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"Advances In Skin Absorption For Transdermal Drug Delivery Through 3d Printing Technologies"

[1]Vaishnavi R. Wath,[2] Pratik P. Jadhav,[3]Dr.(prof) Sachin J. Dighade

[1]Student, [2]Asssistant Professor, [3]Principal,

[1] Department of B Pharmacy,

[1]Institute of Pharmacy and Research, Badnera,Amravati, India.

ABSTRACT: Recent advancements in skin absorption mechanisms and transdermal drug delivery have significantly enhanced the effectiveness of therapeutic treatments. The integration of 3D printing technologies into this field has opened new possibilities for personalized, precise, and controlled drug administration. 3D printing allows for the fabrication of custom drug delivery systems, such as patches or microneedles, that can be tailored to individual patient needs. These systems can improve skin absorption by optimizing the design and delivery rate of active ingredients through the stratum corneum. Moreover, innovations in material science and the ability to print bioactive compounds directly onto skin-adhering substrates have accelerated the development of transdermal delivery devices that bypass the first-pass metabolism, ensuring higher bioavailability. This review explores the latest advancements in 3D printing for transdermal drug delivery, examining materials used, fabrication techniques, and their implications for enhanced skin absorption. Additionally, the challenges and future prospects of these technologies in clinical applications are discussed, highlighting the potential for 3D-printed systems to revolutionize the way drugs are delivered through the skin.

INDEX TERMS - Skin Absorption, 3D Printing, Personalized Medicine, Customizable patches.

1.INTRODUCTION:

Transdermal drug delivery systems (TDDS) are self-contained dosage forms that deliver drugs through intact skin at a controlled rate [1]. A Transdermal Drug Delivery System (TDDS) is a method for delivering drugs via the skin for local or systemic therapeutic effects, alongside oral medicine and injectables, being a primary study topic [2]. Transdermal drug delivery systems (TDDS), also known as "Patches," can deliver drugs in a controlled manner for extended period through the skin's transdermal route. Matrix type TDDS are devices where the drug is embedded in a matrix bed, allowing controlled release. Although the stratum corneum (SC) barrier makes it difficult for most medications to penetrate the skin, transdermal drug delivery has the potential to overcome the drawbacks of oral administration. The efficacy of this approach may be increased by using vesicular carriers to promote medication vesiculation throughout the SC. A novel approach of drug delivery called transdermal delivery makes it possible to administer medications consistently, predictably, and consistently [3]. Transdermal patches are a method of administering medication through the skin and into the bloodstream. FDA-approved in 1981, they are used for various conditions like motion sickness, cardiovascular disease, chronic pain, and smoking cessation. High concentrations of active ingredients that stay on the skin for a long time can be found in transdermal patches. One of the first transdermal patches developed in 1985 was the nitroglycerin patch. The medication is absorbed through the skin and into the systemic circulation, providing a sustained release of drug over a period of time, often several hours or even days. These patches provide controlled, constant administration, with short biological half-lives and eliminate pulsed entry into systemic circulation [4]. 3D printing technology is a significant innovation in drug development, transforming the healthcare system. It is used in tissue engineering, dentistry, aerospace engineering, and construction. 3D printing involves computer-aided design (CAD) to formulate pharmaceutical dosage forms, achieving flexibility, time-saving. 3D printing technology is expected to revolutionize patient treatment, enhancing therapeutic activity and reducing adverse effects for patients with pharmacogenetics, polymorphism, and chronic diseases. 3D printing is utilized in creating various dosage forms like sustained-release tablets, pills, and transdermal patches, which contain multiple units of a single dose, capable of curing multiple diseases. The primary foundation of 3D printing technology is the virtual design included in computer-aided design files, which may be produced with a 3D scanner to build a 3D digital copy using 3D software [5].

2.ROUTES OF DRUG ABSORPTION THROUGH SKIN:

2.1.Transfollicular route:

The transfollicular route is the shortest route for drugs to reach systemic circulation, allowing for large drug diffusion. Skin's sweat glands, oil glands, hair follicles, and pores open to the skin's outer surface via ducts, providing a continuous channel for drug transport. Factors like gland secretion and amount of secretion affect this route's effectiveness. However the transappendageal route, which only occupies 0.1% of the total skin surface, makes a minimal contribution [6].

2.2.Transcellular route:

The transcellular route is the most common route for drug delivery, passing through the cytoplasm of cells. This route is suitable for hydrophilic drugs, as it involves a number of partitioning and diffusion steps. The drug then passes through the stratum corneum corneocytes, which have highly hydrated keratin, creating a hydrophilic pathway.

2.3.Intercellular route:

The drug diffuses through the intercellular pathway, passing through a tortuous structure formed by corneocytes. It then passes through the alternating lipid and aqueous domain, partitioning into the lipid bilayer and diffusing to the inner side. This route is suitable for uncharged lipophilic drugs as water travels 50 times more [7].

3.TYPES OF TDDS:

3.1.Reservoir System:

Drugs in reservoir systems are encased in an impermeable backing laminate and a microporous or nonporous membrane. The medication is suspended in a viscous liquid medium and evenly dispersed within a solid polymer matrix to form a paste. Membrane thickness, permeability, diffusion, and abrasion rate all affect the release rate. An impermeable metallic backing supports the entire system [8].

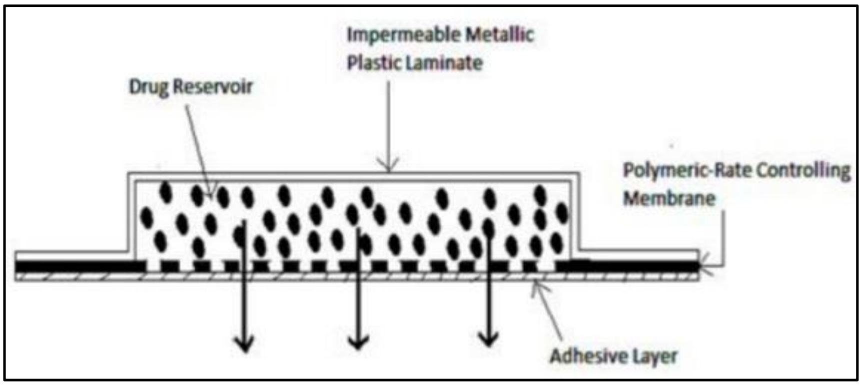

Figure No. 01: Reservoir system of drug delivery

3.2.Matrix Diffusion System:

In matrix diffusion systems, drugs are uniformly distributed in hydrophilic or lipophilic polymeric materials. The release rate of the drug is determined by the rate of erosion, layer thickness, and film surface area. No other rate-controlling membrane is present in these systems. These are also known as monolithic systems. Adhesive layers are spread around the polymer disc circumference [9].

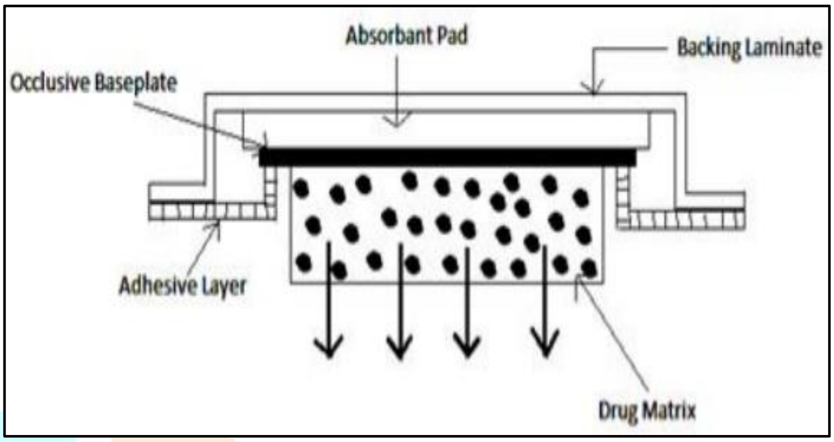

Figure No. 02: Matrix diffusion system of drug delivery

3.3.Drug in Adhesive System:

The drug is dispersed in the adhesive layer of a patch, which not only adheres the patch components to the skin but also controls drug delivery rate. The adhesive layer is surrounded by a liner. In single-layer patches, a single drug is present, while in multilayer patches, one layer is used for immediate drug release [10].

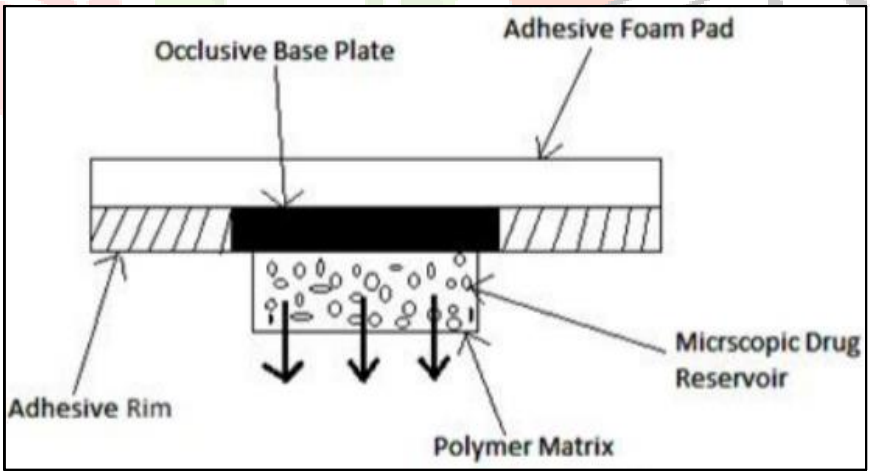

Figure No. 03: Drug in adhesive layer system

3.4.Microreservoir System:

The micro reservoir system is a combination of a matrix and reservoir system, where a drug is suspended in a hydrophilic polymer solution and mixed with a lipophilic polymer using a high shear mechanical stirrer. The in-situ cross-linking stabilizes the system and forming a medicated polymer disc of specific area and thickness [11].

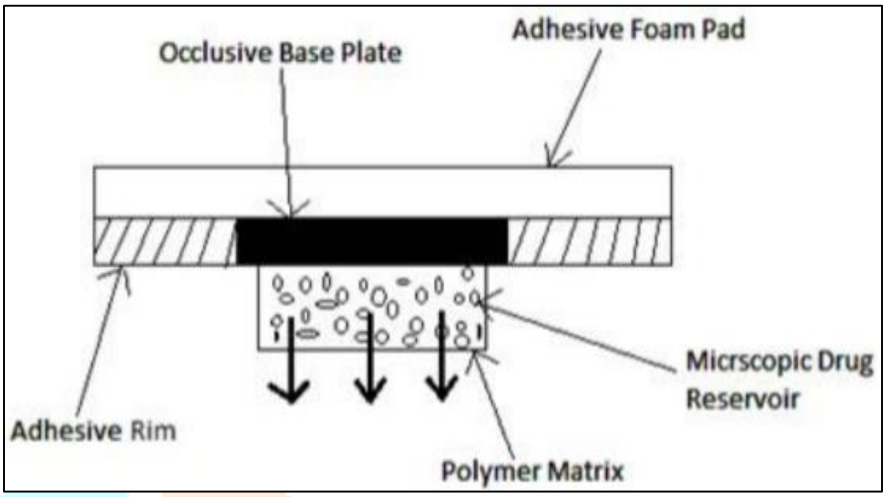

Figure No. 04: Microreservoir system

4.TYPES OF 3D PRINTING TECHNOLOGIES:

4.1.Inkjet printing:

Inkjet printing refers to devices that produce digitally controlled formulations and placement of small liquid drops onto a substrate. The classification of this process is based on the droplet size and formation method, which can be achieved through thermal or piezoelectric methods [12].

4.2.Extrusion-based printing:

Extrusion-based printers are user-friendly, versatile, and inexpensive. This process involves melting of printing material and depositing it in thin layers for bottom-up 3D object construction [13].

4.3.Stereolithography (SLA):

SLA is a widely researched photopolymerisation technology used for creating skin delivery platforms. The terms "photolithography" and "stereo (solid) " refer to "writing with light." The components used in SLA methods effectively solidify UV light, making it photopolymerizable upon exposure to light [14].

4.4.Fused deposition modeling (FDM):

FDM is a common extrusion-based 3DP method used in the pharmaceutical industry for creating personalized tablets or capsules. The printing process is influenced by various factors such as the material, nozzle size, pressure difference, feed rate, printing temperature, and layer thickness [15].

4.5.Two-photon polymerization (2PP):

The discovery of 2PP allowed production of intricate micro and nanoscale structures. This technique selectively polymerizes photosensitive resins using ultrashort laser pulses from a near-infrared femtosecond laser source [16].

5.Pharmaceutical potentials of 3D printing:

5.1.Personalization:

The growing importance of 3D printing in various industries is often called a new industrial revolution. Traditionally, businesses focused on mass production, automation, and standardization to cut costs and increase profits. Now, with 3D printing technology, there is a shift towards on-demand manufacturing. This method enables the creation of small quantities or even unique items that can be customized affordably. Moreover, complex designs can be produced and modified quickly to meet specific needs without significant extra costs.

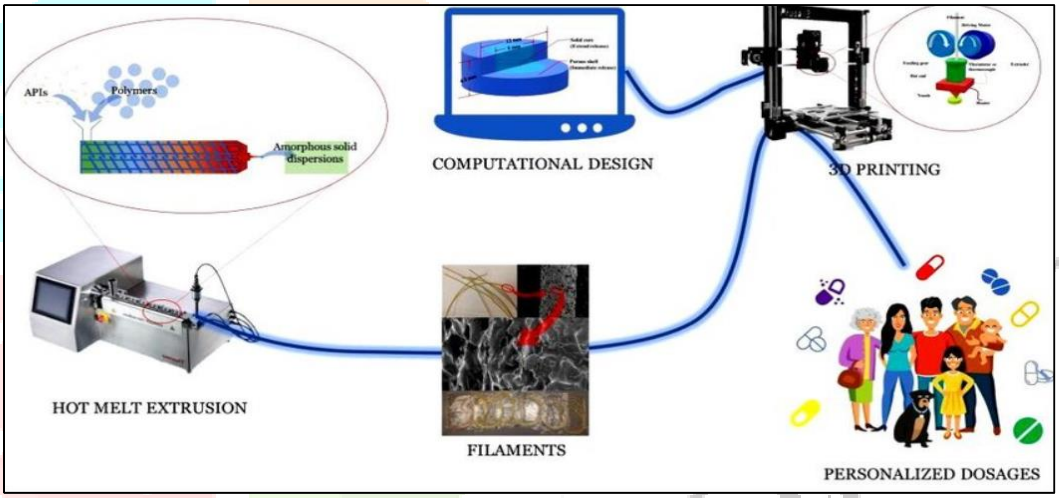

Figure No. 05: Personalized Dosage through Additive Manufacturing

5.2.Tailored medication:

3D printing allows for the creation of personalized medications that meet the unique needs of patients or the specific characteristics of the drugs. This method is particularly useful for children, as their dosage needs can vary widely. Moreover, the design of the medication can be changed to help those who have trouble swallowing. The adaptability and ease of 3D printing make it a great way to modify the shape and size of medication forms.

5.3.Create complex shapes:

3D printing enables the creation of intricate shapes while delivering precise amounts of medication or active ingredients, even as low as 10-12 moles per tablet. This precision helps minimize side effects that can occur from high doses. Unlike traditional methods, which struggle with complex designs, 3D printing makes it easy to achieve them. Additionally, varying shapes and sizes can lead to different release patterns. These complex designs allow for controlled release, tailored drug loading, and can help mask the taste of the medication.

5.4.Sustained release:

3D printing allows for easy control and targeting of drug release. By printing a binder within the layers of the matrix powder, a barrier is formed between the layers of active pharmaceutical ingredients (API). This method enables changes in the release profile.

5.5.Unique dosage form:

In the process of making pharmaceuticals, 3D printing can produce unique and endless types of dosage forms. It is used to develop new dosage forms [17].

3D printing	Dosage form	Drug
FDM	Catheter	Nitrofurantoin
FDM	Implant CR	Dye
FDM	General Device	Gentamicin sulphate, Methotrexate
FDM	Implant	Nitrofurantoin, Hydroxyapatite
Thermal Inkjet printer	Tablet	Prednisolone
Inkjet Printing	Implant	Levofloxacin
Thermal inkjet printer	Solution	Salbutamol
Inkjet printing	Nanoparticles	Rifampicin
Thermal inkjet printer	Nanosuspension	Folic acid
Desktop 3D printer	Tablet	Guaifenesin
A lab-scale 3DP machine	Capsule	Pseudoephedrine
Extrusion printing	Tablet	Captopril, Nifedipine, Glipizide
3D printer	Microfluidic pump	Saline solution
Stereolithography printer	Anti-acne patch	Salicylic acid
3D printer	Fast disintegrating	Paracetamol
3D printer	Tablets	Paracetamol

Table: Fabrication of dosage forms by 3D printing technology

6.FUTURE ASPECTS OF 3D PRINTING IN TDDS:

Recently, the application of 3D printing technology in dentistry has been expanding rapidly. In-situ bioprinting allows for the printing of living organs during surgical procedures. This innovative approach holds promise for the future, particularly in the repair of organs such as skin, as well as partially damaged or malfunctioning internal organs and tissues [18]. The application of 3D printing technology in the repair of internal organs represents a significant advancement in the fields of science, technology, and robotics. [19,20]. The application of 3D printing technology in transdermal drug development allows for sophisticated advancements, enabling the modulation of drug concentration through the incorporation of various pharmaceuticals within the printed layers. This capability significantly enhances therapeutic efficacy by facilitating precise control over the delivery of active ingredients [21]. Systems can be designed incorporating physiological factors that do not interfere with transdermal patches, allowing for prolonged application while maintaining the desired release rate and improving therapeutic effectiveness with a reduction in side effects [22].

7.CONCLUSION:

The safest, most pleasant, least painful, and possibly most effective way to administer regular dosages of many drugs is through transdermal drug delivery. A large variety of medications can be administered for better drug absorption, less problems and adverse effects, low cost, and ease of administration. 3D printing has a great chance to change the TDDS industry. It provides valuable possibilities in drug development, formulation, and administration because of its ability to create new medical products efficiently and flexibly. This can lead to more personalized and effective drug delivery options for patients around the world. The field is complex, and more research is necessary to grasp the full effects of 3D printing on TDDS. Innovations in skin absorption techniques, combined with 3D-printed drug delivery systems, improve drug bioavailability and patient compliance. Continued research and development are essential to fully realize the benefits of 3D printing in revolutionizing transdermal drug delivery. Still, the potential advantages are considerable, and the future for this innovative technology appears bright.

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