdermal achievement :-

It was first used in a transdermal form as a smoking reduction and cessation aid in the year 1984. One of the study shows a significant levels of nicotine in the saliva between 30 and 90 minutes, after the topical application of 9 mg of nicotine base in a 30% aqueous solution to the forearm of a volunteer and also there was an increase in pulse and the systolic Blood pressure (Rose et al., 1984). A study showed a reduced craving in 10 cigarette smokers after application of 8 mg of nicotine base on a 30% aqueous solution in a polyethylene patch in comparison to an inactive placebo solution (Rose et al., 1985). The first German patches having nicotine which was proved to be successful in suppressing the urge to smoke during clinical trials in Münster/Germany in the year1989 (Buchkremer et al., 1989). In one of the first United states patents which are dealing with the transdermal drug delivery of nicotine claims an occlusive transdermal pad and it is attached to the skin with a reservoir liquid on a nicotine base (Etscorn, 1986). So, In this invention, the drug delivery of nicotine from this device which was controlled with the use of a microporous membrane and also its duration of drug delivery around 30–45 min, thus requiring the application of several patches over the course of a day to maintain its nicotine plasma levels. A patent, which is subsequent is disclosed a monolithic patch with a polyurethane matrix layer that contained between 5 and 50% nicotine. This system was used to delivered the nicotine through human skin atleast 24 hours (Baker and Kochinke, 1989). later United States patent suggests that the concentration of nicotine in the patch reservoir which should preferably be on the range of a thermodynamic activity which is less than 0.50 (Osborne et al., 1991). Between the end of the year 1991 and early 1992, four nicotine patches containing a proper different designs, all are obviously

approved by the US FDA, and also it reaches the US market within a few months. Those nicotine patch products are Ciba-Geigy/Lohmann Therapie-Systeme (LTS): Habitrol® (matrix); Lederle/Elan: Prostep® (matrix); Marion Merrell Dow/Alza: Nicoderm® (reservoir/membrane); and Warner-Lambert/Cygnus: Nicotrol® (DIA). Collectively, the products became a huge commercial success with total sales approaching US $1 billion during their year of its introduction. Million smokers gave up smoking with the help of these nicotine patches (Prausnitz et al., 2004).

3. Design of patches based upon engineering and pharmacokinetic principles :-

The Reservoir and rate-controlling membrane:- The dosing and possible transfer variability of the active to others with ointment and cream transdermal systems has been emphasized and need to have a controlled, occluded and safer delivery systems. This has been a major driver in the development of the TTSs that are commonly known as 'transdermal patches'. And it was a combination of a reservoir containing the active and a rate-controlling membrane pioneered in the year 1970s by the entrepreneur Alejandro Zaffaroni by his company which was named Alza. His first commercialized TTS was a scopolamine TTS. Alza championed the view that the co-existence of a reservoir and rate-limiting membrane on their system requires a key element to minimize its variability in skin permeability within and between individuals and subsequent drug blood levels. A key premise was that the device, and not the skin, controlled drug input into the bloodstream (Shaw and Theeuwes 1985). In turn, the precisely controlled delivery into the systemic circulation through intact skin not only attained an adequate therapeutic effect to prevent the motion sickness but also it has its minimized and undesired central nervous system (CNS) adverse events such as drowsiness and confusion (Shaw and Urquhart, 1979). The reservoir/membrane patch design which is illustrated in the Figure 1H. This type of patch design (also known as form-fill-seal design), and the drug contains a compartment and which is usually present in the liquid form (i.e; solution (or) suspension (or) gel). This liquid or gel reservoir from a continuous adhesive layer by a permeable membrane is separated and that will controls the release of the active from of its device. Figure 2A and B shows, for the reservoir patch, the process of form-filling-sealing and coating-drying respectively.



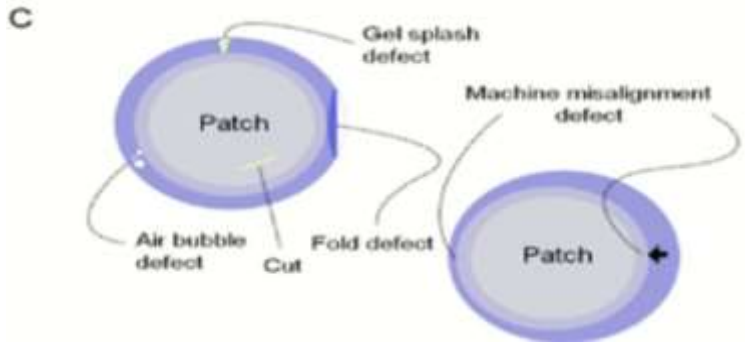


Fig (02) :- Manufacturing process for and potential failures of reservior patches;

(a) Form filling and sealing process (b) Coating and drying process

(c) Potential problems arising during patch reservoir manufacturing process.

In this system, The major limitation is the potential for its leakage which is sealed the liquid reservoir that could arise from an aberration in the patch manufacturing . Uncontrolled drug release from the reservoir and also the drug overdosing (a dose-dumping effect) could arise, from an accidental rupture of a backing membrane (Govil, 1988; Peterson et al., 1997). It needed form-fill-seal type of fentanyl patches which were apparently associated with this problem and also facing such similar problems in the early 2000s. Figure 2C shows some examples of issues that may arise with this patch design. In addition, the use of reservoir solution can also lead to other difficulties. Example, a design fault in the Estraderm® device, patented by Alza in the year 1984 (US Patent 4,460,372) (Campbell and Chandrasekaran, 1984) that leads to an unexpected drug delivery profile despite of the presence of a rate-controlling membrane (Paoletti et al., 2001). In this system, a 'rate-controlling' membrane, the putative membrane will affect the overall flux of both the drug and the enhancer.

4. **DRUG CANDIDATES FOR TRANSDERMAL DELIVERY :-** The drugs which are used that can penetrate into the skin, which are sufficiently potent to be active and that needs a clinical need. Based on the recent studies, for transdermal administration nearly two dozen molecules have been approved by the regulatory authorities reached the market. The overriding commercial need for any new product is, as Watkinson (2012) puts it, the 'meeting of unmet medical needs' at 'a reasonable cost'. The maximal skin penetration flux of a drug which was determined by the product based upon its solubility in the stratum corneum and the diffusivity on the stratum corneum (Kasting et al., 1987; Roberts, 2013). The solubility can be related to the melting point (MP), and also the drug–stratum corneum interactions and diffusivity can be related to its molecular weight (MW) or molar volume (Roberts and Cross, 2002) but the molecular size can dominate the other variables with a wide variety of drugs which are used to study the percutaneous penetration (Magnusson et al., 2004). In topical and transdermal patches, the drugs have a limited size range. The Table (1) shows the the current drugs in transdermal patches and its properties. Recently, Wiedersberg and Guy (2014) used some of these properties, a combination of MW and drug–solvent interaction parameters [such as aqueous solubility (S_{aq}) and log octanol–water partition coefficient (log P)], to estimate its drug delivery rate of drugs through human skin.

Drug	MW[a] (Da)	MP (°C)[a] Unionized	log *P*[b]	S_{aq} (mg·mL^{-1})[a] Unionized(25°C)
Buprenorphine	**468**	**209**	**3.8**	0.047, 0.008[h] (32°C)
Clonidine	**230**	**130**	**2.7**	0.17, 13.58[i]
Oestradiol	**272**	**173-179**	**4.2**	0.003, 0.003[j] (30°C), 0.0015 1[k] (25°C)
Ethinyl oestradiol	**296**	**141-146**	**4.3**	0.039, 0.0092[k] (25°C)
Fentanyl	**337**	**83-84**	**3.9**	0.15, 0.2[j] (30°C), 0.2[l] (25°C)
Levonorgestrel	**312**	**235-237**	**3.8**	**0.017**
Testosterone	**288**	**155**	**3.6**	0.02, 0.02[j] (25°C)

Table (01) :- physiochemical, pharmacokinetic and safety data for currently marketed transdermal drugs.

5. VARIABILITY , SAFETY AND REGULATORY ISSUES FOR PATCHES :-

5.1 Site of application :-

The human skin penetration fluxes are highly dependent upon the site of application (Feldmann and Maibach, 1967; Scheuplein and Blank, 1971; Roberts et al., 1982; Roberts and Walters, 1998). And some parts of the body (trunk and upper arm) appear to have similar fluxes, which are enables its patches to be interchangeably placed at those sites and to achieve a similar plasma concentrations. For instance, MacGregor et al. (1985) showed that plasma concentrations obtained after the application of a 3.5 cm^2 clonidine patch (Catapres-TTS) on chest and arm were not significantly different over the recommended wear time. Schenkel et al. (1986) also showed that Estraderm could be applied to different sites of the trunk and to the upper arm without significant differences in the oestradiol uptake. Gorsline et al. (1992) later showed that bioequivalent ($AUC_{0–t}$, $AUC_{0–\infty}$ and T_{max}) plasma were achieved irrespective of the application site on the upper body (upper back, upper outer arm, upper chest) from Nicoderm 14 mg per 24 h. Yu et al. (1997) it showed that testosterone hormone transdermal system (D-Trans testosterone gel system®) could be applied as interchangeably on the upper buttocks of the skin, upper arms or upper back, giving similar drug plasma concentrations at three different skin sites ($AUC_{0–27}$, C_{max} parameters not significantly different). The plasma concentrations of norelgestromin and ethinyl oestradiol after its application of the contraceptive patch named Ortho Evra® remained in its reference ranges during the wear-period after application on abdomen, buttock, arm and torso (Abrams et al., 2002). However, Lefèvre et al. (2007) shows a higher plasma exposure of the drug rivastigmine ($AUC_{0–\infty}$ and $AUC_{0–last}$) after the application of Exelon® 8.5 mg per 24 hours and the patch on the upper back, chest, thigh and abdomen. Similarly, Taggart et al. (2000) showed that the extent of drug absorption ($AUC_{0–168}$ and $AUC_{0–last}$) from an oestradiol patch (Climara 0.1 mg per 24 h) application on buttock was significantly higher than when applied to the abdomen. For both sites, the observed plasma drug concentrations were consistent with physiological oestradiol levels required to relief its menopausal symptoms (Taggart et al., 2000). Finally, the systemic exposure of nicotine from Nicorette 15 mg per 16 hours applied on the upper arm was highly compared with the abdomen but it was

equivalent to the back (Sobue et al., 2005). The transdermal systems should not be applied on the waistline as a tight clothing it may rub or remove the patch , practically.

5.2 Safety:-

The safety ratio for the systemic percutaneous absorption of drugs which are presently marketed in patches relative to the maximum dose for the drug and it is usually atleast 10 or more. Mainly these safety ratios relates to the adult skin. Liebelt and Shannon (1993) pointed out that many over-the-counter (OTC) topical medications are commonly used and including methyl salicylate, camphor, topical imidazolines and benzocaine, which can cause serious toxicity in children when ingested in small doses. In full-term infants, The barrier function is fully developed, and also that in premature infants is incomplete in the stage (Fluhr et al., 2010; Delgado-Charro and Guy, 2014). The transdermal administration has been used to deliver drugs like theophylline and caffeine to the premature infant, for whom dosing by conventional routes of administration will be difficult (Barrett and Rutter, 1994). However, this impaired skin barrier function in neonates can also puts them more at risk (Kalia et al., 1998; Delgado-Charro and Guy, 2014) so that any unplanned percutaneous absorption in neonates is potentially hazardous (Rutter, 1987).

The Manufacturing defects (i.e. seal and membrane defects) with the possibility of dangerous drug leakage during use have led to patches being recalled in the year's 2004 and 2008. The leakage may expose patients at a potentially fatal overdose.

5.3 Regulatory :-

The product quality will attributes the typical includes, polymorphism and microbial limits**.** The Other quality attributes may be description (visual examination of the patch), identification, assay (content of drug product), impurities, dosage form uniformity, residual solvent levels, cold flow property (adhesive migration out of the edge of the patch during storage or when the patch product-specific such as water content (for hydroalcoholic reservoir patches), particle size (when the drug substance is suspended in the patch), crystal formation test (when a patch contains dissolved drug substance) and leak test (for liquid reservoir patch) (Van Buskirk et al., 2012; USP, 2014a). In vitro drug product performance usually involves three tests: *in vitro* drug release, *in vitro* skin permeation studies and *in vitro* adhesive tests. Basically, from a transdermal patch , the In vitro tests on drug release will evaluate the rate and the extent of drug release as described in both European Pharmacopoeia (Ph Eur) and as per the United States of Pharmacopoeia, which also includes the paddle over disk method (USP Apparatus 5/Ph Eur 2.9.4.1), the rotating cylinder method (USP Appartus 6/Ph Eur 2.9.4.3) and the reciprocating holder method (USP Apparatus 7) (USP, 2014b; Ph Eur, 2015).

Regulatory aspect - the required amount of unused drug which is left in the patch when it is removed from the skin surface, it is defined by the FDA's guidance in August 2011 as a Residual Drug in Transdermal and Related Drug Delivery Systems (FDA, 2011).

6. THE RECENT ADVANCEMENTS IN TRANSDERMAL PATCHES :-

There are so many new developments has came out in the field of transdermal drug delivery system as discussed below ;

SMART PATCHES	The Smart patches are equipped with sensors and other technologies that can monitor patient conditions and adjust drug delivery and This patch uses a conducting polymer such as poly-(3,4-ethylenedioxythiophene) (PEDOT) for glucose detection and also as a electrical mediator and also used as a immobilizing agent for the glucose-specific co-enzyme glucose oxidase (GOx). The patch will painlessly penetrates into the interstitial fluid in between the subcutaneous skin cells. For the resulted development in a smart insulin will release the patch, which contains around 121 microneedles, and also contains the nanoparticles. the Smart patches used to deliver natural compounds such as curcumin and the delivery yield of curcumin is good and satisfactory.
DISSOLVING/ DEGRADABLE PATCHES	These patches are designed to dissolve on the skin and do not need to be removed and discarded. These patches are made from biodegradable materials that are absorbed by the body after its use. The Dissolving microneedles (MNs) shows a high efficiency in the delivery of poorly permeable drugs and vaccines. A two-step injection and centrifugation process was used to localize insulin to the needle and achieve efficient transdermal delivery of insulin. The relative pharmacological availability and relative bioavailability (RBA) of insulin from Microneedle patches were around 95.6% and 85.7%. This study demonstrates that these dissolving patches are used for the insulin delivery achieves a satisfactory relative bioavailability (RBA) and also compared to the conventional subcutaneous injection, which will demonstrates the effectiveness of these dissolving patches for diabetes treatment.
	The three-dimensional (3D) printing technique called continuous liquid interface production (CLIP) was used to design and fabricate transdermal patches. The multifaceted microneedle design increased the surface area compared to the smooth

THREE DIMENSIONAL(3D)–PRINTED PATCHES	square pyramid design, ultimately resulting in the improved surface coating of model vaccine components (ovalbumin and CpG). A group of researchers designed and printed the patch using stereolithography (SLA) technology with a proprietary class I resin. They showed that these patches can be used for transdermal delivery of high molecular weight antibiotics such as rifampicin (M(w) 822.94 g/mol). This drug will suffer from the gastric chemical instability, the reduced bioavailability, and also the severe hepatotoxicity. The patch was engineered with sub-apical holes present in one-quarter of the needle tip to enhance the mechanical strength and integrity of the patch array. The administration of the rifampicin drug through a 3D patch shows a desirable bioavailability and efficient penetration.
HIGH LOADING/ RELEASING PATCHES	The Long-acting transdermal drug delivery requires high drug loading and controlled drug release. To improve a drug-polymer miscibility and achieve a good controlled drug release, a hydroxyphenyl (HP)-modified pressure-sensitive adhesive (PSA) was developed. The results will show that the dual-ionic H-bonds between R(3)N and R(2)NH-type drugs and HP-PSA are completely reversible and also relatively strong, unlike all the ionic and neutral H-bonds. This allowed patches to significantly increase the drug loading from 1.5- to 7-fold and control the drug release rate from 1/5 to 1/2 without changing the overall release profile.
TRANSDERMAL PATCHES FOR VACCINATION	The transdermal patches will deliver the vaccines through the skin, and potentially offering a more convenient and less painful alternative to injections. Example – a microneedle-based smallpox will be used as a vaccine patch and also this vaccine patch was applied to mice, neutralize the antibodies which were induced upto 3 weeks after the immunization. Levels were maintained for 12 weeks, and there was a significant increase in IFN-γ secreting cells, suggesting that the transdermal patch could serve as an alternative delivery system for vaccination and preservation
TRANSDERMAL PATCHES FOR GENE THEAPY	The transdermal patches are co-loaded with p53 DNA and IR820 (a near infrared dye) were prepared by a two-step casting procedure. Before p53 DNA and IR820 which were primarily loaded upon the patches, The Hyaluronic acid was first constructed as the matrix, The patches are efficiently penetrated towards the stratum corneum and it will rapidly dissolved to release the p53 DNA and IR820 at subcutaneous tumor sites. In the

	in vivo drug release , the patch shows an excellent anti-tumor effect which is due to the synergistic effect of gene therapy and photothermal agents.
TRANSDERMAL PATCHES FOR INSULIN DELIVERY	The Transdermal patches for insulin delivery can provide a convenient and discreet alternative to traditional methods of insulin delivery, such as injections and insulin pumps. The patches are typically applied to the skin on the abdomen, upper arm, or thigh and are designed to release a consistent dose of insulin over a specific period of time.

6.1 FUTURE PROSPECTS OF TRANSDERMAL PATCHES AND TRANSDERMAL DRUG DELIVERY SYSTEM:-

There is a move towards 'active' transdermal delivery systems in today , that can be use as minimally invasive technologies, to enhance drug delivery across the skin as well as challenging drug candidates, the actives which have a low penetration flux and low potency such as; iontophoresis, microneedles, electroporation and sonophoresis, (Naik et al., 2000; Gratieri et al., 2013). The active patches development has been associated with much false hope with its initial commercial success and it is being hampered by most of the commercial, technical and consumer issues (Watkinson, 2012). The most recent focus for a drug delivery system is the use of microneedles being on single-dose vaccine delivery (Quinn et al., 2014). For instance, the Nanopatch® (Figure 1N) requires a second-order lower dose of antigen which is delivered to the skin to achieve the antibody responses and it is comparable to conventional through an intramuscular injection (Fernando et al., 2010). For long-term treatment, the usage of microneedles has also been recently investigated for its treatment of opiate and alcohol dependence with naltrexone, which is an opioid antagonist (Wermeling et al., 2008). A parathyroid hormone (1–34)-coated microneedle patch, developed by Zosano Pharma (formerly, Macroflux® Alza Corporation) for the treatment of osteoporosis, it has been shown to be efficacious in the clinical trial Phase II (Daddona et al., 2011).

For the transdermal delivery systems, particularly the transdermal patches, which are increasing and also it is being used in a paediatric population. A range of transdermal patches (i.e. about 10 drugs) which have been used in children and also some have been specifically developed for paediatric purpose, for the treatment of attention deficit hyperactivity disorder (ADHD) the methylphenidate drug is used. So, the transdermal

drug delivery which will be regarded as a convenient non-invasive method patch of drug delivery for term infants and older children requires a smaller doses than adults, and also the formulation challenges remain for premature neonates with an immature skin barrier (Delgado-Charro and Guy, 2014).

7. CONCLUSION :-

Since the arrival of man, the Topical delivery systems which have been used for various ailments and also cosmetics. For Over time, there has been a definition for suitable drug candidates for transdermal drug delivery and also it is associated with the development of technologies, both passive and active, which has led to delivery enhancement, precision in drug dosing and a better meeting o individual needs. A focus in the further development of drugs in transdermal patches and associated delivery forms remains the finding of sufficiently potent drugs that can penetrate the skin with an appropriate transdermal technology. The Transdermal patches have the potential to provide a convenient and effective means of drug delivery for a variety of ailments, but some challenges lies ahead, such as the possibility of self-inflicted toxicity due to improper dosing, poor adhesion, low drug penetration, potential trigger for skin irritation, or patch failure. All of this warrants for a good research and development in future to optimize the safety and efficacy of this delivery system.

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