Review Article

Transdermal Drug Delivery Technology – A Prospective Review

VENKATESAN RADHAKRISHNAN[1*] , PETER CHRISTOPER G.V. [2] MANASA.SINGIRIKONDA[3], MOHAMMED HABIBUDDIN[4]

[1]Apotex Research Private Limited, Bangalore - 560099 India, [2]Lupin Limited Goa-403722 [3]Department of Industrial Pharmaceutics, Alliance Institute of Advanced Pharmaceuticals and Health Sciences, Hyderabad-500 038, India, [4]Adept Pharma & Bioscience Excellence Pvt. Ltd., Hyderabad, India.

[*]Address correspondence to this author at the
Venkatesan Radhakrishnan
Apotex research private limited, Bangalore - 560099 India
India: Tel:+91 90361 55340.
E- mail: esavenkat@gmail.com

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ABSTRACT

Transdermal drug delivery system (TDDS) has turn out to be a grand field for discovery and patents in drug delivery technology. The innovations in delivering the drug to systemic circulation by overcoming the hurdles related to API Characteristics like molecular size, lipophilicity, permeability, through physical or chemical enhancers is being achieved by using this drug delivery platform. More than 100 different kind of transdermal patch medications are available in market for various treatments, having more than 5 billon dollar worth sales. This mainly includes the class of drugs such as narcotics, analgesics, anti-anginal and contraceptives. Comparative study on risk factor on various dosage form shows transdermal drug delivery has less risk than other dosage forms and self-administration is possible, hence the patient compliance is higher for this dosage form. The patent application and literature search show the development of transdermal drug delivery in pharmaceutical field as remarkable area of research. Carrier mediated delivery is most recent advancement in this dosage form this includes liposomes, niosomes, proniosomes etc. This review presents basic sciences involved in Transdermal drug delivery system developments, market, literature, recent patents for transdermal formulation composition & system design & search from (USPTO), risk evaluation it also focus on current technologies future developments, manufacturing consideration, safety evaluation & Regulatory overview.

Key words: Chemical enhancement, Iontophoresis, Physical enhancement, Sonophoresis, Transdermal drug delivery system, Transdermal market, Transdermal patent, Transdermal patch types, Risk factor analysis.

INTRODUCTION

For the past twenty-five years there has been drastic changes in formulation technology. Innovations in drug delivery systems are not only related with novel pharmaceutical dosage forms but also resulted in development of new formulation for the treatment using existing drugs. These innovations in drug delivery system offer advantages, like improved patient compliance, maintaining steady state concentration levels of drug for prolonged period, reduced dosing frequency, drug targeting to desired site of action and reduced side effects. The manufacture of transdermal drug delivery systems (TDDS) has higher number of advantages over the oral route of administration [1, 2]. It avoids vagaries associated with gastrointestinal absorption due to pH enzymatic activity, drug food interaction etc, substitutes enteral administration when the dosage administration route is inappropriate for ailment like vomiting, diarrhea, avoids hepatic first pass effects, avoids risk and inconvenience of parental therapy also reduces the frequency of dosing, rapid termination effect of drug by removal of patch from the site of administration, suitability for self-administration [3-7]. The drugs which are available in market and studied widely for the use of TDDS are nifedipine[8, 9], nitroglycerin[10,11], captopril[12], chlorpheniramine [13], propranolol [14,15,16], aspirin[17], norethindrone [18], hydrocortisone[19], acyclovir[20], fentanyl[21], theophylline[22], nicotine[23,24], testosterone[25], clonidine[26,27], lidocaine[28], scopolamine[29], estrogen[30], norelgestromin[31], estradiol[32,33], triptolide[34], rivastigmine[35], terbinafine[36], primaquine[37], rotigotine[38], methylphenidate[39] and selegiline[40]. TDDS not only have pronounced advantages but also limitations like skin irritation, penetration and permeation which depend upon physicochemical properties of drug and varies from

patient to patient[3,7]. The transdermal drug delivery system technique is not new in pharmaceuticals. It has been used for chest congestion with help of mustard seed paste as a drug in past. The first transdermal patch product approved in 1981 for scopolamine by USFDA [41].

Barriers to Transdermal drug delivery

From figure No.1 it is clearly evident that the main barrier to this drug delivery system is the skin. Skin is an impermeable protective barrier, but over a time due to studies &investigations it was proved about utility of skin as a route for drug administration [1-7]. Skin is the most important and easily reachable organ of the body, a fraction of millimeter of tissue separates its surface from the underlying capillary network [20]. The second important thing is to know the physicochemical properties of the drug molecule which is to be designed as TDDS [36].

Skin

Skin is the external protective cover of human body. Skin protects the underlying ligaments, muscles, bones and internal organs. It serves as barrier not only from environment but also to drug substances. The layers of skin which acts as barrier are shown in Figure no.1as follows:

Epidermis

Epidermis is the comparatively skinny, hard layer and it is the outer layer of the skin it is depicted in Figure no.1. Majority of the cells in the epidermis are keratinocytes. These cells from cells in the inner layers of the epidermis which is known to be the basal layer. These are brick wall like structure made up of dead cells and it is the outermost portion of the epidermis. This layer acts as a barrier, as most of the drugs cannot penetrate stratum corneum, however lipophilic drug penetrate easier than hydrophilic drug [42-44].

Dermis

Dermis is lower layer of epidermis shown in Figure no.1; it is a thick layer of fibrous and elastic tissue. It contains nerve endings, sweat glands, oil glands, hair follicles, and blood vessels. The sebaceous glands secrete sebum into hair follicles. Sebum is oil, which keeps the skin moist and soft. This layer transmits drug patch into hypodermis [42-44].

Hypodermis

Hypodermis lies below the dermis shown in Figure no.1, it is a layer of fat that helps to insulate the body from heat and cold, provides protective padding, and serves as an energy storage area [42-45].

Blood vessels

The dermis receives a rich blood supply with superficial artery plexus and subcutaneous venous networks shown in Figure.no.1. It acts as barrier when there is a poor blood flow [3-7].

Physicochemical properties of drug

Solubility

The solubility of drug is most important factor for drug delivery through skin. The drug shall possess optimum lipophilic character for permeation. Permeation is the rate limiting step when drug is present in a saturated solution. Lipophilic drugs show better permeation than hydrophilic drugs.

Permeation co-efficient

This parameter is a combination of diffusion co-efficient, membrane thickness and partition co-efficient of drug substance. The physicochemical aspect of the applied medium, chemical structure of drug and characteristics of skin decides the permeation coefficient. It is described by the formula given below [3]:

$$M\_t = (K \times D\_sc \times C\_s)/h\_sc \ \{t - h_{sc}/(6D\_sc)\} \quad -1$$

M_t - Amount of drug passing through a unit area of skin

t - Time taken for drug permeation

KC_S - Saturated concentration of drug within the skin surface

D_{sc} - Effective diffusion coefficient

h_{sc} - Effective thickness of stratum corneum.

Permeation coefficient is the flux at which the drug passes through the skin available for systemic circulation. Drugs with low permeation coefficient cannot penetrate through the skin which is critical for drug delivery. But currently by means of various penetration enhancers, drugs with low permeation coefficient can be delivered using technologies like iontophoresis, sonophoresis etc. Permeation coefficient directly depends on molecular size of drug particles, lipophilicity & log P.

Molecular weight and molecular size

The drug shall have molecular weight of less than 500daltonsapproximate. For smaller molecules, molecular volume can be related to molecular weight. The drug shall possess affinity for both hydrophilic and lipophilic phases. Intense separation characteristics are not favorable to facilitate successful drug delivery through skin. The drug shall have low melting point and along with these afore said attributes the drug shall importantly be potent, half-lifewithin10hrsand be non-irritating. Molecular size and molecular weight

are directly proportional and smaller the molecule, faster and easier the permeability [3-7].

Overcoming barriers using penetration enhancers

To overcome the above barrier there are various techniques employed namely physical and chemical enhancement techniques. Various examples for chemical enhancement [22] are listed in table no.1 and physical enhancement [24] techniques like iontophoresis, electroporation, sonophoresis, micro fabricated micro needles and microchips, vesicular approaches are presented in table no. 2. Drug carriers like liposomes, niosomes, micro emulsions can be used for enhanced drug penetration [54, 55].

Structure and types of transdermal patches

A typical transdermal patch is provided in figure no. 2, consist of the following parts:

a) An impermeable backing layer,
b) A reservoir,
c) Rate controlling membrane,
d) An adhesive ,
e) A release liner.

Impermeable backing layer

It is an inert layer that helps mechanically and prevents the back flow of the drug Refer Figure No. 2. It is commonly made of polyester film; ethyl vinyl copolymer and polyurethane film [114].

Drug

The drug shall have low melting point and importantly be potent, with short half-life and be non-irritating Figure No.2 illustrate the presence of the drug in the system. The drug can be delivered through a reservoir system or matrix system or micro reservoir system.

Reservoir systems

Reservoir system consists of a drug reserve from where the drug is released, depicted in Figure no. 2. Drug release is controlled by a rate controlling membrane which shall be of porous or non-porous nature. The drug in the drug reservoir shall be in the form of suspension, liquid or gel. Below the rate controlling membrane a thin hypoallergenic, compatible, adhesive polymer is used for application [48].

Matrix systems

The drug substances are dispersed in the adhesive containing a polymer matrix, depicted in Figure no. 2. Drug release is controlled by component of matrix. When the thickness of the matrix is high the rate of absorption decrease slowly as the drug molecule on the surface will be absorbed rapidly while the drug molecule away from skin will be transferred slowly. Matrix system may not provide zero-order release because the drug molecule which is closest to skin will be released at faster rate than the drug molecules that is far from the skin but this factor does not affect the rate of drug absorption significantly [71, 72].

Drug-in-adhesive system

The matrix is produced by placing the drug in adhesive polymer and film is formed by solvent casting or melting technique which is illustrated in Figure no. 2. Then it is spread on an impervious backing layer [73].

Matrix-dispersion system

Hydrophilic or lipophilic polymer is used as base to disperse the drug homogenously and spread on an impervious layer [42, 74].

Micro reservoir system

This system is formed by combining the principles of reservoir and matrix-dispersion systems which is depicted in Figure no. 2. Drug is suspended in an aqueous solution of water-soluble polymer to drug reservoir and the solution is homogeneously dispersed in a lipophilic polymer to form multiple numbers of unleachable, microscopic spheres of drug reservoirs. This thermodynamically unbalanced dispersion shall be made stable promptly by immediate cross-linking of the polymer in situ [75].

Rate controlling membrane

This will be a non-reactive membrane which shall be porous or non-porous, comprising of active agent that passes through the membrane at a predetermined controlled rate. In porous membrane the drug diffuse through the membrane and non-porous membrane the rate is related to solubility of the drug, hence the choice of membrane selection shall be based upon nature of drug [76]. The input rate of a drug through skin can be determined from transdermal system by calculating the volume of distribution (V_d), total body clearance (Cl_t) and therapeutic concentration (Cp_{ss}) under stable circumstances, the drug input rate from its transdermal system is likely to be equal to its output rate [52-56], this shall be estimated from total body clearance and therapeutic plasma concentration [66-70].

This relationship can be expressed using following mass balance equation:

Input rate = dosing rate x bioavailable factor (F).

Output rate = total body clearance x steady state plasma concentration.
Input rate = output rate

$$F \times dosingrate = Cl_t \times Cp_{ss} \quad -2$$

Cl_t - total body clearance,
Cp_{ss} - steady state plasma concentration.
Since epidermis is metabolically inert, F = 1.
For most drug compounds, total body clearance is the product of volume of distribution (V_d) and total elimination rate (K_e),

$$Cl_t = K_e \times V_d \quad -3$$

Where K_e – elimination rate constant.
Thus the required flux (J_{ss}) from a transdermal patch can be calculated by normalizing the dosing rate from Equation. 2

$$J_{ss} = Cl_t \times {}^{Cp_{ss}}/_{A} \quad -4$$

Where A – Area of transdermal patch.

Adhesives

The binding of all transdermal devices to the skin is usually by means of a pressure sensitive adhesive which will be positioned on the face of the device or in the backside of the device which extends peripherally. Both types of adhesive system shall possess the following criteria:

a) It shall stick on to the skin aggressively.
b) It shall be easily removable.
c) It shall not leave any unwashable remains on the skin.
d) It shall not annoy or sensitize the skin.

The adhesive system should also possess physical and chemical compatibility with the drug, excipients and enhancers present in the device which is very important. Permeation of drug shall not be affected and the delivery of simple or blended permeation enhancers shall also not be altered [73, 77]. Examples are as follows: PVP, Rubber silicones, polyvinyl acetate, phenol formaldehyde, ethylene vinyl acetate and cyanoacrylate.

Release liner

The patch with drug shall be enclosed in a protective liner which is removed immediately before the application of the patch to the skin. It is thus considered as a protective layer and part of the primary packaging material rather than the part of the dosage form delivering the active principle. However, as the liner is in close contact with the dosage form, it shall conform with precise requirements concerning about chemical inertness and permeation of the drug, penetration enhancer, and water. When cross-linking is made between the adhesive and the release liner, the strength required to take away the liner will be unacceptably high [78].

Marketed product and Market share of transdermal drugs

The marketed products for hormonal replacement therapy are as follows Climara® by 3 M Pharmaceuticals / Berlex Labs, Estraderm® by Alza / Novartis, Ortho Evra™ by Ortho-McNeil, Nuvelle TS® by Ethical Holdings / Schering, Climaderm® by Ethical Holdings / Wyeth Ayerst, Fempatch® by Parke-Davis, Fematrix® by Ethical holdings/Solvay Healthcare, Testoderm® by Alza, Alora® by Thera Tech / Proctol And Gamble, Androderm® by Thera Tech / GlaxcoSmithKline, Evra® by Janssen-Cllag. Followed by anti-anginal brand Nitrodics® by Robert Pharmaceuticals, Deponit® by Schwarz-Pharma, Nitro-dur® by Key Pharmaceuticals, Transderm-nitro® by Alza / Novaritis, Minitran® by 3M Pharmaceuticals. For smoking cessation Prostep® by Elan Corporation / Lederle labs, Nicotinell® by Novartis, Transdermscop® by Alza / Novartis. For analgesic and antinflammatory brands like Martin® by Nycomed, Duragesic® by Alza /Janssen Pharmaceuticals, Nupatch®100 by Zydus Cadila. For anticolinergic Oxytrol® by Watson Pharma, Scopoderm® by Novaritis. For central nervous system Neupro® by UCB and Schwarz Pharma, Emsam® by Somerset. For antihypertension CatapresTTS® by Alza / Boehinger Ingelheim. From figure no.3 it is apparent that in the market share of transdermal sales the first place is fentanyl (analgesic) 31%, the second is for nitroglycerin (antianginal) 27%, 14% estradiol for birth control but 2% estradiol combo is not included, and 7% for nicotine (smoking cession), clonidine and testosterone have 6% other have less than 2%. Fentanyl patch have greater use in transdermal drug delivery than in other dosage forms Table no.3display the marketed product details. The most important lifesaving drug nitroglycerin has greater impact on the transdermal drug delivery. Instead for oral dosage form at critical time it serves to have steady plasma blood concentration. The most important is usage of steroids in birth control it serves as a better drug delivery than to take daily dose of steroid which is even poorly absorbed in gastro intestinal tract [80].

International Transdermal Drug Delivery Systems Market was valued at $32,516 million in 2016 and is expected to make $61,689 million by 2023 [103].

Literature search on transdermal

As the researchers are exploring this dosage form and more improvement are in pipeline as an evidence the literature search is done in the website pubmed central

(https://www.ncbi.nlm.nih.gov/pubmed) this search engine is based on number of articles that are accessed to that search database and pubmed central have accessed to more than 1500 journals and in the literature search on May 22nd 2018. And the results are as follows:

- 41,813 articles for transdermal was found and in that 35796 are abstracts, 32230 are full text articles and 7917 are free full text articles.
- 30371 articles for transdermal drug was found and in that 27058 are abstracts, 24236 are full text articles and 5530 are free full text articles,
- 7137 articles for transdermal delivery was found in that 6921 are abstracts, 1421 are full text articles and 6336 are free full text articles,
- 37220 articles for transdermal drug delivery was found and in that 31558 are abstracts, 6744 are full text articles and 28519 are free full text articles,
- 4742 articles for transdermal drug delivery system was found and in that 4580 are abstracts, 905 are full text article and 3823 are free full text articles,
- 2349 articles for transdermal patches was found in that 2233 are abstracts, 1894 are full text articles and 476 are free full text articles,
- 534 articles for transdermal patch design was found and in that 531 are abstracts, 469 are full text articles and 120 are free full text articles,
- 2770 articles for transdermal estrogen was found and in that 2531 are abstracts, 2135 are full text articles and 428 are free full text articles,
- 1208 articles for transdermal fentanyl was found and in that 1000 are abstracts, 963 are full text articles and 216 are free full text articles,
- 393 articles for transdermal scopolamine was found and in that 304 are abstracts, 263 are full text articles and 56 are free full text articles,
- 909 articles for transdermal nitroglycerin was found and in that 716 are abstracts, 584 are full text articles and 169 are free full text articles,
- 255 articles for transdermal delivery insulin was found and in that 245 are abstracts, 213 are full text articles and 43 are free full text articles,
- 1208 articles for transdermal delivery protein was found and in that 1188 are abstracts, 1107 are full text articles and 330 are free full text articles,
- 944 articles for transdermal testosterone was found and in that 879 are abstracts, 816 are full text articles and 198 are free full text articles,
- 278 articles for transdermal cancer pain management was found and in that 272 are abstracts, 234 are full text articles and 62 free full text articles.
- 352 articles for transdermal buprenorphine was found and in that 321 are abstracts, 73 are full text article and 302 free full text articles. The details are tabulated in table No. 6.

History and current Patent son transdermal drug delivery system

The first patent in this field of transdermal goes back to the year 1971 is attained by the biochemist and entrepreneur Alejandro Zaffaroni (1923–2014) for transdermal drug delivery from a bandage [104]. The recent patent was obtained from United States Patent and Trademark Office (PTO) to Corplex Donepezil Transdermal Delivery System (TDS), which is a weekly once patch that delivers the most frequently given medicine for Alzheimer's patients U.S. Patent No. 9,993,466[105]. The patent for composition and technique for topical or transdermal delivery, and treatment of metabolic conditions is gained by the Inventor: Nicholas V. Perricone & the Assignee: Transdermal Biotechnology, Inc. [106]. The compositions and technique for transdermal drug delivery, which includes treatment and avoidance of learning and memory disorders, and enhancement of learning or memory is gained by the Inventor: Nicholas V. Perricone & the Assignee: Transdermal Biotechnology, Inc [107].

The patent on compositions and technique for topical or transdermal delivery and treatment of wounds and/or facilitating wound healing is gained by the Inventor: Nicholas V. Perricone & the Assignee: Transdermal Biotechnology, Inc [108].

ElKhoury, George F gained a patent for pharmaceutical composition for topical composition [109], Osborne et al transdermal delivery device for treatment of hypertension[110], Mittur et al obtained a patent for the trans-body-surface drug delivery device [111], The patent of Chang, Yunik Describes transdermal drug delivery system with dual permeation enhancers [112]. The patents are mainly attained for compositions used in drug delivery system & design of the drug delivery system.

As the researchers are exploring this dosage form and more improvement are in pipeline the patent application and patent search as per USPTO website [113] areas follows 1382 patents and 1715 patent applications on keyword transdermal, 242 patents and 230 patent applications on keyword transdermal drug, 199 patents and 211 patent applications on keyword transdermal drug delivery, 49 patents and 62 patent applications on keyword transdermal delivery system, 39 patents

and 30 patent applications on keyword transdermal drug delivery system, 2 patents and 2 patent applications on keyword transdermal pharmaceutical composition, 7 patents and 15 patent applications on keyword transdermal formulations, 63 patents and 75 patent applications on keyword transdermal patch, 16 patents and 16 patent applications on keyword transdermal device and no patent of patent application on the keyword transdermal patch design. The details are tabulated in table no. 4& table no. 5.

Risk factor analysis

Risk factor analysis is performed by considering following factors and details are tabulated in table no. 7

The scale of risk factors for P (f) as probability of fault

1. Appearance,
2. Penetration,
3. Assay & content,
4. Dissolution
5. Life risk.

For factors C is

1. Physical characteristic
2. Patient convenience
3. Dose and dosing frequency
4. Metabolism
5. Pain and hospitality

For factors V is

1. Physical and chemical characteristics
2. Unit operation
3. Resources
4. Microbial contamination.

For safety concern S

1. Physical and chemical characteristics
2. Patient related factors and time
3. Dose and drug
4. Contamination.

Abbreviations

P (f) - Probability of a fault,
C - Consequences of fault in the function as faced by the customer,
V - Consequences of fault in the function as faced by the vendor,
Re (f) - Risk Exposure of a function.

Calculation of risk factors

The Table no. 8 explains the various risk involved in each dosage form in addition with safety concerns rated using various scaling factors based on the risk severity, Figure no. 7 elucidate the risk analysis which was calculated by the average of severity of scaling factor of each dosage form.

Severity of each dosage form is as follows

Tablets

Contains probability of fault occurring due to factors like coating, hardness, thickness, uniformity of content, dissolution. Customer facing faults like bitter taste, crushing of tablet, dose missing, frequency of dosing, first pass metabolism, half tablet (breaking of tablet) and patient cooperation. Vendor facing faults like granulation, mixing, packing, and safety concerns are dose dumping, alcoholism, fatty diet, empty stomach, peristaltic movement.

Capsule

Contains probability of fault occurring factors P (f) like shell breaking, sticking, rupture, exact dose filling, uniformity of content and dissolution. Customer facing faults(C) like crushing of capsule, dose missing, frequency of dosing, odor, patient cooperation, sticking, first pass metabolism. Vendor facing faults (V) like granulation, mixing, microbial contamination, and packing. Safety concerns like dose dumping, alcoholism, fatty diet, empty stomach, peristaltic movement.

Oral liquids

Contains probability of fault occurring factor like caking, creaming, viscosity, and dissolution. Customer facing faults like bitter taste, exact dose of administration, dose missing, frequency of dosing. Vendor faces faults like microbial contamination, packing. Safety concerns like particle size.

Injectables

Contains probability of fault occurring factor like visible particles, leakages, leaching, anaphylaxis and aseptic processing. Customer facing faults like frequency of dosing, personal administration, pain, hospitality. Vendor facing faults like microbial contamination, isotonicity, packing, skilled man power. Safety concerns like particle size, isotonicity, risk of contamination, drug recovery.

Topical

Contains probability of fault occurring factor like uniformity of mixing, penetration viscosity. Customer facing faults creaming, excess application of drug. Vendor facing faults like leaking, microbial contamination and packing. Safety concerns like area of application.

Transdermal

Contains probability of fault occurring factor like penetration. Customer facing faults like site of administration, time period. Vendor facing faults

like size of patch, drug distribution. Safety concerns like lag time.

Risk factor analysis

The analysis of risk factor of various drugs of different dosage form being used for the treatment of different class of diseases (Refer table no.9) by taking into consideration of parameters like P (f), C, and V with the following formulae

$$Re(f) = P(f) \times \frac{C+V}{2} \qquad -5$$

- P(f) - Probability of a fault,
- C - Consequences of fault in the function as faced by the customer,
- V - Consequences of fault in the function as faced by the vendor,
- Re (f) - Risk Exposure of a function.

From table no.7it is clear that the highest risk factor is for injections having 8.125, followed by oral liquids of 5.5, capsules of 4.568, topicals of 4.3, tablets of 4.28 and transdermal having least of 3. From The highest percentage of risk factor 27% for injectables, 19% for oral liquids, 15% for capsules and topical, 14% for tablets and transdermal having least of all 10% Refer Figure no.7.

Current technologies and future prospective

The place where needle reuse take life of at least 1.3 million public per year due to hepatitis B and AIDS, needle-free, patch-based vaccination possibly will have great impact. For a drug development it takes more than 15 years for R&D with cost of more than 500 million and may face problem like first pass metabolism, adverse effect, side effects which can overcome by TDDS which takes development time of 4 to 6 years with cost of only 10 to 15 million. TDDS is one of the painless therapies so it became a great field of discovery and patents &the growth of TDDS is drastically increased in past 5 years. The emerging systems in TDDS are as ultrasound, electroporation, iontophoresis, sonophoresis, magnetic matrixes. The very recent trend in the market is Jet injectors, Thermal poration, and micro fabricated micro needles and microchips [88]. Ultrasound, mainly at low frequencies, is shown to enhance the flux of large molecular weight substances through the skin over five thousand times than the normal fluxes have been achieved, for the molecules the size of insulin or larger. Microneedles present an additional move toward less invasive drug delivery where array of suitable tiny needles can be positioned on the skin to present greater fluxes [89, 90]. Electroporation is used for the short-term pore creation in the skin and has permitted the release of even larger molecules like heparin and oligonucleotides through human cadaver skin. The pores are created by providing higher voltage pulses for shorter time periods [91]. Iontophoresis can even deliver low molecular weight molecules as well as decapeptides these are electrical approaches shows enhanced transport of drug [92].

Manufacturing considerations for efficient drug delivery system

The following critical parameters shall be considered to ensure homogeneity of the dosage forms - Shear sensitivity, Settling and Sedimentation rates, Viscosity (rheology), Solubility of the API, salvation, crystal morphology, polymorphism and dissolution of the API, Stability of components used in formulations (actives, antioxidants, etc.)

The attributes like Particle, drop, or globule size, heat or cold requirements, pH are also very important which needs to be considered and controlled.

Other physicochemical properties which have an impact are (e.g., crystal morphology, solvation, polymorphism of active component) [93].

- The matrix system involves coating of the solution over the surface of the film and the films are made into the individual systems and pouched.
- For reservoir system, the homogeneous gel, liquids are placed over the cards which are then cut into the individual systems. The manufacturing unit operations involve Mixing, Coating, Drying, and Laminating Process, Slitting/ Relaminating Process, Pouching Process and Packaging process.
- Critical process parameters like temperature, agitation speed, agitation time have direct impact on critical attributes like viscosity, assay and homogeneity.
- Examples of critical process parameters throughout the different stages of manufacturing are temperature of the oven, rate of the airflow, and the speed of the web during the transdermal coating process; and the temperature (heat), pressure applied for sealing in product pouching process [94].
- The quantity of API each dosage forms possess determines the quality of the dosage form and which in turn leads to intended action. The application process of the solution/gel plays a critical step in the manufacturing as the mixing step.

Mixing

Both types Reservoir & Matrix consists of mixing process as the first step

Mixing plays a critical role in ensuring bulk uniformity and content uniformity improper mixing lead to increased content or decreased content in dosage forms which leads to undesired effects with administration of such dosage forms.

The design of product-mixing operations shall be built based on the type of mixing which is required to the creation of product to achieve preferred homogeneity.

Types of mixing usually performed during manufacture of topical products

- Blending of multicomponent systems
- Dispersing of solids into liquids
- Emulsifying one liquid into another

Increasing the heat transfer among the manufactured product and vessel wall

Mixing processes requires correctly designed mixing equipments it is also governed by the rates at which materials are added, mixing time, mixing speed, temperature nature of materials used etc.

Mixing can be classified as macroscale and microscale mixing which are defined as follows:

Macroscale mixing (Pumping process): Mixing that achieve sufficient product flow in all areas of the mixing container both top-to-bottom and side-to-side to avert stratification and to ensure macroscopic homogeneity.

Microscale mixing (Shearing process): Mixing that achieve division or dispersal of individual components (particles, droplets, etc.) to attain the desired particle size distribution [95].

The sampling plan shall be made and samples shall be collected from various locations to confirm the uniformity of mixing after the mixing process is completed [94].

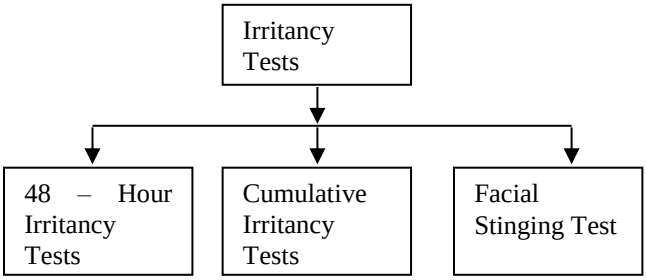
Safety evaluation of TDDS

The safety of the TDDS is an important aspect which shall be evaluated and to be established to minimize the risk of problems associated with these types of drug delivery systems.

There are many procedures available to evaluate the safety aspects, generally the evaluations are performed and primary tests are as follows:

- Irritancy tests
- Sensitization tests
- Photosensitive tests.

The tests are designed to identify if the drug delivery system is harmful to the skin and to understand the nature and reactions when it is in contact with skin. Factors to be considered - Age, sex, type of skin (Ex. dry, oily), adverse reactions, hard, soft skin, differences in areas of patch administration as this affects the penetration, presence of wrinkles or smooth skin. The testings starts with simple irritancy tests which is the first and important response which helps on further development of dosage form to next levels [96].



48-Hour irritancy tests

The test is carried out in 2 phases 1st phase – 24h and 2nd phase – 24h and further extension of the study can be designed based on the necessity. Usually the study is stopped after 24 hours and shall be reinitiated, the gap between tests leads to evaluate and assessment of response and to terminate the study if serious reactions occurs. If required the tests shall be extended for 72hrs also when conclusion are not possible to make. The study includes positive and negative controls and the study involves 25-30 people. There are also differences in the results with respect to age, types of skin and sex [97].

Cumulative Irritancy Tests

In cumulative irritancy tests the product is repeatedly applied on same place to simulate worst case scenario. The area of exposure is also occluded in some cases to study the maximum possible effect that can happen in this way the nature of skin is disturbed thus helping to identify the maximum harmful effect that could happen.

The cumulative irritancy assay normally consists of either a 14- or 21-day application period. Thus this study helps to identify the risks involved in day to day use. This also helps to identify the weak and strong irritant substances.

Different range of formulations with various concentrations of substances and different places of administration with different kind of people like Pediatrics, adults, geriatrics shall be useful to understand the safety of the product [96].

Facial-Stinging Test

Products could exceed tests such as the cumulative irritancy test, but still will lead to problems for the consumer. Unpleasant feel may happen, mainly whilst products are applied to sensitive areas such as face. A frequent complaint is stinging or burning or itching feeling after application. Signs of irritation, such as erythema or scaliness, may not necessarily occur in this situation. The cause for such feelings is because the facial skin is highly permeable and possess more nerve supply. It also faces weather plus a constant attack of cosmetics and cleansers. All these factors together leads to high sensitivity in this area. There is a method to evaluate the stinging ability of topical material has been described [97].

Advantages of evaluating the systems

- The testing are essential to understand the behavior of the drug delivery system.
- Testing helps to identify the product whether it possess the desired characteristics or not for example physical and chemical examinations helps to identify the important quality attributes are being met or not. The attributes like Homogeneity of systems, Content Uniformity of the actives in the system, Adhesive nature, release nature, appearance, texture helps to determine the consistency of the product.
- By testing the performance of drug delivery system like dissolution, drug release using an artificial membrane and skin penetration testing, the role of product design and formulation design shall be studied.
- The results of dissolution and skin permeation can together tell about the involvement of the patch and the skin in controlling absorption [98].
- The transdermal patches are usually loaded with excess actives than required to treat the patient situation during its administration. This overload quantity is essential to preserve the clinically required rate of release this also helps to use least patch surface area. The quantity of the active shall be close to its saturation limit and it poses a risk of crystallization during storage.
- The actives leftover in the patch may also create risks to the people, environment and others. There is more opportunity and high risk of misuse of discarded patches. It is safe and required to minimize the quantity of left over active substance in the patch as much as possible.
- US FDA has published a guidance to measure the residual drugs in these drug delivery systems [99].
- The important details of the products shall be clearly defined and detailed like Strength, as the mean dose provided per unit time, usually quantity delivered *in vivo* per 24 hours; *In vivo* release rate or strength per piece area (i.e. mass delivered *in vivo*/unit area/unit time), The quantity and position of API in the drug product, API consumption (% of total active substance absorbed per patient administration); Patch area activity (active substance utilization/patch area); Residual (mass of active substance remaining in the drug product after completion of administration); directions for use, together with the use of any overlay; and Patch period of use, Patch type, with respect to the control of drug release (e.g., reservoir, drug in adhesive); The appearance and purpose of all layers of the laminated product; The ingredients of each layer, including the role and the grade of the excipients (the grade is normally considered to be a critical quality attribute for transdermal delivery). Backing layers and release liners shall also be described; Overlay description (if applicable); Patch size, area and thickness (area weight may be considered if justified); and Appearance, including shape, colour and markings.
- Drug product design feature linking to patient administration and use throughout the duration of use shall also be explained. The data described are critical and shall be established by developing suitable study plan and methods are important and challenging too. These are critical for submission purpose also.
- The evaluation and/or assessment of these quality essentials like product strength, active substance consumption, remaining and appropriateness of administration and use can only be attained by appropriate valid clinical studies and not possible to derive

directly or indirectly (using surrogate markers) by quality tests [98].

Regulatory overview

For all kinds of drug delivery systems there is a regulatory standard which are set by the regulatory agencies and available in guidances of the relevant drug delivery systems and these requirements needs to be met.

The guidance and excerpts from the guidance recommendations are as follows which shows the views of the agencies [100].

Adhesion of this drug delivery systems plays a critical role as this factor decides the quantity of drug delivered. Hence, the system should remain adhered throughout the intended period of wear. Due to the importance of this factor US FDA issued a draft guidance for industry which outlines the various requirements but not limited to this kind of dosage forms.

The guidance also recommends the adhesion scoring system, adhesion study requirements and also the factors to be considered for statistical analysis. It also suggests the how a combined study can be performed a study that evaluates the adhesion evaluation and PK BE, it highlights the importance of strengths in the study.

Recommendations on the format of Data Submission.

The recommendation of the format for data submission is outlined which is as follows:

Separate line listing shall be provided for test product and reference product

The details like identification of the subject, study center, age, gender, race, treatment test article duration, application sequence number shall be identified.

The detailed records shall be maintained which is very important for the study and for submission requirement also, the records shall include

Location of dose administration: individual test article placing position, Application date/time

Number of days/hours since TDS application, Adhesion evaluation /scoring date/time,

Initials of adhesion assessor, TDS complete detachment - status (yes or no), Date and time of complete detachment, Treatment discontinued (yes or no), Date and time of treatment discontinuation, Reasons for treatment discontinuation, period of Treatment: time (hours) from individual test article application to removal or complete detachment, Included in Per Protocol (PP) population for adhesion analysis (yes/no), Reason for elimination from PP population for adhesion analysis

All other details including computer programs used for the primary analysis and sensitivity analysis shall be submitted [102]. The submission process shall be followed as per electronic submission guidance [101].

Guidance for Industry

Residual Drug in Transdermal and Related Drug Delivery Systems [99] states that all the units administered for PK studies shall be removed after the study period or during the study period shall be tested for residual drug content it also suggests that the PK samples shall be collected and analyzed from all subjects in PK subpopulation regardless of adhesion score and at all-time points and all the obtained results to be reported.

The guidance advice the developers to reduce the residual drug in the final product as very minimal and if any associated risk need to be mitigated.

EU Recommendations

Study design / study conditions

As per EU the following things are suggested for performing permeation study using *ex vivo* human skin. The deviations from the proposed test conditions shall be justified.

Diffusion cell

Franz type or flow through; Receiving phase, to imitate *in vivo* situation that also give active substance sink conditions, degassed, e.g., in an ultrasound bath to avoid the air build up pockets; The medium might be aqueous buffer and can consist of acceptable solubilising agents and / or protein; Receptor phase shall be constantly agitated and shall stay in contact with the skin. The stirring speed shall be justified; Temperature - the surface of the skin, in the diffusion cell, shall be maintained at a temperature in line with the physiological human skin temperature (32°C±1°C). The skin surface temperature shall be correctly confirmed before dose application by using an infrared thermometer; Humidity – Extremes of relative humidity conditions in the laboratory shall be avoided, i.e. RH conditions over 70% and lower than 30%; Human skin integrity shall be determined at the start of the research; The correctness of integrity test e.g., (TEWL), permeation of tritiated water, electrical resistance or visual examination (but not accepted for pivotal

studies) and criterion for acceptance shall be completely discussed; Number of replicates – The preference of the number of samples shall be justified with regard to the scope of the experimentation and demonstrated to be statistically related; Number of skin donors – minimum 2 different donors; Skin anatomical region –torso (breast, abdomen or back) or relevant to the site of clinical application [98].

Current & Future Developments

Transdermal drug delivery system is a widely researchable area for painless treatment, to reduce side effects and most important to bypass first pass metabolism. And presently research works that focuses on insulin and anticancer agent have offered certain hope for physicians to achieve maximum patient compliance. The hurdles of low permeability through skin can be overcome using these techniques like iontophoresis, sonophoresis, electroporation which will helps in making the TDDS a better drug delivery.

More on future prospective, there is emerging TDDS on cancer therapy to have eminent treatment and also reduces the side effects of the treatment associated with current method of treatments. The risk factor for TDDS is low compared to other dosage forms and it can be used by different age group of patients which is believed to show very less patient to patient variability, steady state plasma concentration & reduced dosing.

CONCLUSION

The TDDS in the last decade have undergone a exponential growth in research development & patents filing, this was proven by the attention towards this drug delivery platform from academic and industries led to increase in patent applications year by year which is a healthy situation. This will facilitate an efficient approach to alleviate the pain, patient sufferings and problems associated with other kinds of drug delivery system thereby improving patient compliance.

The overall review also shows that this is a preferred type of drug delivery to all patient groups from geriatrics to pediatrics, because of its painless and reduced dosing frequency. Moreover, the global market is expected to make $61,689 million by 2023, hence it has a greater scope and demand in future. The hurdle of drug delivery to through skin can be overcome by the techniques like, as ultrasound, electroporation, iontophoresis, sonophoresis, and magnetic matrixes.

The overall risk evaluated is very minimal when compared to other dosage forms, however the onset of action time need to be considered during medication.

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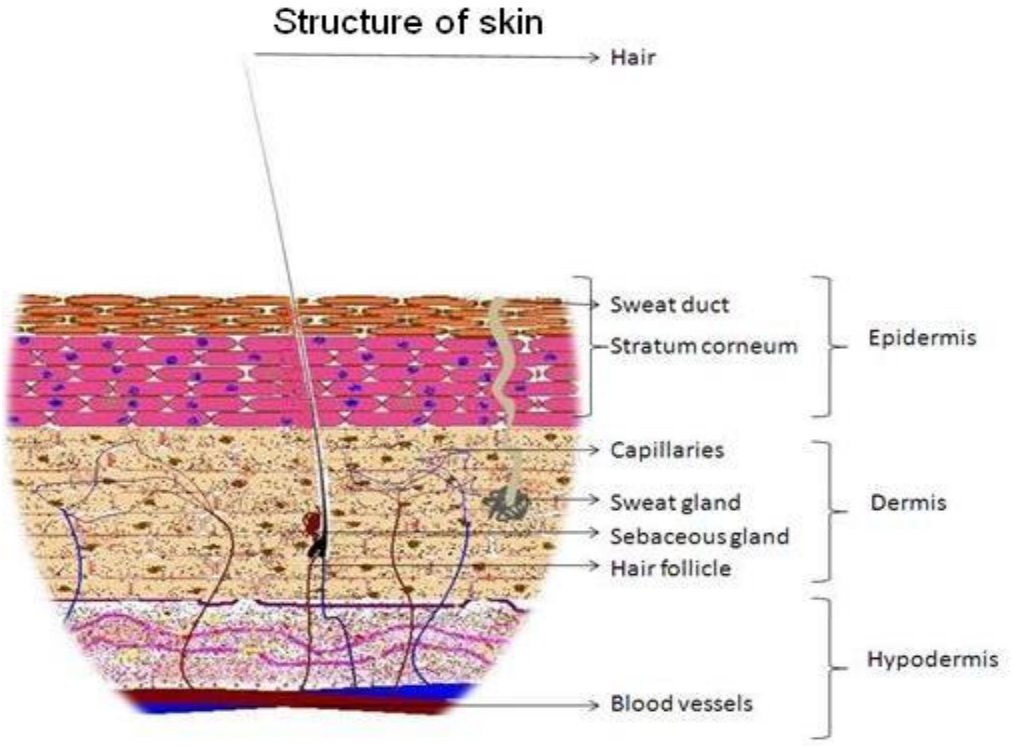

Figure No. 1: Structure of skin

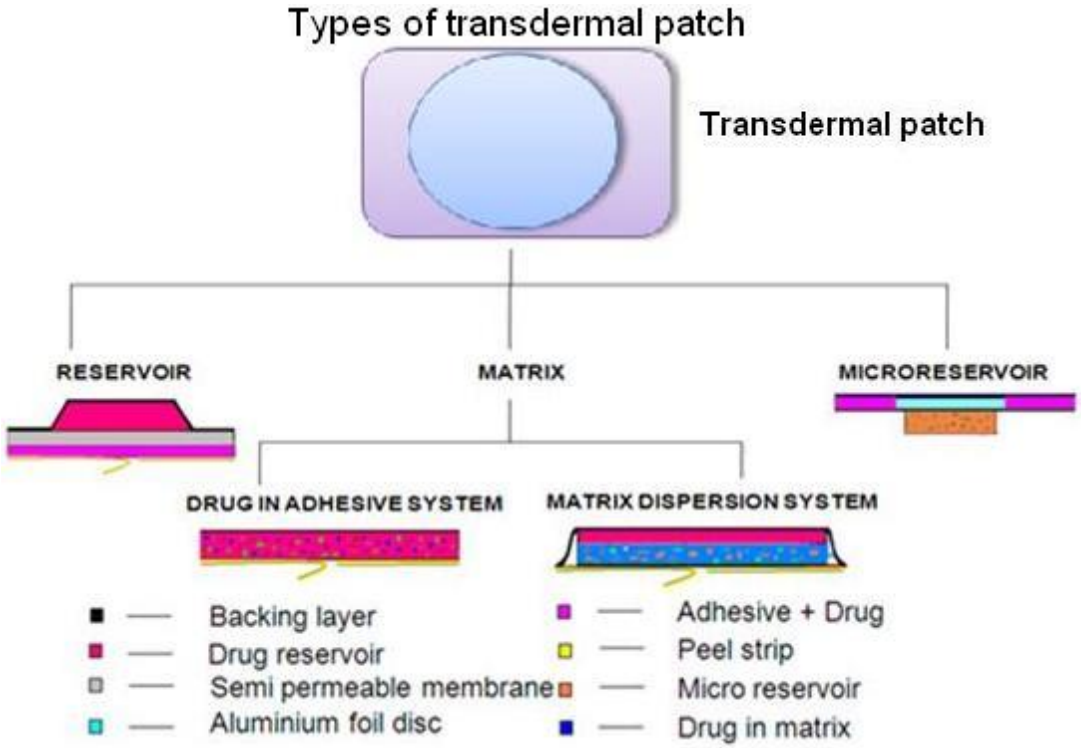

Figure No. 2: Types of transdermal drug delivery systems

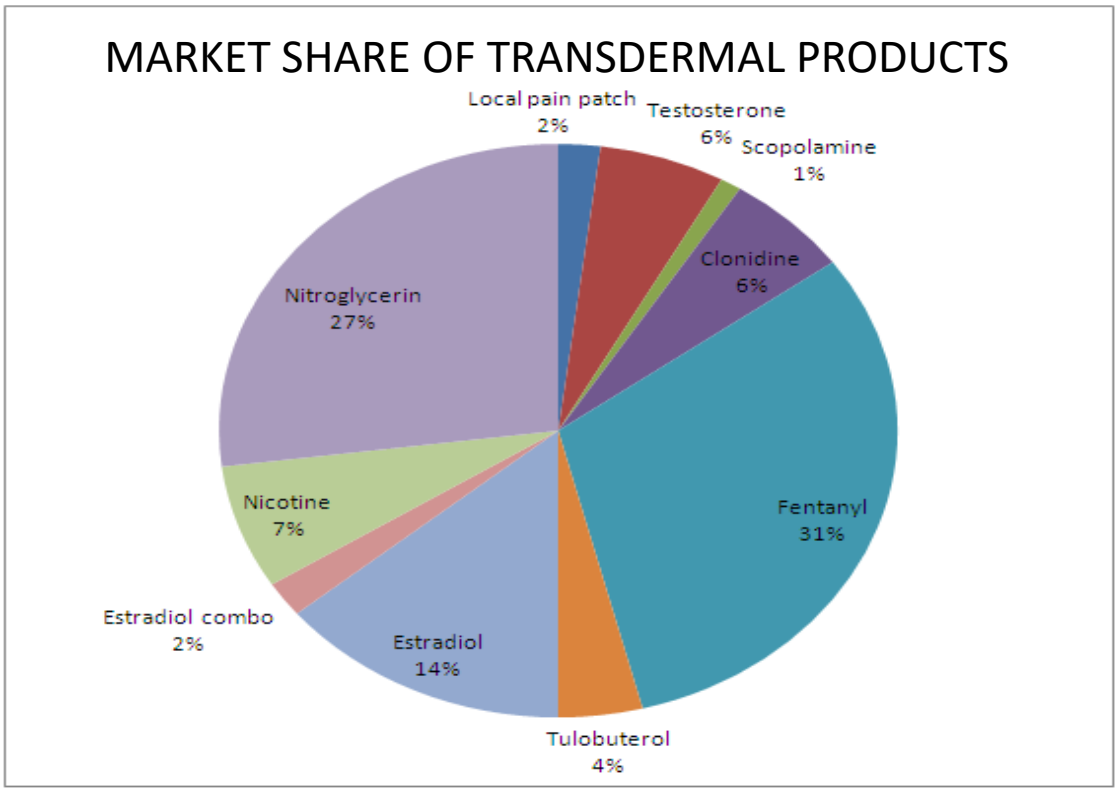

Figure No. 3: Market share of transdermal drug

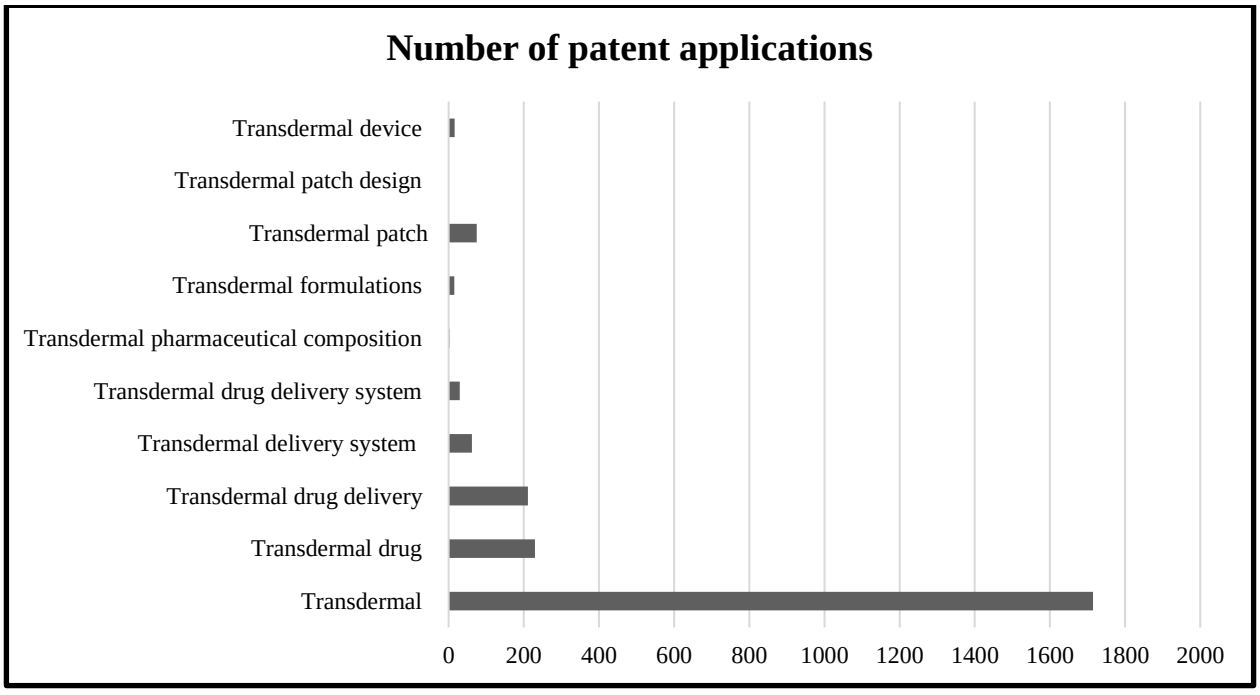

Figure No. 4: Statistics on Patent applications for transdermal

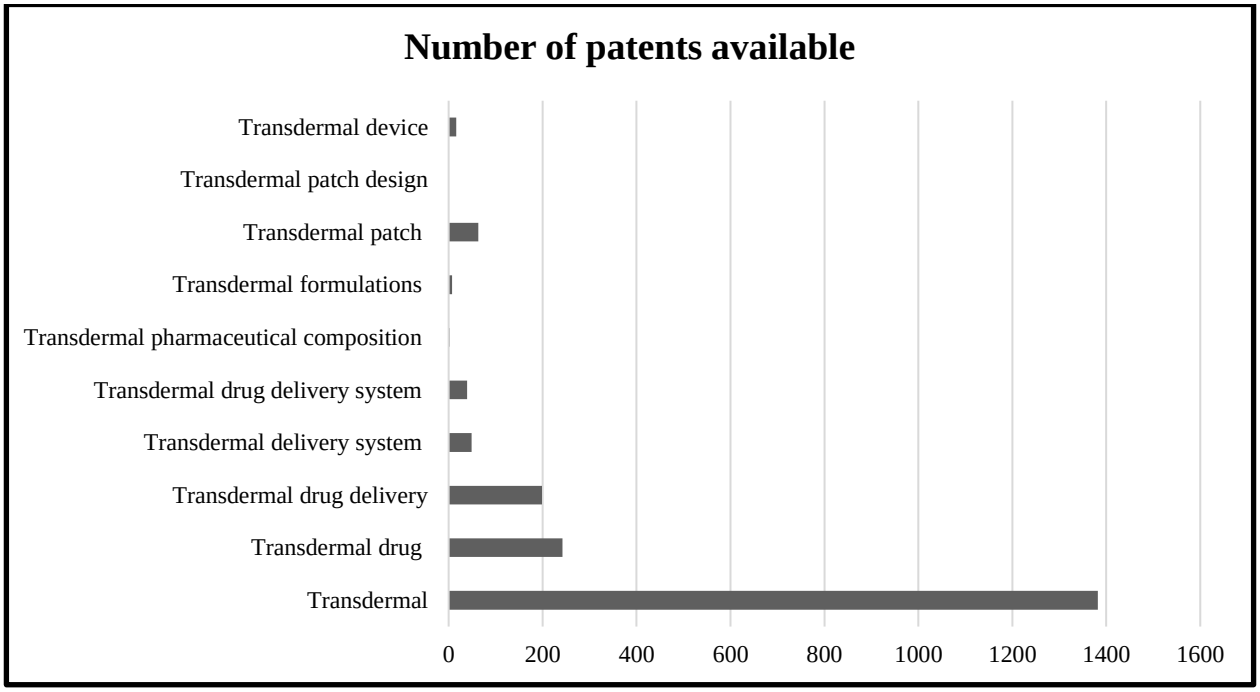

Figure No. 5: Statistics on Patents for transdermal

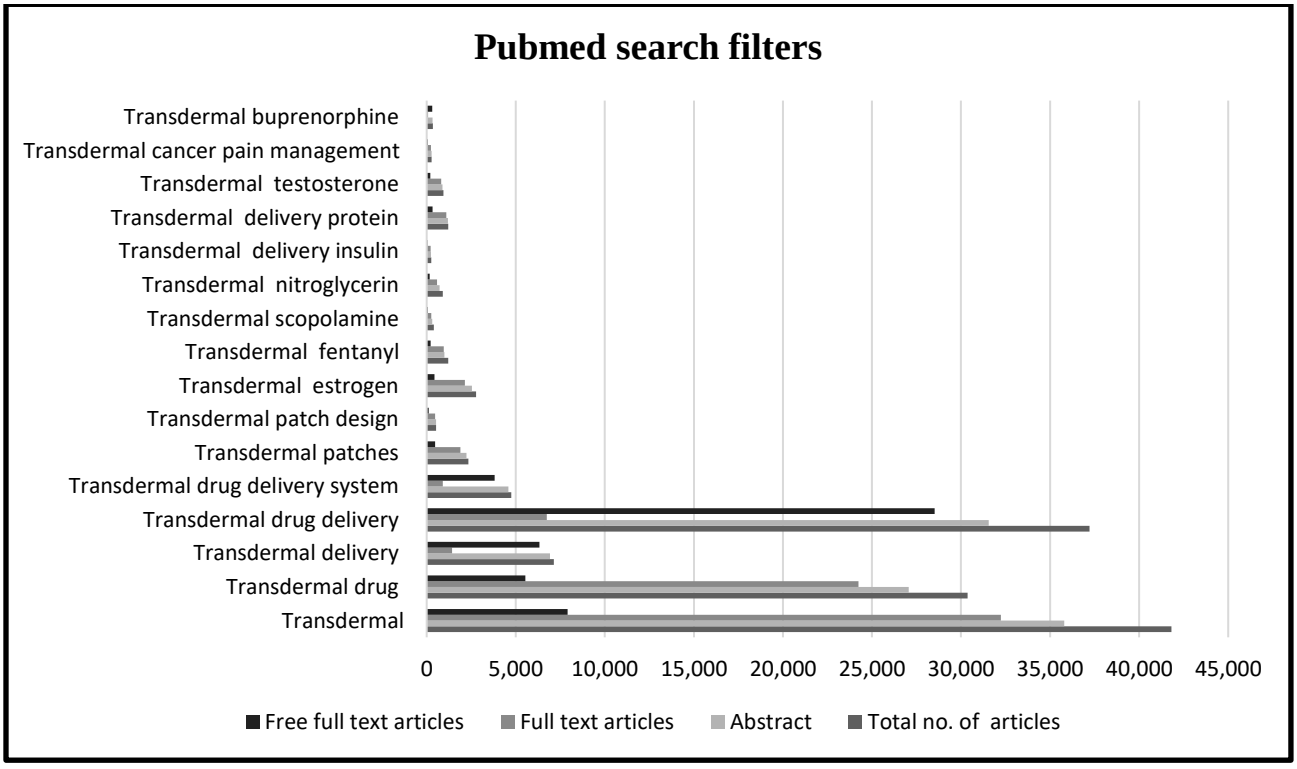

Figure No. 6: Statistics on Pubmed search and filters

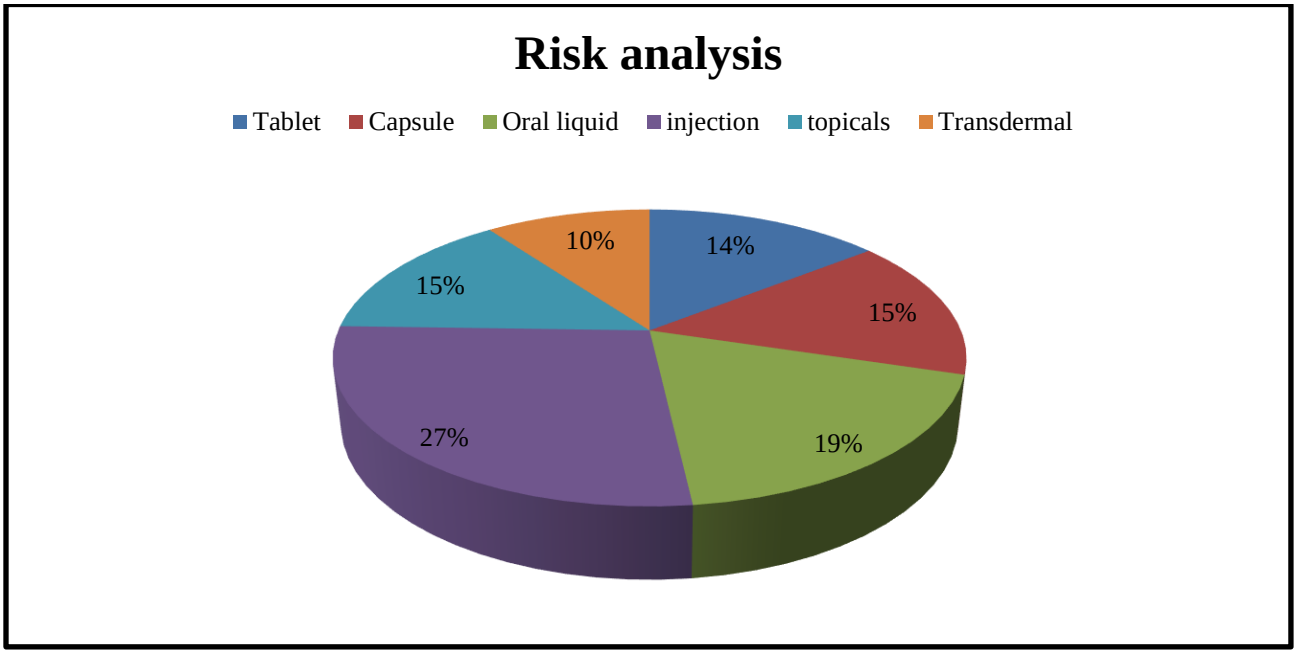

Figure No. 7: Risk analysis on dosage forms

Table No. 1: Drug penetration enhancers (used in chemical methods).

Drug	Brand name	Penetration enhancer used	References
Fentanyl	Duragesic®	Ethanol	49
Tri nitro glycerin	Nitrodisc® Nitrol®	Isopropyl palmitate Isopropyl palmitate and Lauryl alcohol	50
Estradiol	Estraderm® Trial®	Ethanol Oleic acid and Propylene glycol	51
Testosterone	Androderm®	Glyceryl mono-oleate, methyl laurate, ethanol.	52

Table No. 2: Physical enhancement techniques

Techniques	Drug	Brand name	References
Sonophoresis	Insulin	Phase III trails	1,56,57,58
Iontophoresis	Sumatriptan Acyclovir Terbinafine	Zelrix® Clinical trials	7,20,36,59,60
Electroporation	Metaprolol Flurbiprofen Cyclosporine Heparin Fentanyl Oligonucleotides	Phase II and III trails	1,61
Microfabricated Microneedles and Microchips	Human growth hormone	Macroflux®	62,63,64,65

Table No. 3 Marketed transdermal products

Therapeutic class	Brand name	Drug	Manufacturer	Indications	References
Hormonal replacement therapy	Climara ®	Estradiol	3 M Pharmaceuticals / Berlex Labs	Postmenopausal syndrome	1
	Estraderm®	Estradiol	Alza/ Novartis	Postmenopausal syndrome	2
	Ortho Evra™	Norelgostromin	Ortho-McNeil	Postmenopausal syndrome	3
	Nuvelle TS®	Estrogen/ Progesterone	Ethical Holdings / Schering	Hormone replacement therapy	4
	Climaderm®	Estradiol	Ethical Holdings / Wyeth Ayerst	Postmenopausal syndrome	6
	Fempatch®	Estradiol	Parke-Davis	Postmenopausal syndrome	79
	Fematrix®	Estrogen	Ethical holdings/Solvay Healthcare	Postmenopausal syndrome	5
	Testoderm®	Testosterone	Alza	Hypogonadism in male	79
	Alora®	Estradiol	Thera Tech/ Proctol And Gamble	Postmenopausal syndrome	7
	Androderm®	Testosterone	Thera Tech/ GlaxcoSmithKline	Hypogonadism in male	8
	Evra®	Norelgestromin	Janssen-Cllag	Postmenopausal syndrome	80
Analgesic/ Antinflammatory	Martin®	Fentanyl	Nycomed	Narcotic analgesic	81
	Duragesic®	Fentanyl	Alza/Janssen Pharmaceuticals	Analgesic	9
	Nupatch®100	Diclofenacdiethylamine	Zydus Cadila	Anti Inflammatory/Analgesic	10
Antianginal (Cardio Vascular System)	Nitrodics®	Nitroglycerin	Robert Pharmaceuticals	AnginaPectoris	11
	Deponit®	Nitroglycerin	Schwarz-Pharma	Anginapectoris	12

Therapeutic class	Brand name	Drug	Manufacturer	Indications	References
	Nitro-dur®	Nitroglycerin	Key Pharmaceuticals	AnginaPectoris	13
	Transderm-nitro®	Nitroglycerin	Alza/Novaritis	AnginaPectoris	14
	Minitran®	Nitroglycerin	3M Pharmaceuticals	AnginaPectoris	15
Smoking cessation[17]	Prostep®	Nicotine	Elan Corporation/ Lederle labs	Smoking cessation	16
	Nicotinell®	Nicotine	Novartis	Smoking cessation	83
	Transdermscop®	Scopolamine	Alza/Novartis	Motion sickness	17
Anticholinergic	Oxytrol®	Oxybutyin	Watson Pharma	Overactive Bladder	18
	Scopoderm®	Scopolamine	Novaritis	Motion sickness	85
Antihypertension	CatapresTTS®	Clonidine	Alza/Boehinger Ingelheim	Hypertension	19
Central nervous system	Neupro®	Rigotine	UCB and Schwarz Pharma	Parkinson disease	20
	Emsam®	Selegiline	Somerset	monoamine oxidase inhibitor	87

Literature search on Transdermal

Table No. 4: Patent application search. (www.uspto.gov); March 15th 2018 - September 30th 2001

Sr.No	Patent application for approval (Keywords)	Number of application
1.	Transdermal	1715
2.	Transdermal drug	230
3.	Transdermal drug delivery	211
4.	Transdermal delivery system	62
5.	Transdermal drug delivery system	30
6.	Transdermal pharmaceutical composition	2
7.	Transdermal formulations	15
8.	Transdermal patch	75
9.	Transdermal patch design	0
10.	Transdermal device	16

Table No. 5 Patent search.

Sr.No	Patents (Keywords)	Number of patents available
1.	Transdermal	1382
2.	Transdermal drug	242
3.	Transdermal drug delivery	199
4.	Transdermal delivery system	49

5.	Transdermal drug delivery system	39
6.	Transdermal pharmaceutical composition	2
7.	Transdermal formulations	7
8	Transdermal patch	63
9	Transdermal patch design	0
10	Transdermal device	16

Table No. 6: Pubmed search and filters used.

Sr.No	Filters (Keywords)	Total no. of articles	Abstract	Full text articles	Free full text articles
1.	Transdermal	41,813	35796	32230	7917
2.	Transdermal drug	30371	27058	24236	5530
3.	Transdermal delivery	7137	6921	1421	6336
4.	Transdermal drug delivery	37220	31558	6744	28519
5.	Transdermal drug delivery system	4742	4580	905	3823
6.	Transdermal patches	2349	2233	1894	476
7.	Transdermal patch design	534	531	469	120
8	Transdermal estrogen	2770	2531	2135	428
9	Transdermal fentanyl	1208	1000	963	216
10	Transdermal scopolamine	393	304	263	56
11.	Transdermal nitroglycerin	909	716	584	169
12.	Transdermal delivery insulin	255	245	213	43
13.	Transdermal delivery protein	1208	1188	1107	330
14.	Transdermal testosterone	944	879	816	198
15.	Transdermal cancer pain management	278	272	234	62
16.	Transdermal buprenorphine	352	321	73	302

Table No. 7: Scaling of risk factors

Scale of Risk factor P(f)				
Appearance	Penetration	Assay & content	Dissolution	Life risk
1	2	3	4	5
Scale of risk factor C				
Physical Characteristic	Patient convenience	Dose and Dosing frequency	Metabolism	Pain and Hospitality
1	2	3	4	5

Scale of risk factor V			
Physical and chemical Characteristics	Unit operation	Resources	Microbial contamination
1	2	3	4
Scale of safety factor S			
Physical and chemical Characteristics	Patient related Factors and Time	Dose and Drug	Contamination
1	2	3	4

Table No. 8: Calculation of risk factor for dosage forms.

Sr.No	Dosage form	Probability of fault P(f)	Faults faced by consumer C	Faults faced by Vendor V	Safetyconcerns S
1	Tablets	1.Coating 2.Hardness 3.Thickness 4.Uniformity of content 5.Dissolution	1.Bitter taste 2.Crushing of tablet 3.Dose missing 4.Frequency of dosing 5.First pass metabolism 6.Half tablet (breaking of tablet) 7. Patient cooperation	1.Granulation 2.Mixing 3.Packing	1.Dose dumping 2.Alcholism 3.Fatty diet 4.Empty stomach 5.Peristaltic movement
2	Capsules	1.Shell breaking 2.Sticking 3.Rupture 4.Exact dose filling 5.Uniformity of content 6.Dissolution	1.Crushing of capsule 2.Dose missing 3.Frequency of dosing 4.Odor 5.Patient cooperation 6.Sticking 7. First pass metabolism	1.Granulation 2.Mixing 3. Microbial contamination 4.Packing	1.Dose dumping 2.Alcholism 3.Fatty diet 4.Empty stomach 5.Peristaltic movement
3	Oral Liquids	1.Caking 2.Creaming 3.Viscosity 4.Dissolution	1.Bitter taste 2. Exact dose of administration 3.Dose missing 4.Frequency of dosing	1.Microbial contamination 2.Packing	1.Particle size
4	Injectables	1.Visible particles 2.Leakages 3.Leaching	1.Frequency of dosing 2.Personal administration	1. Microbial contamination 2.Isotonicity 3.Packing	1.Particle size 2.Isotonicity 3.Risk of contamination

		4.Anaphylaxis 5.Aspetic processing	3.Pain 4.Hospitality	4.Skilled man power	4.Drug recovery
5	Topicals	1.Uniformity of mixing 2. Penetration 3.Viscocity	1.Creaming 2.Excess application of drug	1.Leaking 2. Microbial contamination 3. Packing	1.Area of application
6	Transdermal	1.Penetration	1.Site of administration 2.Time Period	1.Size of Patch 2.Drug distribution	1.Lag time

Table No. 9: Available dosage form on market and risk calculation.

Sr. No	Disease	Drug	Tablets	Capsule	Oral liquids	Injection	Topical	Transdermal
1.	Angina pectoris	Nitroglycerin	✓	-	-	✓	✓	✓
2.	Hypertension	Captopril	✓	-	-	-	-	✓
3.	Hypertension	Clonidine	✓	✓	-	✓	-	✓
4.	Smoking disorder	Nicotine	✓	✓	✓	✓	✓	✓
5.	Nausea and vomiting	Granisetron	✓	-	-	✓	-	✓
6.	Alzheimer's	Rivastigmine	✓	✓	-	-	-	✓
7.	Parkinson's disease	Selegiline	✓	✓	-	-	✓	✓
8.	Hyperactive disorder	Methlyphenidate	✓	✓	✓	-	✓	✓
9.	Hormonal replacement therapy	Estrogen	✓	-	-	✓	✓	✓
10.	Overactive bladder	Oxybutin	✓	-	-	-	-	✓
11.	Antivertigo	Scopolamine	✓	-	✓	✓	✓	✓
12.	Neuropathic pain	Lidocaine	-	-	✓	✓	✓	✓
13.	Hypogonadism	Testosterone	-	✓	-	✓	-	✓
14.	Rheumatoid arthritis	Diclofenac	✓	✓	-	✓	✓	✓
15.	Risk factor analysis		4.280	4.568	5.500	8.125	4.300	3.000