

POLYMERS USED IN TRANSDERMAL DRUG DELIVERY: AN OVERVIEW**Hemalatha P. C.* and Dr. V. Chandrakala**

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Received on: 28/05/2021

Revised on: 18/06/2021

Accepted on: 08/07/2021

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Bangalore, Karnataka, India.**ABSTRACT**

Transdermal drug delivery systems (TDDS) are dosage forms that involve drug transport to viable epidermal and or dermal tissues of the skin for local therapeutic effect while a very major fraction of drug is transported into the systemic blood circulation. It is one of the best pharmaceutical dosage forms for patients, who cannot take medicaments orally. On the application of transdermal patches, the delivery of the drug across the dermis gives the systemic effect. Advances in transdermal delivery systems (TDS) and the technology involved have been rapid because of the sophistication of polymer science which now allows the incorporation of polymeric additives in TDS in adequate quantity.^[1] Careful polymer selection is essential to control the drug loading, release rate, and duration of release. Many polymers can be formulated into various drug delivery systems to address the controlled release, Targeted delivery and solubility enhancement strategies enable improved drug efficacy. The most critical factor in polymer selection is considering the interaction of the drug and polymer. Polymer selection will determine the mechanism of drug release (bulk erosion, system degradation) and the choice of polymer properties (molecular weight, surface charge) will influence release rate and impact pharmacokinetics. This article summarizes the factors contributing to polymers for the formulation aspects of the transdermal drug delivery system and emphasizes the selection criteria and various release patterns of polymers. In addition, Applications, Manufacturing considerations and recent developments of TDDS have also been reviewed.^[2]

KEYWORDS: Biodegradable polymers, Non biodegradable polymers, Transdermal drug delivery, Drug release mechanism, Stability.**INTRODUCTION^[3,4]**

The skin is the most expansive and readily accessible organ of the human body. It has been used as an administration site of pharmaceutical drugs with local action on it and on muscle beneath and other drugs with systemic action can also be introduced through the skin. With the creation of the current time of pharmaceutical dosage forms, the transdermal drug delivery system (TDDS) recognized itself as an important part of novel drug delivery systems. Transdermal drug delivery systems are becoming popular because of their exclusive advantages. Improved bioavailability, controlled absorption, painless and uniform plasma levels. For the drug to be administered transdermally, it has to be potent. The first criteria should be feasibility it can be accessed from the daily dose. The second criteria, the molecules should be small, have a low melting point, and have a log K_{oct} of ~ 2. Other factors to be considered are the nature of the functional groups on the molecule, the ionization potential, and hence the pKa of the drug. The skin has a surface pH of around 4 to 5 and a good buffer capacity, owing to the free fatty acids that make an important component of the stratum corneum lipids. For a nitroglycerine compound, it has physicochemical

properties for transdermal delivery from a patch area, not more than 40 to 50mg per day can be delivered.

Main ingredients used for the preparation of transdermal drug delivery system^[5]

Liners-It protects patches during storage and the liner should be removed previous to use.

Adhesive-It served to adhere the components of the patch together along with adhering the patch to the skin.

Membrane-Its controls the drug releases from the multilayer patches. It is also known as the permeation enhancer.

Drug-Drug reservoir in direct contact with the release liner.

Backing-Protects the patches from the outer environment.

Kinetics for successful development of TDDS involves the following steps: ^[6,7]

1. Penetration: The entry of a substance into a particular layer of the skin;

2. Partitioning from the stratum corneum into the aqueous viable epidermis;
3. Diffusion through the viable epidermis and into the upper dermis;
4. Permeation: The penetration of molecules from one layer into another, which is different both functionally and structurally from the first layer;
5. Absorption: The uptake of a substance into the systemic circulation.

Advantages of transdermal drug delivery system^[5, 9]

1. The hepatic first-pass metabolism is avoided.
2. Provides utilization of drugs with short biological half-lives.
3. Painless and suitable administration.
4. A stable rate of absorption is possible in a huge variety of adverse patient populations.
5. Maintain plasma concentration of potent drugs.
6. At some stage in the application of gel amount and area of application are not specify but in the patch both are specific.
7. Direct access to target or diseased site.
8. Avoidance of gastrointestinal incompatibility.

Disadvantages of transdermal drug delivery system^[5, 9]

1. Drugs with very low or high partition coefficients fail to reach blood circulation.
2. Easy Elimination of drug delivery in case of toxicity.
3. Only relatively potent drugs are suitable candidates for TDDS because of the natural limits of drug entry imposed by the skin impermeability.
4. Clinical need is another area that has to be examined carefully before a decision is made to develop a transdermal product.
5. The skin barrier function changes from one site to another on the same person, from person to person, and with age.

Considerations of selection polymers^[10]

Polymers are employed in skin preparation and it strengthens the foundation of TDDS. Polymer selection and designs are of prime importance in this system. The Surface and bulk properties of the polymer can give the desired chemical, interfacial, mechanical, and biological functions. Choice of polymer, in addition to its physicochemical properties, is dependent on the need for extensive biochemical characterization and specific preclinical tests to prove its safety. Surface properties such as hydrophilicity, lubricity, smoothness, and surface energy govern the biocompatibility with tissues and blood, in addition to influencing the physical properties such as durability, permeability, and degradability. Structural properties of the matrix, its micromorphology, and pore size are important to mass transport (of water) into and (of drug) out of the polymer.

Careful polymer selection is essential to control the drug loading, release rate, and duration of release. Many

polymers can be formulated into various drug delivery systems to address the controlled release. Targeted delivery and solubility enhancement strategies enable improved drug efficacy. The most critical factor in polymer selection is considering the interaction of the drug and polymer. Polymer selection will determine the mechanism of drug release (bulk erosion, system degradation) and the choice of polymer properties (molecular weight, surface charge) will influence release rate and impact pharmacokinetics.

Ideal properties of polymers to be used in TDDS^[5,11]

1. The polymer should permit the fabrication of a device with a large amount of drug.
2. The polymer must not decompose in the presence of a drug and other excipients used in the formulation under storage conditions or conditions of device usage.
3. The Polymer must not affect the stability of the drug.
4. There should not be any change in the mechanical properties of a polymer when a large amount of drug is incorporated into it.
5. The Polymer should be inexpensive.
6. The Polymer should be easily fabricated into the desired device without expensive or complicated chemical or physical treatments.
7. The Polymer must maintain its integral properties under the labeled storage conditions for the predetermined duration of shelf life.
8. The Polymer must not allow diffusion and release of the specific drug.
9. The Polymer must be easily available.
10. The Polymer should be easy to handle during various steps of manufacturing the process.
11. The Polymer and its degradation products must be non-toxic and non-irritant to the skin.
12. The Polymer must not produce hypersensitivity reactions.

Additionally, a polymer to be used in a transdermal system must satisfy some of the following criteria^[12]

It should be easily available, fabricated, and manufactured into desired formulations.

The properties of polymer e.g. molecular weight, glass transition temperature, melting point, and chemical functionality, etc. should be such that the drug can easily be diffused through it and with other components of a system.

It must be soluble and easy to synthesize.

The mechanical properties of the polymer should not deteriorate excessively when a large number of active agents are incorporated.

It should provide a consistent release of a drug throughout the life of the system.

Should be biodegradable or be eliminated from the body after its function is over.

Classification of polymers^[13]

Polymers are macromolecules having very large chains that contain a variety of functional groups, can be blended with low and high molecular weight materials, Polymers are becoming increasingly important in the field of drug delivery.

Polymers are classified in several ways. For use in pharmaceutical purposes, they are simply classified into natural and synthetic polymers. As biodegradability plays a major role in drug delivery systems, they are further classified into two subgroups as biodegradable and non- biodegradable.

Biodegradable Polymers

A biodegradable polymer is a polymer in which the degradation results from the action of naturally occurring microorganisms such as bacteria, algae or fungi. Biodegradable polymers are widely used as biomedical devices and in tissue engineering applications.^[13]

Classification of biodegradable polymers^[14]

a) Natural and modified natural polymers:

i. Proteins

Ex: albumin, collagen and gelatin

ii. Polysaccharides

Ex: cellulose, dextran, insulin and hyaluronic acid, starch.

b) Synthetic polymers

i. Aliphatic poly(esters)

Poly (glycolic acid) and its copolymers

Poly (lactic acid) and its copolymers

Poly (E-caprolactone) and its copolymers

Poly (F-dioxanone)

Poly (hydroxybutyrate)

Poly (E-malic acid)

ii. Poly (Phosphoester)

iii. Polyanhydride

iv. Polyphosphazene

v. Pseudo amino acids

vi. Poly(orthoesters)

Advantages of Biodegradable polymers

- Biodegradable polymers play the role of a drug depot providing a more or less long-term supply of the drug to the blood at a constant rate.
- The polymer carrier would degrade into nontoxic, absorbable subunits which would be subsequently metabolized.
- A degradable system eliminates the necessity for surgical removal of the implanted devices following depletion of a drug.

Disadvantages of Biodegradable polymers

- Degradable systems which are administered by an injection of a particulate form are non-retrievable.

- Sometimes degradable polymers exhibit substantial dose dumping at some point.
- A “burst effect” or high initial drug release soon after administration is typical of most systems.

Non- biodegradable polymers^[15,16]

These are inert in the environment of use are eliminated or extracted intact from the site of administration and serve essentially as rate-limiting barriers to the transport and release of drug from the device. These polymers are resistant to environmental degradation. Examples of Non-biodegradable polymers

Polyethene: They are three types

Linear high-density polyethene(HDPE)

Branched low-density polyethene(LDPE)

Ultra-high molecular weight polyethylene(UHMWPE)

These have high strength and lubricity and are also used in orthopedic implants and catheters. They are used in hollow fibers for enzyme immobilization, wiring in aerospace, etc.

One example of a non-degradable delivery system is Norplant which is used successfully in prevention of pregnancy for up to five years. It was one of the drug delivery systems to be widely used in clinical practice, it requires surgical removal once the drug has depleted. Its clinical use has declined, and it has been discontinued in the UK and US. This is largely attributed to the polymers of removal, including the possibility of complications during the retrieval process, the risk of infection, and lack of patient compliance. The use of biodegradable polymers presents a far more attractive option as there is no need for surgical removal once the drug has depleted.^[14]

The polymers used in the transdermal system

1. Natural polymers^[17]

Natural polymers are polysaccharides so they are biocompatible and without any side effects. Natural polymers remain attractive primarily because they are commercial, readily available, capable of a multitude of chemical modifications, potentially degradable, and compatible due to their origin. The applicability of polymers of transdermal drug delivery systems is to control the release of the drug from the TDDS patch/device and may be used to formulate variously controlled and targeted drug delivery systems.

Table 1: Natural polymers used in the transdermal system.^[18]

Natural polymers	Advantages
Zein	Lengthens dissolution time
Shellac	It also lengthens dissolution and disintegration time but on aging because it polymerizes on aging
Waxes	Forms controlled release matrix through both pore formation and diffusion.
Chitosan	Good absorption enhancing and bioadhesive properties.
Gums and their derivatives	These polymers are non-reactive, stable with drugs, easily fabricated with the desired product, and showed inexpensive mucoadhesive properties.
Starch	Ensures minimal interaction with polyphenolic activities sustains drug release

2. Synthetic polymers^[18]

Synthetic polymers have gained significant attention in recent years due to their wide range of varieties that offer added flexibility in terms of their application in DDS's. These are available in a wide variety of compositions with readily adjustable properties; Bulk preparation of synthetic polymers is easy, which also eliminates the additional step of purification in the case of natural polymers. In contrast to natural polymers, these are

considered less prone to bacterial contamination. However synthetic polymers also suffer from some disadvantages, including the following:

- i. Toxicity of the chromium compounds.
- ii. Potential hazards as pollutants.
- iii. Fairly high temperatures (55-70°C) of operation.
- iv. A system can produce similar etching of plastic articles made from synthetic polymers resins.

Table 2: Synthetic polymers used in a transdermal system.

Synthetic polymers	Advantages
Polyvinyl alcohol	For hydrophilicity and strength
Polyethylene	For toughness and lack of swelling
Polyvinyl pyrrolidone	For suspension capabilities, used as adhesives
Polymethyl methacrylates	For physical strength transparency.

3. Semi- synthetic polymers

A Semi synthetic polymer is those which are obtained from nature and are used and applied only after modification.

Table 3: Semi-Synthetic polymers used in the transdermal system.

Semi-Synthetic	Advantages
Hydroxy propyl cellulose	More resistant to attrition
Methyl and Ethyl cellulose	Formation of gel in situ. Drug release is controlled by penetration of water through a gel layer produced by hydration of the polymer and diffusion of the drug through the swollen hydrated matrix.

Table 4: Factors influencing polymer performance^[19]

Stimulus	Hydrogel	Mechanism
pH	Acidic or basic Hydrogel	Change in pH—swelling—release of drug
Ionic strength	Ionic Hydrogel	Change in ionic strength—change in the concentration of ions inside gel—change in swelling—release of drug
Chemical species	The hydrogel containing electron-accepting groups	Electron donating compounds—formation of charge/transfer complex—change in swelling—release of drug
Enzyme substrate	The hydrogel containing immobilized enzymes	Substrate present—enzymatic conversion—product charges swelling of gel—release of drug
Magnetic	Magnetic particles dispersed in alginate microspheres	Applied magnetic field—change in pores in gel—change in swelling—release of drug
Thermal	Thermoresponsive Hydrogel poly(n-isopropyl acrylamide)	Change in temperature—change in polymer—polymer and water—polymer interactions—change in swelling—release of drug
Ultrasound irradiation	Ethylene-vinylalcoholhydrogel	Ultrasound interaction—temperature increase—release of drug

TDDS Classification Based On Their Technical Sophistication^[20]

A. Rate pre-programmed drug delivery system.

B. Activation modulated drug delivery system.

C. Feedback regulated drug delivery system.

D. Carrier-based drug delivery system.

A. Rate preprogrammed Drug Delivery System

In this, the drug release of drug molecule from the delivery system is pre-planned with particular flow rate profile of medicine. The system controls the molecular diffusion of drug molecules in or across the barrier medium within or surrounding the delivery system.

Polymer membrane permeation controlled drug delivery system

In this system, the drug is completely or partially encapsulated in a drug reservoir cubicle. This is covered by the semi-permeable membrane of polymer that regulates the release and having a specific permeability. There is some potential development with the process of membrane permeation are as porous membrane permeation controlled gastrointestinal delivery device, gastric fluid resistance intestinal targeted controlled release gastrointestinal device, and gel diffusion controlled drug delivery system.

1-Polymer matrix diffusion controlled drug delivery system

It is developed by dispersing drug particles in a carrier matrix (in a homogeneous manner) that is rate controlling. E.g. Nitro Dur-It is designed for application on intact skin for 24 hrs that provide a consistent transdermal infusion of nitroglycerine.

2-Microreservoir partitioned controlled drug delivery system.

It involves dispersion of microparticles of suspension of the drug (aqueous) in a polymer using high energy dispersion. E.g. Syncromate implant-Engineered to deliver subdermal administration of norgestomet.

B. Activation Modulated Drug Delivery System.

This type of delivery system can be achieved by

1. Physical means

- Osmotic pressure-activated drug delivery system.
- Hydrodynamic pressure controlled drug delivery system.
- Vapour pressure-activated drug delivery system.
- Mechanically activated drug delivery system.
- Magnetically activated drug delivery system.
- Electrically activated drug delivery system.
- Ultrasound-activated drug delivery system.
- Hydration-activated drug delivery system.

2. Chemical means

- pH-activated drug delivery system.
- Ion-activated drug delivery system.
- Hydrolysis activated drug delivery system.

3. Biochemical means

- Enzyme activated drug delivery system

C. Feedback Regulated Drug Delivery System.

The release of the drug molecules from the transdermal system is facilitated by a triggering agent, which triggers

the release of a drug. Such as a biochemical substance, in the body and also regulated by its concentration through some feedback mechanism.

- Bio-erosion regulated drug delivery system.
- Bio-responsive drug delivery system.
- Self-regulated drug delivery system.

D. Carrier-Based Drug Delivery System.**Colloidal particulates carrier system**

This involves vesicular system like hydrogels, liposomes, niosomes, nanocapsules, Nanoparticles, polymeric complexes, microspheres, nanoerythrocytes, transferases, dendrimers, aquasomes, etc.

DRUG RELEASE MECHANISM**Erosion^[10]**

In these systems, the drug is dispersed throughout the polymer, and the rate of drug release depends on the erosion rate of the polymer. However, some diffusion of the drug from the polymer may also occur. Degradation of the polymer in vivo makes long-term accumulation impossible. Therefore an implant made of degradable polymers does not require surgical removal. However, the surface area over which drug release occurs changes as a function of time, which makes zero-order release unlikely.

To maximize control over the release, it is often desirable for a system to degrade only from its surface. Poly (lactic-co-glycolic acid) (PLGA), the most commonly used degradable polymer, displays bulk erosion with a significant degradation in the matrix interior. In a surface-eroding system, the drug release rate is proportional to the polymer erosion rate and can be controlled by changing system thickness and total drug content. Surface erosion can be achieved when the degradation rate of the polymer matrix surface is much faster than the rate of water penetration into the matrix bulk. Theoretically, the polymer should be hydrophobic with water-labile linkages connecting monomers. Three general chemical mechanisms cause bioerosion.

Type I erosion: This type of erosion is evident with water-soluble polymers cross-linked to form a three-dimensional network. As long as cross-linked forms a three-dimensional network. As long as cross-links remain intact, the network is intact and is insoluble. When it is placed in an aqueous environment, it swells only to the extent permitted by its cross-link density. Generally, degradation of type 1A polymers provides high molecular weight, water-soluble fragments, while degradation of type 1B polymers provides low molecular weight, water-soluble oligomers, and monomers.

Type II erosion: This type of erosion occurs with a polymer that was earlier water-insoluble but converted to water-soluble forms by Ionization, protonation, or hydrolysis of the pendant group. With this mechanism, the polymer does not degrade and its molecular weight remains essentially unchanged, Materials like cellulose

acetate derivatives and partially esterified copolymers of maleic anhydride are displaying type II erosion. These polymers showing type II erosion and become soluble by ionization of the carboxylic group.

Type III erosion: Degradation of insoluble polymers with labile bonds Hydrolysis of labile bonds causes scission of the polymer's backbone, thereby forming low molecular weight, water-soluble molecules. Polymers like, poly (lactic acid), poly (glycolic acid), and their copolymers, poly (orthoesters), undergo type III erosion. The three mechanisms described are not mutually exclusive, combinations of them can occur.

Diffusion^[12, 19, 21]

Diffusion occurs when a drug or other active agent passes through the polymer that forms the controlled-release device. The diffusion can occur on a macroscopic scale as through pores in the polymer matrix or on a molecular level, bypassing between polymer chains. For the diffusion-controlled systems, the drug delivery device is fundamentally stable in the biological environment and does not change its size either through swelling or degradation. In these systems, the combinations of polymer matrices and bioactive agents have chosen must allow for the drug to diffuse through the pores or macromolecular structure of the polymer.

Drug diffusion increases with an increase in polymer content as well as dimension proportionally as well as the interaction between the polymer and solute. Polymer swelling, chain relaxation, hydration, wetting, and enthalpy changes associated are other polymer-related factors affecting drug release. The polymer particle property influences the availability of particle contact points, porosity, viscosity, and tortuosity of matrices. There is an increased resistance to the infiltration of the aqueous medium when the bulk density increases as the porosity decreases.

Swelling^[12, 22, 23]

In this mechanism, the drug is dispersed throughout the polymer and has difficulty in diffusing out of the polymer matrix. In vivo, biological fluid diffuses into the matrix and causes its outer polymer region to swell, allowing the release of the drug entrapped inside the polymer at a predictable rate. This release mechanism

and osmosis-induced drug release are summarized as solvent activation by Langer.

Degradation^[14]

The degradation is primarily the process of chain cleavage leading to a reduction in molecular weight. On the other hand, erosion is the sum of all the processes leading to a reduction in molecular weight. A polymer matrix can erode even without degradation. Conversely, it is possible that the polymer is degraded completely but is not eroded.

The erosion of biodegradable polymer is crucial to its behavior as a carrier material for drug delivery. Polymers degrade in the body at various periods from a few days up to 2-3years. These polymers degrade into non-toxic acids or alcohols that are readily excreted from the body. The in vivo elimination time is determined by the nature of the polymer chemical linkage, the solubility of the degradation products, the size, shape, and density of the device, the molecular weight of the polymer, and the implantation site. Many of the site-specific applications of drugs are for periods of several weeks, requiring polymer-carriers that degrade and are eliminated from the body soon after. From the available polymer, polyanhydrides, collagen, and copolymer of lactide and glycolide are useful for short-term drug release and device elimination in vivo. The degradation of polymer can be either bulk erosion (as in polyhydroxy esters) or surface erosion (as in poly anhydrides, poly (orthoesters). Generally, polymer degradation occurs in two phases.

1. In the first phase, water penetrates the bulk of the device and preferentially attacks the chemical bonds in the amorphous phase leading to the conversion of long-chain polymers into shorter water-soluble fragments.
2. In the second phase, there is a rapid loss of polymer mass due to enzymatic attack and fragment metabolism. In bulk erosion the rate of water penetration into the water-soluble materials.

Stability^[24]

Stability studies are to be conducted according to the ICH guidelines by storing the TDDS samples at 40±0.5°C and 75±5% RH for 6 months. The samples were withdrawn at 0,30,60,90,180 days and analyze suitably for the drug content.

Table 5: List of Polymers used in Transdermal drug Delivery^[25]

POLYMER	TYPE OF TRANSDERMAL SYSTEM
PVA: Chitosan	Drug-free film
PVA	Matrix
HPMC Eudragit RLPO Silicon gum Acrylate polymer	Film-forming polymeric solution
Eudragit E100:Eudragit NE40D	Matrix
HPMC: EC	Matrix
PVA	Matrix

PVP	
Eudragit E100	Matrix
PVA: PVP EC: PVP	Matrix
EC: PVP EC:HPMC	Matrix
Ethyl Cellulose T-50	Matrix
BIO PSA	Adhesive in matrix
Scotch Pak	Backing/Release Liner
MDX-4-421(a silicone)	Matrix
Acrylic PSA emulsion	Drug- in- adhesive
Acrylic adhesives	Drug -in-adhesive
Polyisobutylene	Adhesives
2-Ethylhexylacrylate	Drug-in-adhesive
Acrylic acid copolymer	Matrix
PIB	Matrix
MDX4-4210 silicone elastomer	Matrix
Acrylate copolymer(Gelva-737)	Matrix
Silicone-2920 and 2675	Matrix
2-Ethylhexyl acrylate and acrylic acid copolymer	Drug-in-adhesive

Applications of transdermal drug delivery system^[26, 27, 28]

Transdermal delivery systems are topically administered medicaments in the form of patches that deliver drugs for systemic effects at a pre-determined and controlled rate.

Drugs having very short half-lives like nitroglycerine can be formulated in this fashion, similarly, drugs with narrow therapeutic indices can be formulated as transdermal dosage forms.

These devices are fabricated as multilayer laminate structures in which the drug-polymer matrix or drug reservoir is sandwiched between two polymeric layers.

Polymers employed for this purpose are PVC, PVP polysaccharides polyesters microporous polypropylene ethylene-vinyl acetate copolymer, etc.

The drug release rate from the matrix is rapid initially and falls as the matrix gets depleted.

Drugs commonly presented in this system are nitroglycerine, Clonidine, scopolamine, and estradiol.

The highest selling transdermal patch in the United States of America is the nicotine patch, which releases nicotine in controlled doses to help with the cessation of tobacco smoking. The first commercially available vapor patch to reduce smoking was approved in Europe in 2007.

Two opioid medications used to provide round-the-clock relief for severe pain are often prescribed in patch form, Fentanyl CII (marketed as Duragesic) and buprenorphine CIII (marketed as buTrans).

Hormonal patches

Contraceptive patch (marketed as ortho Evra or Evra) and Testosterone CIII patches for both men (Androderm) and women (Intrinsa).

Nitroglycerin patches are sometimes prescribed for the treatment of angina instead of sublingual pills.

Dextran, the first methylphenidate transdermal delivery system for the treatment of attention deficit hyperactivity disorder (ADHD), was approved by the FDA in April 2006.

Vitamin B12 may also be administered through a transdermal patch.

5-Hydroxytryptophan (5 HTP) can also be administered through a transdermal patch, which was launched in the United Kingdom in early 2014.

Manufacturing considerations for efficient drug delivery system^[29]

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

The attributes like a 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, salvation, polymorphism of active component).

The matrix system involves the coating of the solution over the surface of the film and the films are made into the individual systems and pouched.

For the 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 a direct impact on critical attributes like viscosity, assay, and homogeneity.

Examples of critical process parameters throughout the different stages of manufacturing are the 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 the product pouching process.

The quantity of API each dosage form passes determines the quality of the dosage forms and which in turn leads to the intended action. The application process of the solution/gel plays a critical step in the manufacturing as the mixing step.

Transdermal Market^[30]

The global transdermal drug delivery market is expected to post a CAGR of more than 4% during the period 2019-2023, according to the latest market research report by Technavio. An increasing number of TDD products continue to deliver real therapeutic benefits to patients around the World. More than 35 TDD products have now been approved for sale in the US, and approximately 16 active ingredients are approved for use in TDD products globally. Table 7 gives detail information on the different drugs which are administered by this route and the common names by which they are marketed it also gives the conditions for which the individual system is used.

Table 6: Transdermal patches available in the market ^[31]

Brand Name	Drug	Manufacturer	Indication
Alora	Estradiol	TheraTech/Proctol and Gamble	Postmenstrual syndrome
Androderm	Testosterone	TheraTech/ GlaxoSmithKline	Hypogonadism in males
Catapres TTS	Clonidine	Alza/Boehinger Ingelheim(Four layer patch)	Hypertension
Climaderm	Estradiol	Ethical Holdings/Wyeth-Ayerest	Postmenstrual syndrome
Climara	Estradiol	3M Pharmaceuticals/Berlex Labs(Three-layer patch)	Postmenstrual syndrome
Deponit	Nitroglycerin	Schwarz-Pharma	Angina pectoris
Duragesic	Fentanyl	Alza/Janssen Pharmaceutica(Four-layer patch)	Moderate/severe pain
Estraderm	Estradiol	Alza/Novartis(Four-layer patch)	Postmenstrual syndrome
Fematrix	Estrogen	Ethical Holdings/Solvay Healthcare Ltd.	Postmenstrual syndrome
FemPatch	Estradiol	Parke-Davis	Postmenstrual syndrome
Habitraol	Nicotine	Novartis	Smoking cessation
Minitran	Nitroglycerin	3M Pharmaceuticals	Angina pectoris
Nicoderm	Nicotine	Alza/GlaxoSmithKline	Smoking cessation
Nitrodisc	Nitroglycerin	Roberts Pharmaceuticals	Angina pectoris
Nitro-Dur	Nitroglycerin	Key Pharmaceuticals	Angina pectoris
Nuvelle TS	Estrogen/ Progesterone	Ethical Holdings/Schering	Hormone replacement therapy
Prostep	Nicotine	Elan Corp/Lederle Labs(Multilayer round patch)	Smoking cessation
Testoderm TTS	Testosterone	Alza(Three-layer system)	Hypogonadism in males
Transderm-Scop	Scopolamine	Alza/Novartis	Motion sickness
Transderm-Nitro	Nitroglycerin	Alza/Novartis	Angina pectoris

Key Market Players^[32]

The key players in the transdermal drug delivery systems market are Hisamitsu Pharmaceutical (Japan), Mylan(US), UCB(Belgium), Novartis(Switzerland), and GlaxoSmithKline(UK), Boehinger Ingelheim(Germany), Johnson and Johnson(US), Endo International(Ireland), and Purdue Pharma(US).

Recent Developments^[32]

In January 2018, Hisamitsu Pharmaceutical (Japan) launched ALLESAGA TAPE in the Japanese market.

In July 2018, UCB (Belgium) received the import Drug release (IDL) for its transdermal rotigotine patch-NEUPRO from the China Food and Drug Administration (CFDA).

In August 2018, Luye Pharma (China) signed an agreement with Bayer AG (Switzerland) to acquire global rights to the Apleek contraceptives transdermal patch.

DBV technologies-addressing unmet allergy treatments for young children^[33]

According to the World Health Organization, allergies constitute the world's fourth-largest public health issue and affect 500 million people worldwide. Allergies affect somewhere between 25% and 40% of the adult population and more than 50% of children in developed countries. Environmental, pollution, and changing food habits are contributors to the rapid increase in the prevalence of allergies.

DBV Technologies focuses on food and pediatric allergy desensitization. The company has developed a patented skin patch, Viaskin that puts the allergen into contact with the immune system via immune cells present in the superficial layers of the skin, while avoiding disruption of the blood/skin barrier. This approach, which significantly reduces the risk of serious anaphylactic shock, enables Viaskin to fulfill at least two critically important medical needs that were previously unmet, explains Pierre-Henri Benhamou, CEO of DBV. First, Viaskin targets food allergies, in which the risk of anaphylactic shock is high, and second, the Viaskin patch is suitable for desensitizing children under the age of 5.

"Therefore, we are in a position to address allergies that are not treatable by conventional pharmaceutical therapies, he says."

When Viaskin, containing a specific allergen, is applied on the skin, the allergens are deposited locally on the skin and are taken up by the skin's immune-competent cells, triggering the immune response. The allergens are taken up in the superficial layers of the skin without crossing the basal membrane and preventing the allergen from reaching the bloodstream.

DBV uses two proprietary manufacturing processes to load active dry compounds onto a polymeric film backing via electrostatic force: static powder and electrospray deposit, a precise method of layering a controlling solution of the allergen on the patch so that it is dry and stable.

DBV has developed Viaskin Peanut for peanut allergy, Viaskin milk for treating Igmediated cow's milk allergy, and Viaskin House Dust Mites for preventing asthma in young children. In December 2011, DBV received Fast Track Designation for its Viaskin Peanut clinical development program.

"This designation was very important for us as we believe this translates to a real unmet medical need that patients, regulators, and DBV are willing to fulfill," says Mr. Benhamou.

Scientific and technological advances in recent decades have widened the scope of possibilities for therapies to or via the skin, enabling targeted delivery of drugs to

specific layers of the skin, muscle tissue, or even to the systemic circulation with unprecedented precision and exactitude. Since the advent of the first transdermal patch in the late 1970s, the pharmaceutical industry has witnessed successful delivery of chronic therapies like hormones, nicotine, and NSAIDS systemically via the skin. These innovations have significant advantages over the oral route: patient compliance, improved plasma levels, and reduced side effects. Topical OTC drugs are an important market segment with a forecast worth expected to exceed \$870 million in 2014, according to Datamonitor. Antiseptic cleansers account for the largest part of the topical OTC medicines market at almost 60%, with anti-itch products in second place at almost 28%, followed by anesthetic products, which represent more than 10% of the segment.

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