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Review Article

A Review on Transdermal Patch

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ABSTRACT

Alzheimer's disease (AD) is the most common form of dementia, accounting for 60–70% of global cases and representing a major public health priority due to its progressive neurodegenerative nature and increasing prevalence. Conventional drug delivery for AD is limited by poor oral bioavailability, first-pass metabolism, short drug half-lives, and fluctuating plasma concentrations that contribute to adverse effects and reduced therapeutic efficacy. Transdermal drug delivery systems (TDDS) offer a promising alternative approach by delivering drugs across the skin at a controlled and sustained rate, improving patient compliance, minimizing gastrointestinal complications, and avoiding first-pass metabolism. The skin's multilayered structure—particularly the stratum corneum—acts as a key barrier to permeation, necessitating the use of specialized polymers, permeation enhancers, and adhesive systems in patch design. Various types of transdermal patches, including matrix, reservoir, drug-in-adhesive, vapor patches, and micro-reservoir systems, have been developed to optimize drug release and therapeutic performance. Preparation methods such as solvent casting, membrane-based techniques, and advanced fabrication approaches enable the creation of stable and effective patches, which are evaluated through physicochemical, mechanical, adhesive, and permeability tests. Despite significant advantages, TDDS face challenges related to molecule size limitations, skin irritation, and difficulty achieving high plasma drug levels. Emerging technologies such as microneedles, iontophoresis, and 3D printing may overcome current barriers, offering personalized and scalable transdermal therapeutics. Overall, TDDS represent a rapidly advancing field with the potential to enhance AD treatment and improve patient outcomes.

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurological disorder marked by a gradual decline

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in memory, cognition, and functional independence. Since Alois Alzheimer first reported the condition in the early twentieth century, extensive scientific investigation has identified key pathological features, notably extracellular amyloid-β accumulation and intracellular neurofibrillary tangles formed by abnormal tau protein. Despite significant progress in understanding disease mechanisms, currently available treatments primarily alleviate symptoms rather than altering disease progression. [1]

The global prevalence of AD continues to increase, largely due to population aging, and is projected to rise sharply in the coming decades. Diagnostic frameworks have evolved to incorporate clinical assessment, neuroimaging, and biomarker analysis, enabling recognition of both early and advanced stages of the disease. Nevertheless, effective long-term drug therapy remains challenging, particularly in elderly patients who often experience swallowing difficulties, altered pharmacokinetics, and poor adherence to oral medications. [2] Against this background, alternative drug delivery strategies have gained attention. Transdermal drug delivery systems are designed to transport drugs across the skin at a controlled rate, maintainin relatively constant plasma concentrations and improving tolerability. Such systems are especially relevant for chronic conditions like Alzheimer's disease, where sustained drug exposure and ease of administration are critical for therapeutic success. [3]

Limitations Of Conventional Drug Delivery

- Traditional drug delivery routes present several challenges in Alzheimer's disease management:
- Short drug half-lives that require repeated dosing to adverse effects such as nausea and vomiting
- Discomfort and invasiveness associated with reduced oral bioavailability due to first-pass hepatic metabolism
- Variability in plasma drug levels leading parenteral administration
- Difficulty in achieving and maintaining steady-state drug concentrations. [4]

Transdermal Drug Delivery System

Transdermal drug delivery systems are classified under controlled release technologies and are intended to deliver medications through the skin in a predictable and reproducible manner. The skin, particularly the stratum corneum, acts as the principal barrier to drug penetration. Consequently, effective TDDS design requires consideration of skin anatomy, drug physicochemical characteristics, and formulation components. Compared with oral and injectable routes, TDDS provide several benefits, including avoidance of first- pass metabolism, prolonged drug release, reduced dosing frequency, and improved patient adherence. Continuous drug input also minimizes peak–trough fluctuations in plasma concentration, thereby lowering the risk of dose-related side effects.[5]

ADVANTAGES

- Decreased dosing frequency and improved patient compliance
- Elimination of hepatic first-pass metabolism
- Enhanced systemic availability of suitable drugs
- Non-invasive and user-friendly administration
- Reduced gastrointestinal adverse reactions

- Improved suitability for patients with swallowing difficulties or chronic nausea

Disadvantages

- Limited applicability for drugs with high molecular weight or unsuitable partition coefficients
- Risk of local skin irritation or sensitization
- Challenges in delivering high drug doses
- Interindividual variability in skin permeability
- Potential discomfort during prolonged application. [6]

Skin Structure And Drug Penetration

The skin is the largest organ of the human body, covering approximately two square meters in adults. It is composed of three primary layers: the epidermis, dermis, and hypodermis. The outermost layer of the epidermis, the stratum corneum, serves as the main barrier to transdermal drug transport. Beneath it lies the viable epidermis and the dermis, which contains blood vessels, lymphatics, and skin appendages such as hair follicles and sweat glands. Drug penetration through the skin occurs primarily via intercellular, transcellular, or appendageal pathways. A thorough understanding of these routes is essential for the rational design of effective transdermal formulations. [7]

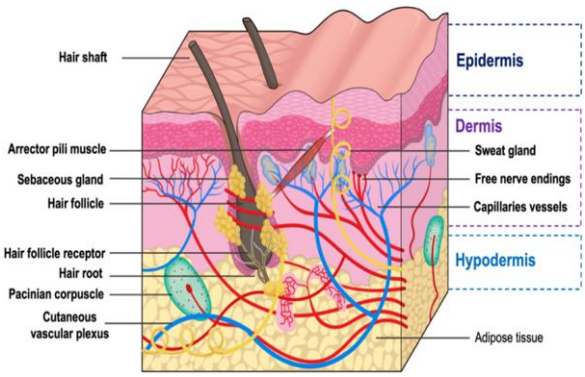

Figure No 1: Schematic illustration of the anatomy of the skin

Site Of Application

The site of application has been demonstrated to affect human skin penetration fluxes. Many parts of the body (trunk and upper arm) appear to have similar fluxes allowing for interchangeable placement of patches to achieve similar plasma concentrations over recommended wear time. Testosterone, nicotine, norelgestromin, oestradiol and clonidine all have evidenced similar drug plasma concentrations, with similar uptake at different skin sites. However, studies have shown that Rivastigmine had demonstrated higher plasma exposure after application to the upper back, chest or upper arm versus the thigh or abdomen. Details of these studies can be accessed, but it is important to follow the advice of trained medical professionals for application to ensure that efficacy is attained by correct dosage and wear. [8]

Type Of Transdermal Patches

1. Single Layer Drug in Adhesive: In this system the drug is included directly within the skin-contacting adhesive. In this type of patch the adhesive layer is responsible for the releasing of the drug, and serves to adhere various layers

together, along with the entire system to the skin. The adhesive layer is surrounded by a temporary liner and a backing releasing of the drug, and serves to adhere various layers together, along with the entire system to the skin. The adhesive layer is surrounded by a temporary liner and a backing.

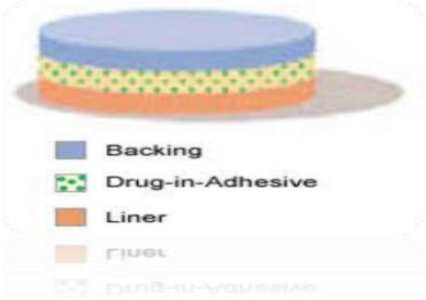

Figure No 2: Single-layer Drug-in-Adhesive

2. Multi -Layer Drug in Adhesive: The Multi-layer Drug-in-Adhesive is a type of drug delivery system that consists of either a membrane or multiple drug in-adhesive layers positioned between two separate drug-in adhesive layers, all of which are placed under a single backing film. This system is similar to the Single-layer Drug-in-Adhesive, in which the drug is directly incorporated into adhesive.

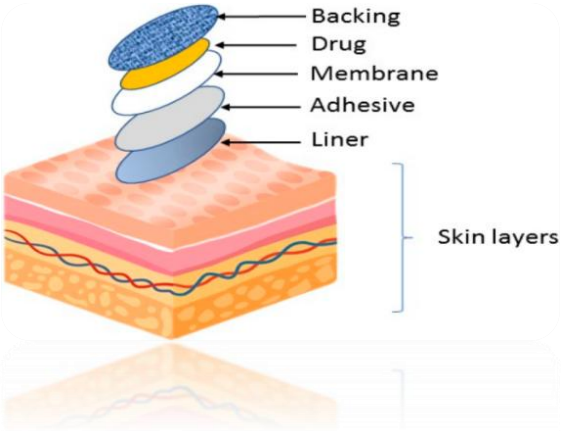

Figure No 3: Multi-layer Drug-in-Adhesive

3. Vapour patch: In this type of patch the role of adhesive layer not only serves to adhere the various layers together but also servesas release vapour. The vapour patches are new to the market, commonly used for releasing of essential oils in decongestion. Various other types of vapour patches are also available in the market which are used to improve the quality of sleep and reduces the cigarette smoking conditions.

4. Reservoir system: In this system the drug reservoir is embedded between an impervious

backing layer and a rate controlling membrane. The drug releases only through the rate controlling membrane, which can be micro porous or non porous. In the drug reservoir compartment, the drug can be in the form of a solution, suspension, gel or dispersed in a solid.

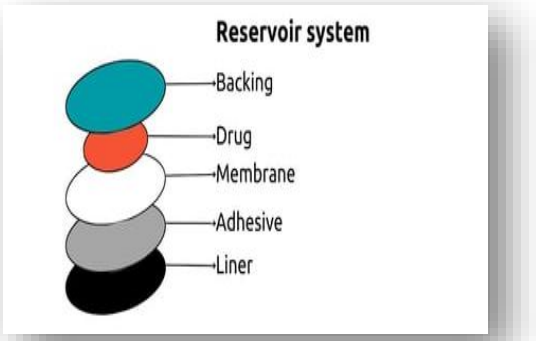

Figure No 4: Reservoir transdermal system

5. Matrix system: The Matrix system has a drug layer of a semisolid matrix containing a drug solution or suspension, which is in direct contact with the release liner. The adhesivelayer in this patch surrounds the drug layer partially overlaying it.

- Drug-in-adhesive system: In this type the drug reservoir is formed by dispersing the drug in an adhesive polymer and then spreading the medicated adhesive polymer by solvent casting or melting (in the case of hotmelt adhesives) on an impervious backing layer. On top of the reservoir, adhesive polymer layers are applied for protection purpose.

- Matrix-dispersion system: In this type the drug is dispersed homogenously in a hydrophilic or lipophilic polymer matrix. This drug containing polymer disk is fixed on to an occlusive base plate in a compartment fabricated from a drug impermeable backing layer. Instead of applying the adhesive on the face of the drug reservoir, it is spread along with the circumference to form a strip of adhesive rim.

Figure No 5: Matrix system

6. Micro-reservoir system:

In this type the drug delivery system is a combination of reservoir and matrix-dispersion system. The drug reservoir is formed by first suspending the drug in an aqueous solution of water soluble polymer and then dispersing the solution homogeneously in a lipophilic polymer to form thousands of unreachable, microscopic spheres of drug reservoirs. This thermodynamically unstable dispersion is stabilized quickly by immediately cross-linking the polymer in situ by using cross linking agents. [9]

Basic Components Of Tdds

- Drug
- Polymer matrix
- Permeation enhancers

- Adhesives
- Backing membrane
- Release Linear

1. Drug

Drug to enable drug absorption through the skin, drugs must exhibit specific physicochemical traits. These include effectiveness, non-irritating properties, low molecular weights [up to 1000 Daltons], low melting points, short half-lives, and affinities for both lipophilic and hydrophilic compounds. The selection of drugs for a Transdermal Drug Delivery System requires careful consideration to ensure successful development.

2. Polymer matrix

Polymer matrix is said to be backbone of TDDS, which control the release of the drug. Polymer should be chemically non-reactive, should not decompose on storage, should be non-toxic, cost should not be high. E.g.: cellulose derivatives, zein, gelatin, shellac, waxes, gums, polybutadiene, hydrin rubber, polyisobutylene, silicon rubber, nitrile, acrylonitrile, neoprene, polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polymethylmethacrylate. [10]

3. Permeation enhancers

The penetration enhancers are usually used to increase the permeability of skin or substances that reduce the permeability of the skin. The selection of permeation enhancer should be based not only on its efficacy in enhancing the skin permeation but also on its physicochemical and biologic compatibility with the system's other component.

4. Adhesives

The fastening of transdermal devices to the skin has so far been done by using a pressure sensitive adhesive. The pressure sensitive adhesive can be positioned on the face of the device or in the back of the device and extending peripherally. Both adhesive systems should fulfill the following criteria.

• Should not irritate or sensitize the skin or cause an imbalance in the normal skin flora.

• Should adhere to the skin aggressively during the dosing interval without its position being disturbed by activities such as bathing, exercise etc.

• Should have excellent (intimate) contact with skin at macroscopic and microscopic level. [11]

5. Backing membrane

Backing membrane are flexible and they provide a good bond to the drug reservoir, prevent drug from leaving the dosage form through the top, and accept printing. It is impermeable and protects the product during use on the skin e.g. metallic plastic laminate, plastic backing with absorbent pad and occlusive base plate a (aluminum foil), adhesive foam pad (flexible polyurethane) with occlusive base plate (aluminum foil disc) etc.

6. Release Linear

During storage release liner prevents the loss of the drug that has migrated into the adhesive layer and contamination. It is therefore regarded as a part of the primary packaging material rather than a part of dosage form for delivering the drug. The release liner is composed of a base layer which may be non-occlusive (paper fabric) or occlusive (polyethylene, polyvinylchloride) and a release coating layer made up of silicon or Teflon. Other materials used for TDDS silicon or Teflon. Other

materials used for TDDS release liner include polyester foil and metalized laminate. [12]

Methods Of Preparation

1. Solvent casting Method

In order to create a transparent solution, the polymers were precisely weigh, dissolve in a solution of water and methanol, and set aside. Drug was dissolve in the solution and thoroughly mixed to produce a clear solution. Polyethylene glycol (PEG) 400 has a plasticizing effect and propylene glycol are employ to improve permeability. The uniformly form solution are pour into a petri dish, grease with glycerine, and allowed to dry for 24 to 48 hours at room temperature. To prevent the solvent from quickly evaporating, an inverted funnel are place on top of the petri dish. The dried patches were removed after 24 hours and kept in a desiccator for future analysis.

2. Asymmetric TPX membrane method:

A prototype patch can be fabricated using a heat sealable polyester film with a concave of 1 cm diameter will be used as the backing membrane. Drug sample is dispensed into concave membrane, covered by TPX {poly- (4methyl-1-pentene)} asymmetric membrane, and sealed by an adhesive. [13]

3. Circular Teflon mould method:

Solutions containing polymers in various ratios are used in an organic solvent. Calculated amount of drug is dissolved in half the quantity of same organic solvent. Enhancers in different concentrations are dissolved in the other half of the organic solvent and then added. Di-N butyl phthalate is added as a plasticizer into drug polymer solution. The total contents are stirred for 12 h and poured into circular Teflon mould. The moulds are placed on a leveled surface and covered with inverted funnel to control solvent vaporization in a laminar flow hood model with an air speed of 0.5 m/s. The solvent is allowed to evaporate for 24 h. The dried films are stored for another 24 h at 25±0.5°C in a desiccators containing silica gel before evaluation to eliminate aging effects.

4. Mercury substrate method:

In this method, drug is dissolved in polymer solution along with plasticizer. The above solution is to be stirred for 10-15 min to produce a homogenous dispersion and poured in to a levelled mercury surface, covered with inverted funnel to control solvent evaporation.[14]

5. EVAC membranes method:

In order to prepare the target transdermal therapeutic system, 1% carbopol reservoir gel, polyethylene (PE), ethylene vinyl acetate copolymer (EVAC) membranes can be used as rate control membranes. If the drug is not soluble in water, propylene glycol is used for the preparation of gel. Drug is dissolved in propylene glycol; carbopol resin will be added to the above solution and neutralized by using 5% w/w sodium hydroxide solution. The drug (in gel form) is placed on a sheet of backing layer covering the specified area. A rate controlling membrane is placed over the gel and the edges are sealed by heat to obtain a leak proof device.

6. Aluminium backed adhesive film method:

Transdermal drug delivery system may produce unstable matrices if the loading dose is greater than 10 mg. Aluminium backed adhesive film method is a suitable one. For preparation of same, chloroform is choice of solvent, because most of the drugs as well as adhesives are soluble in

chloroform. The drug is dissolved in chloroform and adhesive material will be added to the drug solution and dissolved. A custom made aluminium former is lined with aluminium foil and the ends blanked off with tightly fitting cork blocks. [15]

Evaluation Of Trandermal Patch

Physical appearance:

Each of the formulating patches are undergoing to visual inspection to assess factors such as colour, clarity, opacity, transparency, and smoothness.

Drug content:

A specified area of patch is to be dissolve in phosphate buffer solution (pH 7.4). The content was allow to dissolve in solution. Then the solution is to be filtered through a filter medium and absorbance were measured with the help of UV. Each value represents average of three different samples.

Surface pH:

Each film are allow to swell by adding 0.5mL of distilled water on the film surface for 1hr at room temperature. Then, pH was noted by bringing the electrode into contact to the surface of the film and allowing it to equilibrate for 1 min. [16]

Folding endurance:

A strip of specific area is to be cut evenly and repeatedly folded at the same place till it breaks. The number of times the film could be folded at the same place without breaking gives the value of the folding endurance.

Thickness of patches:

The thickness of the patch are assess by using screw gauge at different points of the patch. From each formulation three randomly selected patches were used. The average value for thickness of a single patch was determined.

Weight Variation:

The prepared patches are dried at 60°c for 4hrs before testing. A specified area of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.[17]

Percentage moisture content:

The prepared films are to be weighed individually and to be kept in a desiccators containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs the films are to be reweighed and determine the percentage moisture content from the below mentioned formula.

$$\textbf{Percent Moisture Content} = \frac{\textbf{Final Weight} - \textbf{Initial Weight}}{\textbf{Final Weight}} \boldsymbol{X}\ \mathbf{100}$$

In - vitro skin permeation studies:

An in vitro permeation study can be carried out by using diffusion cell. The cellophane membrane is to be mounted between the compartments of the diffusion cell, with the half portion facing upward into the donor compartment. Sample volume of definite volume is to be removed from the receptor compartment at regular intervals, and an equal volume of fresh medium is to be replaced. Samples are to be filtered through filtering medium and can be analysed by uv spectrophotometer. Flux can be determined directly as the slope of the curve between the steady-state values of the amount of drug permeated (mg cm-2) vs. time in hours and permeability coefficients are deduced by dividing the flux by the initial drug load (mg cm) [18]

Adhesive studies: -

1. Shear adhesion test: - The cohesive strength of an adhesive polymer is determined by this test. The value of strength can be affected by the degree of cross linking, the molecular weight, the composition of polymer and the amount of tackifiers added. An adhesive coated patch is stacked on plate made of stainless steel and specified weight hung from the patch parallel to this plat. The time taken to pull off the patch from the plate determines the cohesive strength. More the time taken, greater is the shear strength.

2. Peel adhesion test: - The measure of patch strength between an adhesive and a substrate is defined as adhesion. The force required removing adhesive coating from the steel used as test substrate. The type and amount of polymer molecular weight and the composition of polymers determine the adhesive properties. The single patch is adhering to test substrate (Steel) and it pulled from the substrate at 1800 angle. No residue on the test substrate indicates failure of adhesive.

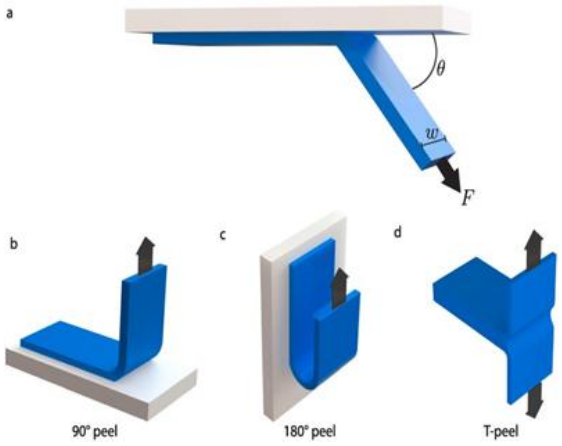

Figure No 6: Peel adhesion test

3. Tack properties: - Tack is the ability of polymer to adhere to a substrate with little figure pressure it's important in transdermal systems which are applied with little figure pressure. Tack is dependent on molecular weight as well as composition of polymer and tackifying resins used in the polymer.

Tests for tack include: -

1. Thumb tack test: - This is subjective test in which evaluation is done by pressing the thumb in to the adhesive. Experience is required for using the test.

2. Rolling ball tack test: - This test involves measurement of distance travelled by a stainless steel along the upward face of adhesive. The diameter of ball is 7/16o inches and it released on inclined track having angle 22.50. More the distance travelled, less the tacky polymer. Distance travelled by ball is measured in inches which determine the tackiness of polymer. It determines the softness of adhesive polymer.

Figure No 6: Rolling ball tack test

3. Peel tack or quick stick test: - The peel force is the force required to break the bond between the adhesive and the test substrate. The patch is pulled away from the substrate at 90o with speed 12 inches/minute. The value of force is expressed in grams/inch or ounces/inch.

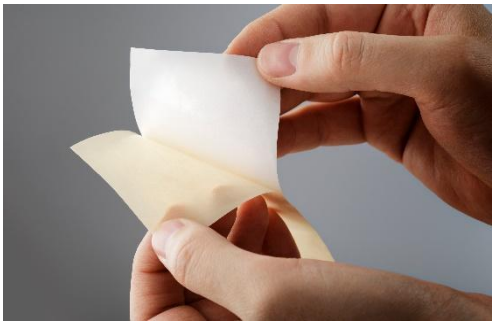

Figure No 7: Peel tack

4. Probe tack test: - In this, the tip of probe with defined surface roughness brought in to contact with adhesive and when the bond is formed between the adhesive an probe, removal of probe at a fixed rate away from the adhesive which break the bond. The force required to break the bond is recorded as tack and it is expressed in grams. [19]

The Future, Technical Consideration And Regulatory Challenges

The future of transdermal drug delivery must be met by an innovation that solves a problem impacting many people, done at a reasonable cost. Currently, patches are generally not seen as having a compelling therapeutic advantage compared to pills, but doctors do see some advantages, for example, in the elderly, people with swallowing problems or those who refuse to take medications orally. Duragesic® is a fentanyl patch manufactured by Johnson and Johnson (J&J) that dominated the transdermal market after its launch in 1990, with global sales peaking at in excess of $2 billion in 2004. This product stands out as an obvious commercial success and should represent a valuable blueprint for TDD as it clearly improved upon commercial pain treatments, yielding high commercial returns. Other examples include transdermal testosterone replacement products, which cannot be administered orally, generating $1.2 billion in the USA in 2010, $900 million of which were generated by Androgel®. The history of TDD has been mixed with success and failure, initial commercial success being hampered by commercial, technical and consumer issues. The push has begun to look at active (MN, iontophoresis, electroporation and sonophoresis) transdermal delivery as opposed to passive techniques, addressing challenges associated with drug molecule physicochemical properties, as well as low penetration flux and low potency. Currently, the paediatric community utilizes TDD systems, as evidenced by methylphenidate patch for ADHD; however, formulation challenges prevail when larger doses are required or for premature neonates with an immature skin barrier. Forbes reports on the lack of interest in investment opportunities associated with transdermal drug delivery. They report that the market, on the whole, is getting smaller (shrinking from $4.6 billion in 2013 to $2.99 billion in 2017), the cost of developing a suitable drug (acceptable physicochemical properties and efficacy)/patch combination is high, competition in the business of delivering generics by patch is intense, and insurance companies would rather pay for cheap mass-produced pills. Forbes elaborates further by commenting how different categories are performing better than others. For example, from 2013 to 2017, contraception patches (growing from $775 million to $849 million) and antinausea (cancer detox, growing from $137 million to $196 million) increased their market-share, however, larger categories are declining within the same time period; Alzheimer's patch revenues fell from $579 million to $273 million, ADHD patch revenue fell from $288 million to $152 million, and pain patches have tumbled at a 17.6% annual rate from $2.6 billion to $1.2 billion. The innovative potential of AM in transdermal drug delivery has generated a lot of excitement, especially with all the research in 3DP of transdermal patches, MN arrays and the introduction of 3DP products such as Invisalign™ and the first FDA-approved oral tablet, SPRITAM®. However, there are many technical and regulatory challenges that need to be considered for AM to become widespread in pharmaceutics. There is a distinct difference between an orodispersible tablet and a medical device such as a TDD patch or MN array, meaning each system would be subjected to different regulatory requirements. Furthermore, concerns about the materials and safety for humans and the

environment are being considered, in addition to its scalability and cost effectiveness.

Cost Effective And Scalabilit

Research conducted by the US Department of Commerce has suggested on a small scale that AM is cost-effective with continued centralized manufacturing, but in many instances when focusing on its applications in industrial sectors such as automotive, consumer electronics and medical, the manufacturing processes of AM exceed that of traditional manufacturing processes. However, the materials used account for the bulk of the cost, and hardware costs associated with AM have declined in the past decade. Also, the speed of printing has been greatly improved, especially in SLA techniques represented by companies like Carbon 3D and 3D Systems, with CLIP technology and the fab-grade 3D printer, respectively. Once the final product has been manufactured, it is difficult to assess the cost of AM as the obvious advantages and capabilities associated with PMDs might not be beneficial if the time and cost that came with designing and fabricating these AM drug delivery systems erodes away at such advantages. It appears now that the advantages of AM lie within the unique manufacturing processes that can be obtained, and it is still too far in its infancy to be considered as a replacement for traditional processes.

Safety And The Environment

Biocompatibility, with both the active drug and excipients, is important for TDD. Irritant contact dermatitis and allergic contact dermatitis represent most of the adverse effects that are associated with drugs in patches; other components of the patch (adjuvants/enhancers, adhesives, etc.) have caused skin side effects to a lesser extent. Manufacturing defects (i.e., seal and membrane defects, leakage) has led to the recall in 2004 and 2008 and redesign of the Duragesic patch in 2009. The presence of metals (e.g., aluminium) in the backing layer of certain TDP has caused burns for patients undergoing an MRI scan, prompting safe practice recommendations to be implemented. Subsequent TDP, such as Butrans®, Exelon and Neupro, warn patients on the exposure of the application site to direct external sources of heat (saunas, heating pads, electric blankets, fever), while wearing the patch as this could result in increased plasma drug concentrations due to temperature-dependent increases in drug release from the patch. 3D printable materials are of big concern regarding introduction of AM into pharmaceutic. One drawback to AM is the relatively limited choice of materials. SLA and vat polymerization (VP) are only compatible with monomers possessing a photocurable functional group such as acrylates, whereas FDM and extrusion-based techniques typically require a thermoplastic (TP) that need to be heated. Each technique offers advantages and limitations, with material availability/versatility being the main limitation as materials tend to be AM process specific. The advantages of techniques such as SLA and FDM would be the removal of solvent in the AM process, and specifically for SLA, the starting monomer(s) may be a relatively toxic acrylate that when polymerized becomes a higher molecular weight and essentially harmless biocompatible polymer. However, there is the potential for unpolymerized toxic material to remain which could potentially require removal and therefore increase processing costs and/or the introduction of solvents. The goal of pharmaceutics and TDD systems is for safe human usage, so aseptic manufacturing, sterilization and disinfection techniques would be required which need to be researched for effects on the biomaterials and API employed.[20]

CONCLUSION

Transdermal drug delivery is one of the fastest-growing methods of giving medicines. It works by allowing drugs to pass through the skin into the bloodstream without breaking or damaging the skin. This makes treatment safer, more comfortable, and often more effective. These systems are designed to release medicine in a controlled way, keeping steady levels in the body. Because the drug enters directly into circulation, smaller doses are needed, which reduces side effects and improves bioavailability. Another advantage is that the medicine avoids the liver's first-pass metabolism, which can otherwise reduce its effectiveness. Pharmaceutical companies worldwide are investing heavily in developing these systems. Current research focuses on improving adhesives that keep patches secure, using penetration enhancers to help drugs cross the skin barrier, and exploring advanced methods such as heat, electricity, ultrasound, and microneedles. These innovations aim to make drug delivery more reliable, precise, and suitable for a wider range of medicines, including those used for chronic diseases.

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