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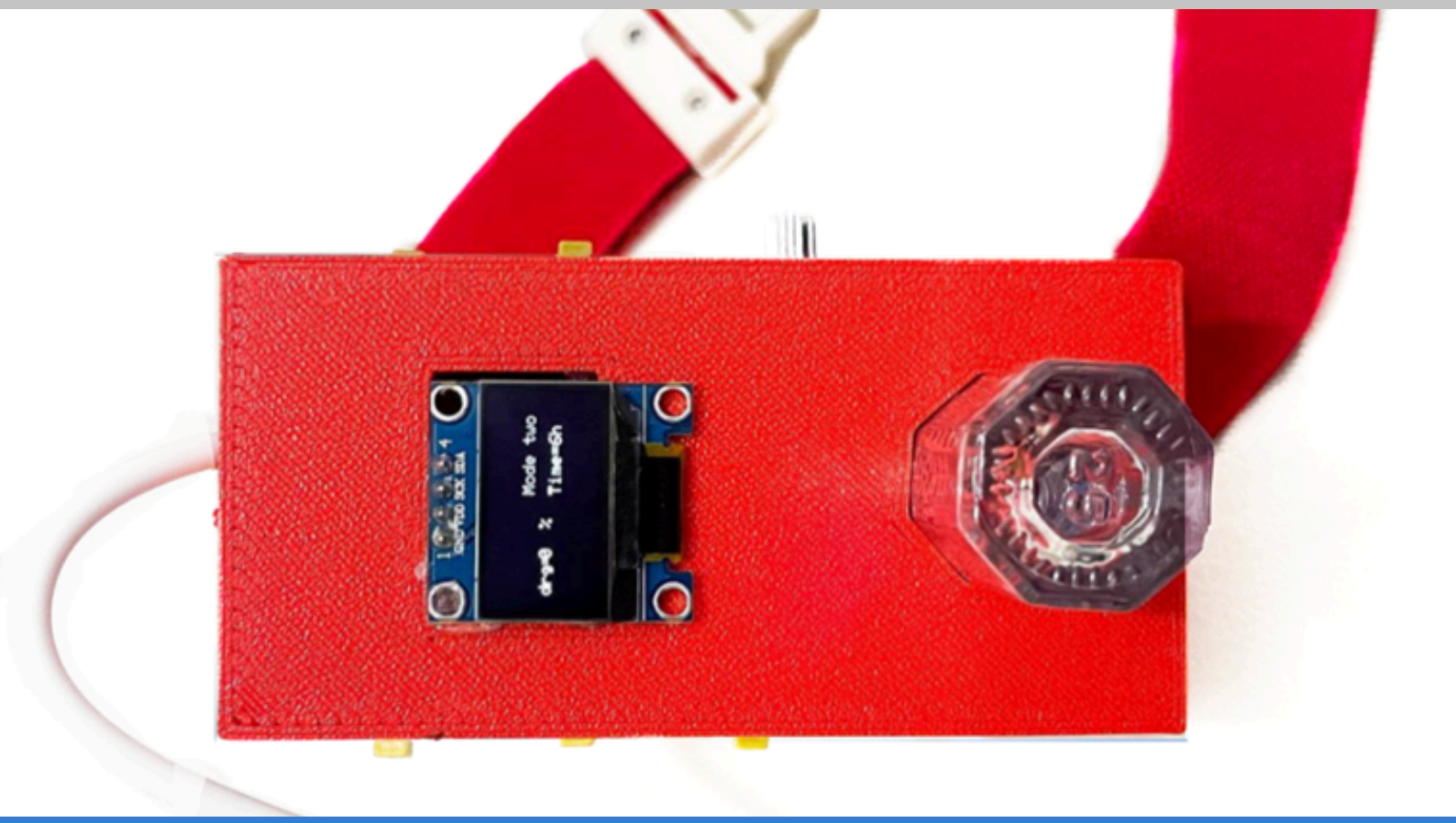

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I would also like to thank the international magazine that gave me the opportunity to share this work with a wide audience, hoping that it will achieve the desired benefit and be a valuable addition to the scientific and cultural community.

ABSTRACT

This project focuses on the design and development of a smart transdermal drug delivery system for administering amphetamines, with a particular emphasis on its applications in addiction treatment and attention deficit hyperactivity disorder (ADHD) management. Amphetamines, including dextroamphetamine and methamphetamine, have shown therapeutic efficacy in addressing stimulant-related substance use disorders and ADHD symptoms. The proposed transdermal drug delivery system integrates advanced materials, microelectronics, and sensor technologies to optimise drug delivery, enhance patient adherence, and enable real-time monitoring of drug release and patient response. Through feasibility assessments, optimisation of drug release mechanisms, and evaluation of therapeutic efficacy, the project aims to advance understanding of transdermal delivery of amphetamines and its potential benefits in addiction treatment and ADHD management.

The project aims to advance smart transdermal drug delivery technologies to improve therapeutic outcomes and enhance patient experiences in addiction treatment and ADHD management. By offering convenient, non-invasive drug delivery and real-time monitoring capabilities, the system holds promise for addressing the complex healthcare needs of individuals with addiction and ADHD.

We've selected Transdermal Drug Delivery (TDD) for its painless systemic drug delivery through intact skin, providing non-invasiveness and placement flexibility.

To advance research in this area, we must address the significant ethical and regulatory considerations surrounding the use of controlled substances in clinical trials. Ultimately, the project aims to contribute to the advancement of drug delivery technologies and improve healthcare outcomes for individuals with addiction and ADHD.

Keywords (Drug delivery technology. Pharmaceutical formulation. Medication adherence)

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LIST OF SYMBOLS/

ABBREVIATIONS

Symbol	Description	Units
TDD	Transdermal Drug Delivery	
DDS	Drug Delivery System	
SDDS	Smart Drug Delivery System	
CR	Controlled Release	
NPs	Nanoparticles	
PLGA	Poly (lactic-co-glycolic acid)	
WSN	Wireless sensor network	
WSNs	Wireless sensor networks	
SC	Stratum Corneum	

Chapter One: Project Overview

1.1Project Overview:

Smart Transdermal Drug Delivery System for Addiction Treatment and ADHD Management

The project aims to design and develop a smart transdermal drug delivery system capable of administering amphetamines for addiction treatment and attention deficit hyperactivity disorder (ADHD) management. Amphetamines, including dextroamphetamine and methamphetamine, are central nervous system stimulants known for their therapeutic effects in enhancing alertness, attention, and energy. Traditionally administered orally, recent interest in transdermal drug delivery has sparked investigations into its feasibility for delivering amphetamines through the skin.

1.2 suggested formula and methods:

Amphetamines exhibit lipophilic properties, enhancing their ability to penetrate the skin barrier. Leveraging this property, the project explores the development of an effective transdermal formulation for amphetamines. Additionally, the project investigates the use

of advanced materials, microelectronics, and sensors to optimize drug delivery and ensure safety in a smart transdermal system.

1.3 Smart System Components:

The proposed smart wearable patch system comprises various components, including supporting substrates, adhesive films, flexible circuits, sensors, therapeutic systems, and data transmission systems. This system allows for real-time monitoring of drug release and patient response, with the potential for triggered drug delivery based on physiological signals or external stimuli.

1.4 Applications in Addiction Treatment and ADHD Management:

The project recognizes the urgent need for innovative approaches in addiction treatment and ADHD management. The smart transdermal drug delivery system offers promising solutions for both as follows:

1.4.1 Addiction Treatment:

By delivering medications through patches applied directly to the skin, the system bypasses barriers to seeking traditional treatment, such as medication nonadherence, stigma, and geographical limitations. Continuous release of amphetamines may reduce the risk of misuse and enhance treatment adherence, addressing both physical and psychological aspects of addiction. The system holds particular significance for stimulant-related substance use disorders, where amphetamines play a crucial role in treatment.

1.4.2 ADHD Management:

Transdermal delivery of amphetamines offers advantages over oral administration, including steady drug release, avoidance of gastrointestinal side effects, and improved adherence. The system's ability to provide controlled and gradual drug release may enhance patient compliance and therapeutic efficacy in managing ADHD symptoms, promoting better outcomes for individuals with ADHD.

1.5 Objectives

1. Design and Development: Develop a smart transdermal drug delivery system for administering amphetamines, focusing on addiction treatment and ADHD management.

2. Integration of Advanced Technologies: Integrate advanced materials, microelectronics, and sensor technologies into the system for real-time monitoring of drug release and patient response.

3. Suggest drug Release Mechanisms: Suggest new drug release mechanisms to achieve controlled and gradual delivery of amphetamines for precise dosing and therapeutic efficacy.

4. Enhancement of Patient Adherence and Safety: Explore strategies to enhance patient adherence and safety through user-friendly interfaces and safety features.

5. Documentation and Knowledge Sharing: Document the design, development, and evaluation processes of the system and disseminate findings through scientific publications and knowledge sharing platforms.

Chapter Tow: Literature Review

2.1 Chapter Overview

The chapter overview explores into the expansive landscape of transdermal drug delivery systems (TDDS), tracing its roots from ancient practices to modern advancements. It highlights the evolution of controlled release technologies, beginning with the pioneering Transderm-SCOP patch approved by the US FDA in 1979. The discussion extends to recent drug delivery systems, emphasizing the significant progress made in utilizing organic, inorganic, and hybrid nanoparticles for active targeting, particularly in chemotherapy. The overview underscores the advantages offered by drug delivery systems, including increased bioavailability, sustained drug release, and reduced adverse effects, leading to improved patient compliance. Furthermore, it explores the challenges and successes in smart drug delivery, encompassing biosensor integration, targeted drug delivery, and advancements in nanotechnology. The section on technological advancements in transdermal drug delivery focuses on microneedle technology and nanotechnology, elucidating their roles in enhancing drug permeation and integrating with controlled release mechanisms. Additionally, the overview discusses the application of amphetamines in treating stimulant-related illnesses and ADHD, highlighting the diverse formulations available and the potential for smart transdermal devices to enhance adherence and patient well-being.

2.2 Definition and Historical Development of Transdermal Drug Delivery

The term TDDS may be of recent origin, yet the understanding and historical use of transdermal drug delivery can be traced back to ancient civilizations. For many years, various cultures have employed ointments, pastes, plasters, and intricate inunctions as methods for treating a range of ailments[1]. The implementation of controlled release drug administration concepts and techniques facilitated the development of innovative drug delivery systems. These systems not only prolonged the efficacy of existing medications but also reduced the extent and costs associated with the testing necessary for FDA approval. This novel methodology contributed to advancements in transdermal patch technology during the 1970s, culminating in the approval of the first patch by the US FDA in 1979, known as Transderm-SCOP.[2], aA three-day transdermal patch that administers scopolamine for the treatment of motion sickness has been developed. Transdermal drug delivery systems are advanced technologies designed to encapsulate and preserve drug molecules in appropriate formats, such as tablets or solutions, for effective administration. These systems facilitate the rapid delivery of medications to designated sites within the body, thereby enhancing therapeutic effectiveness while reducing unintended accumulation of the drug in non-target areas. [3][4] Drugs have various routes through which they can be introduced into the body; they include, but are not limited to, the oral route of administration [5][6] , buccal and sublingual routes of administration [7] , nasal and ophthalmic [8], Transdermal and subcutaneous delivery methods are characterized by the specific physiochemical properties of the drug components, which play a crucial role in the physiological changes they induce within the body upon administration. In recent decades, drug delivery systems (DDS) have been successfully utilized in disease management and health enhancement, primarily

due to their ability to enhance systemic circulation and regulate the pharmacological effects of medications. The progress in pharmacology and pharmacokinetics has underscored the significance of drug release mechanisms in establishing therapeutic efficacy, leading to the development of controlled release strategies[9] .

2.2.1 Recent drug delivery systems and application

Considerable advancements have been achieved in recent years in the effective development of drug delivery systems utilizing organic, inorganic, and hybrid nanoparticles as carriers for targeted drug administration, especially in the context of chemotherapy. Contemporary drug delivery systems (DDS) are designed with enhanced characteristics, including reduced particle size, enhanced permeability, improved solubility, greater efficacy, precise site targeting, stability, reduced toxicity, and prolonged delivery. These innovations can markedly enhance the performance of therapeutic agents compared to traditional dosage forms.[10][11] .The different types of drug delivery systems are depicted in Figure 1

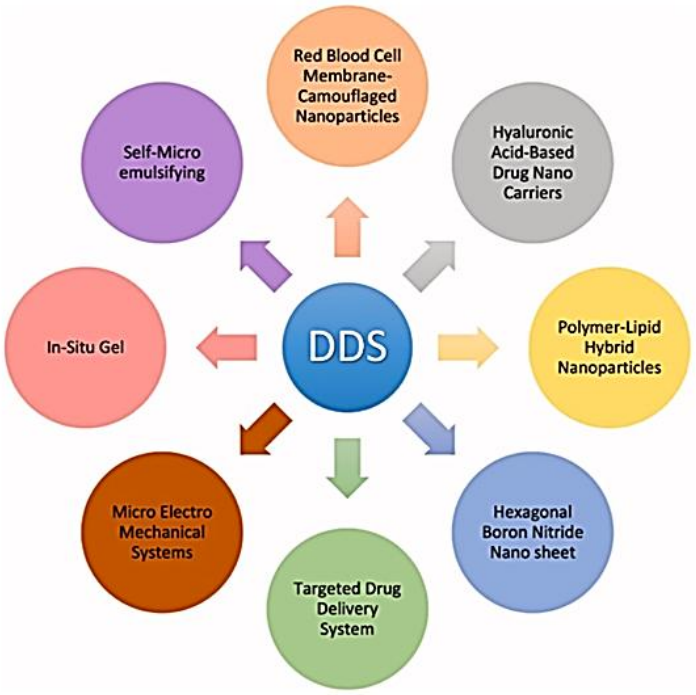

Figure 2.1: several types of recent drug delivery systems for different therapeutic purposes [12**]**

The drug delivery system offers several advantages, enhancing the effectiveness of pharmaceutical interventions such as:

1. Increases bioavailability.
2. Can be used for long-term treatments of chronic illnesses.
3. Sustained maintenance of plasma drug levels.
4. Decreased adverse drug effects.[12][13]
5. Decrease in the total amount of drugs required thus reducing side effects.

Improved patient compliance due to reduction in number and frequency of doses required.

6. There is less damage sustained by normal tissue due to targeted drug delivery.
7. Reduction in cost by developing newer delivery systems for existing molecules [14][15].

2.2.2 Evolution of controlled release technologies

Delivery strategies have played a crucial role in converting potential therapeutics into successful treatment options[16]. As the field of therapy progressed, the methods and technologies for drug delivery rapidly adjusted to meet the evolving requirements of medication administration. Several decades ago, small-molecule drugs dominated the therapeutic landscape. The delivery of these small molecules is primarily governed by their physicochemical characteristics, which significantly affect the drugs' bioavailability. Consequently, initial delivery strategies concentrated on enhancing drug solubility, regulating their release, expanding their therapeutic activity, and fine-tuning their pharmacokinetics (PKs)[17][18]. Over the years, the development of advanced therapeutic modalities, including proteins and peptides, monoclonal antibodies (mAbs), nucleic acids, and live cells, has significantly enhanced treatment options. Nevertheless, these innovations have also brought forth new obstacles, particularly in terms of stability (especially for proteins and peptides), the necessity for effective intracellular delivery (particularly for nucleic acids), and the maintenance and proliferation of live cells. As a result, drug delivery methods have had to evolve to address these issues. The subsequent sections will provide a detailed discussion on this subject

2.2.2.1 Matrix Systems

There are various types of controlled drug delivery systems designed to release medication continuously through mechanisms governed by both dissolution and diffusion. To regulate the release of drugs with varying solubility characteristics, the drug is incorporated into swellable hydrophilic substances, an insoluble matrix composed of rigid, non-swellable hydrophobic materials, or plastic materials[19][16].

Matrix systems are extensively utilized for sustained release applications. This release mechanism is designed to extend and regulate the liberation of a drug that is either dissolved or dispersed within it. Specifically, a matrix is characterized as a thoroughly blended composite of one or more active pharmaceutical ingredients combined with a gelling agent, i.e., hydrophilic polymers.[20] The sustained release method enables the attainment of therapeutically effective concentrations in the systemic circulation for an extended duration, thereby enhancing patient compliance. A variety of sustained release oral dosage forms have been developed, including membrane-controlled systems, matrices composed of water-soluble or insoluble polymers or waxes, and osmotic systems. Recent research efforts have concentrated on the design of sustained release systems specifically for poorly water-soluble drugs.[21]

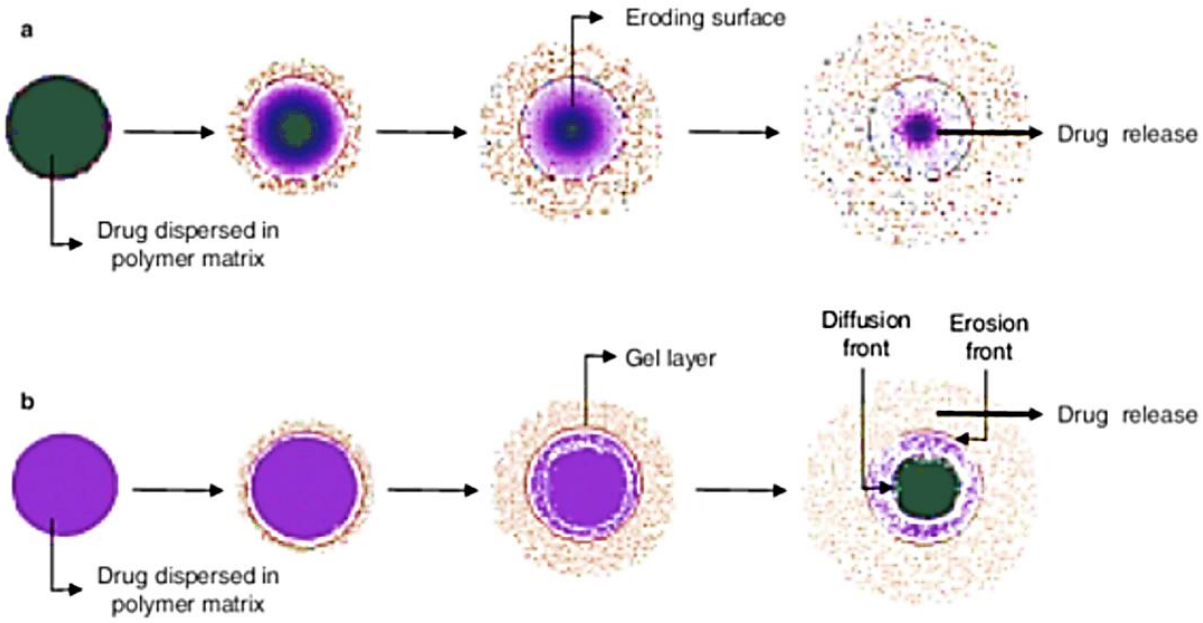

Figure 1.2:A diagram illustrating the release of a drug from matrix diffusion-controlled release drug delivery systems, in which the drug is uniformly distributed throughout the matrix: (a) A polymer matrix that is subject to erosion.; and (b) a hydrophilic, swell able polymer matrix

- Easy to manufacture
- Versatile, effective, and low-cost
- Can be made to release high-molecular-weight compounds
- The sustained-release formulations may maintain therapeutic concentrations over prolonged periods.
- The use of sustained-release formulations avoids the high blood concentration.
- Sustain-release formulations have the potential to improve patient compliance.
- Disadvantages of matrix tablets
- The remaining matrix must be removed after the drug has been released.

- High cost of preparation.
- The release rates are affected by various factors, such as food and the rate of transit through the gut. The drug release rates vary with the square root of time.[22][23]

2.2.2.2 Reservoir Systems

The reservoir-based system represents one of the most prevalent controlled drug delivery mechanisms currently in use. In this configuration, a core containing the drug is encased in a polymeric film, with the rate of drug release being regulated by various factors, including the characteristics of the polymer (such as its composition and molecular weight), the thickness of the coating, and the physicochemical attributes of the drug itself, including its solubility, particle size, and molecular weight [20][24] Reservoir-based systems are most beneficial for one of the following two applications:

1- The administration of a medication over a mid- to long-term period, specifically targeted to a particular region such as an organ or body cavity, is often employed when the targeted area is challenging to access through systemic administration, as seen with the eye or ear. Additionally, this approach may be necessary when the medications involved are toxic and necessitate prolonged dosing regimens, such as those used in cancer therapies.

2- A pharmaceutical depot designed for prolonged systemic delivery. This is typically administered via intramuscular or subcutaneous injection, or through implantation.

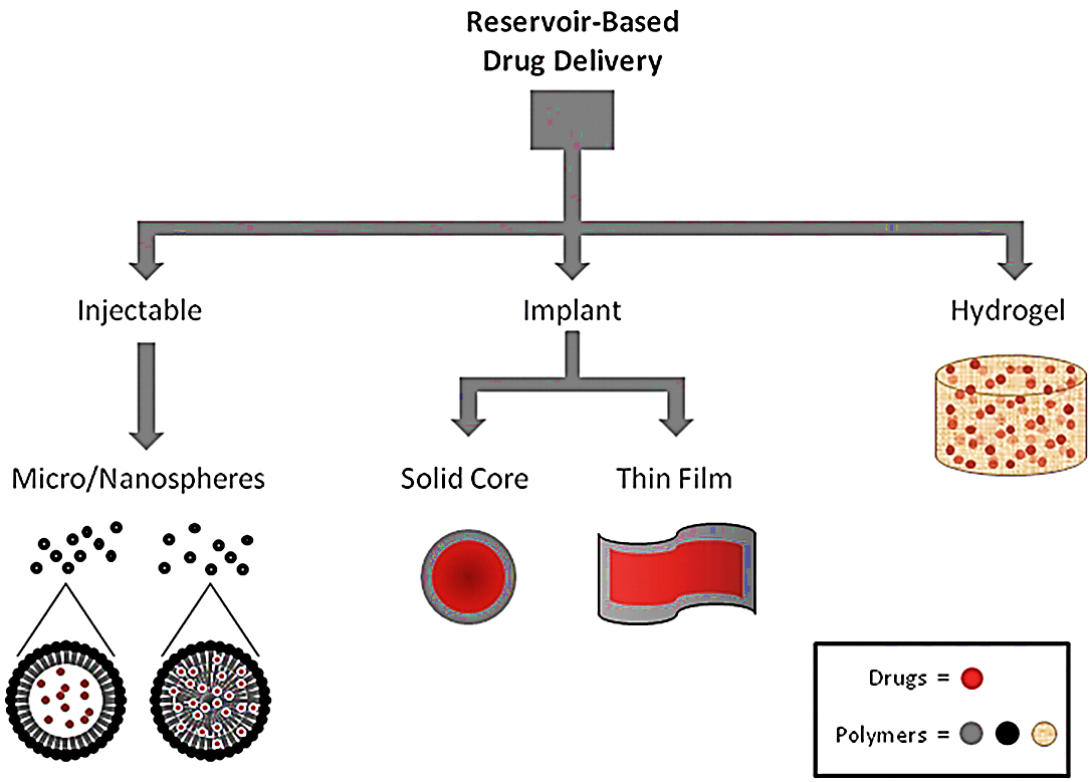

Figure 2.3: Resveratrol-Based Drug Delivery Systems

2.3 Review of Smart Drug Delivery Systems

A smart drug delivery system (SDDS) represents a sophisticated approach to targeted drug delivery (DT). To improve therapeutic outcomes and minimize associated side effects, it is essential for active drug molecules to selectively concentrate in the affected area for an extended duration while maintaining a high level of control. Drug delivery encompasses the various methods, formulations, technologies, and systems designed to transport therapeutics into the body as required, ensuring their safe and effective achievement of intended therapeutic effects [25]. The smart drug delivered by this system fulfills the criteria:

1- Increase the doses of the delivered drug to the targeted body part of interest (tissue/cells/organs).
2- Not be degraded by any of the body fluids.
3- Diminish side effects by improving the efficacy of drug treatment.
4- Absorption of the delivered drug must cross a biological membrane.,
5- and the drug is released in appropriate dosages to the body part of interest [26].Drug delivery systems (DDS), ranging from implantable electronic devices to single polymer chains, are required to be compatible with processes in the body (biocompatibility) as well as with the drug to be delivered [26]. DDS modifies the biodistribution and pharmacokinetics of the corresponding drug, which refers to the time-dependent proportion of the administered dose present in various organs throughout the body. Additionally, challenges emerge from factors such as poor drug solubility, degradation due to environmental or enzymatic influences, rapid clearance rates, non-specific toxicity, and the difficulty in traversing biological

barriers. [27] . It is designed for improving the communication of cellular compounds and the biodistribution of drugs in specific body parts without affecting the normal tissue [28].

2.3.1 Emergence of Smart Technologies in Drug Delivery

A drug delivery system designed to enhance pharmacokinetic and pharmacodynamic characteristics ,while also improving specificity for cells and tissues, as well as biocompatibility[29].The advancement of new drug delivery systems and the establishment of mechanisms for their regulation are essential, resulting in significant progress in the next generation of drug delivery technologies[30].

A targeted drug delivery system is preferred over conventional drug delivery systems for three main reasons.

- The first is a pharmaceutical reason. Conventional drugs have low solubility and more drug instability in comparison to targeted drug delivery systems.
- Second, conventional drugs also have poor absorption, a shorter half-life, and require a large volume of distribution. These constitute its pharmacokinetic properties.

• The third reason is the pharmacodynamic properties of drugs. The conventional drugs have low specificity and a low therapeutic effect as compared to SDDS.[31].

Mostly, SDDS possess advantages including site-specific drug targeting for various diseases, being highly exploited for controlled drug release, prolonged circulation in the blood, facilitating extravasation, avoiding opsonization owing to a particle size less than

100nm and high concentration with prolonged action, as well as enhancing the targeting of the drug to specific sites. [30]. Therefore, the therapeutic value of drugs presently being used could be improved efficiently by delivering them to biological targets, and drugs that failed clinical trials might be reconsidered using SDDS.[28].The contents of this section extend to encompass the following sections.

2.3.1.1 Microfabricated Systems

The application of microfabrication in drug delivery systems has yielded numerous benefits across various dimensions, attributed to characteristics such as electrical sensitivity, precise sizing, and the capability for high reproducibility within the delivery mechanism.[32][33].Microfabrication offers distinct advantages over other methodologies, including chemistry, biology, electronics, and mechanics, enabling it to effectively tackle challenges associated with drug delivery. This technique facilitates precise control over the dimensions of devices, which is crucial in the context of drug delivery. Furthermore, the invasiveness of drug delivery systems can be significantly minimized through the use of alternative administration methods. [34].

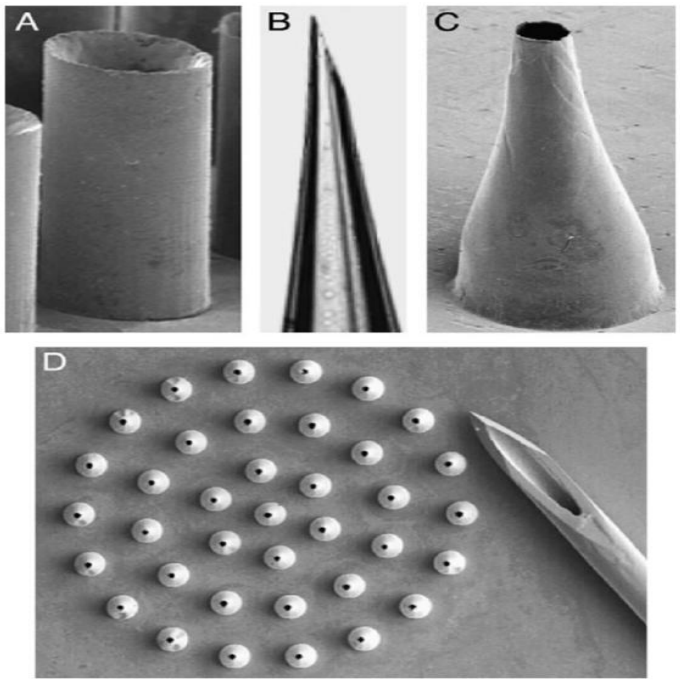

Figure 2.4: Optical and SEM images of silicon, metal, and glass hollow microneedles. (A) Straight-walled metal microneedle from a 100-needle array fabricated by electrode position onto a polymer mould (200 m tall), (B) tip of a tapered, bevelled, glass microneedle made by conventional micropipette puller (900 m length shown), (C) tapered metal microneedle (500 m tall) from a 37-needle array, and (D) array of tapered metal microneedles (500 m tall) shown next to the tip of a 26- gauge hypodermic needle.

Biosensor-integrated drug delivery systems have been the subject of significant research, particularly in the context of managing chronic conditions such as cardiovascular diseases (CVD), diabetes mellitus, and cancer, where the need for consistent drug administration and ongoing monitoring is critical.[35][36] . Traditional treatment methods have been linked to significant adverse effects; consequently, in recent years,

controlled drug delivery systems have been investigated as a viable alternative to enhance both efficacy and safety by fine-tuning the duration and kinetics of drug release. Furthermore, the implementation of systems capable of initially detecting markers related to regenerative medicine and various diseases, followed by the targeted release of therapeutic agents, has demonstrated a substantial influence on the management of chronic illnesses[37]. Biosensors are analytical devices composed of two main components: a bio-recognition element and a transducer [38]. The bio-recognition component of the sensor detects the specific analyte, whereas a transducer transforms the outcome of the molecular recognition into an electrical signal.

2.3.2 Successes and Challenges in Smart Drug Delivery

Innovations in drug delivery systems and technologies seek to address the shortcomings of traditional drug delivery methods by enhancing bioavailability and therapeutic index, minimizing side effects, and fostering better patient acceptance and compliance[39]. The objective of contemporary drug delivery systems is to enhance pharmacokinetics and pharmacodynamics, which are crucial for therapeutic effectiveness and the overall operation of bodily systems. Certain delivery systems utilize large particles as carriers; however, this approach is not ideal for treatment due to potential issues such as inadequate absorption and solubility, instability in vivo, low bioavailability, complications in target-specific delivery, and various adverse side effects following administration.[40]The application of significantly smaller particles for the purpose of delivery to the human biological system presents a viable solution to the challenges associated with the utilization of larger particles. Additionally, the toxicity of the particles employed in delivery poses a considerable obstacle for drug delivery systems

as a whole. Certain nanomaterials utilized in this context may pose risks to both human health and the environment.[41].

2.3.2.1 Achievements in Targeted Drug Delivery

Achievements in targeted drug delivery have significantly advanced the field of medicine and pharmacology.

Enhanced Therapeutic Efficacy: Targeted drug delivery systems have allowed for more precise administration of medication directly to the site of action, resulting in improved therapeutic efficacy while minimizing off-target effects.

1. Personalized Medicine: Advancements in targeted drug delivery have paved the way for personalized treatment strategies tailored to individual patient needs, leading to more effective and efficient therapies[42].
2. Prolonged Drug Release: The development of controlled and sustained release systems has enabled prolonged drug release at the target site, reducing the frequency of dosing and improving patient compliance.
3. Advancements in Nanotechnology: The application of nanotechnology in targeted drug delivery has led to the development of nanocarriers capable of transporting drugs to specific tissues or crossing biological barriers, opening up new possibilities for drug delivery. [43][44]

2.3.2.2 Challenges in Long-Term Stability and Reliability

Challenges arise in maintaining adhesive strength over time, especially in scenarios involving repeated application and removal, perspiration, or exposure to oils and lotions. Variations in drug content, patch design, or manufacturing processes can impact dose uniformity and compromise the system's reliability. Addressing these challenges requires a multifaceted approach, encompassing advanced formulation development, rigorous stability testing, robust material selection, and patient-centric design considerations[20]. Furthermore, ongoing post-market surveillance and feedback mechanisms are vital for continuously improving the long-term stability and reliability of transdermal drug delivery systems, ultimately ensuring their effectiveness in chronic disease management and drug therapy.

2.3.2.3 Addressing Biocompatibility Concerns

Biocompatibility captured the interest of researchers from 1940 to 1980, particularly concerning medical implants and their interactions with the human body, which could be either detrimental or advantageous. It is only in the last twenty years that this term has been formally defined in terms of its conceptual meaning rather than through practical descriptions. “The ability of a material to perform with an appropriate host response in a specific situation” [45] . The three fundamental principles that are crucial to this definition include the requirement that a material must fulfill its designated functions rather than simply existing within the tissue, the necessity for the induced reaction to be appropriate for the intended use, and the understanding that the response to a specific material and its appropriateness may vary depending on the context. [46]. In 2010, Kohane and Langer explained biocompatibility in the context of drug delivery

and defined biocompatibility as “an expression of the benignity of the relationship between a material and its biological environment” [47]. Some researchers have broadened that definition by emphasizing the significance of a biomaterial's acceptable functionality within a specific biological context. [47]. Williams has conducted a thorough examination of the biocompatibility concept pertaining to long-term implantable medical devices and tissue engineering products. [45].

A high level of biocompatibility is typically attained when a material engages with the body without provoking any adverse toxic, immunogenic, thrombogenic, or carcinogenic reactions. (Fig. 2-5).[48]

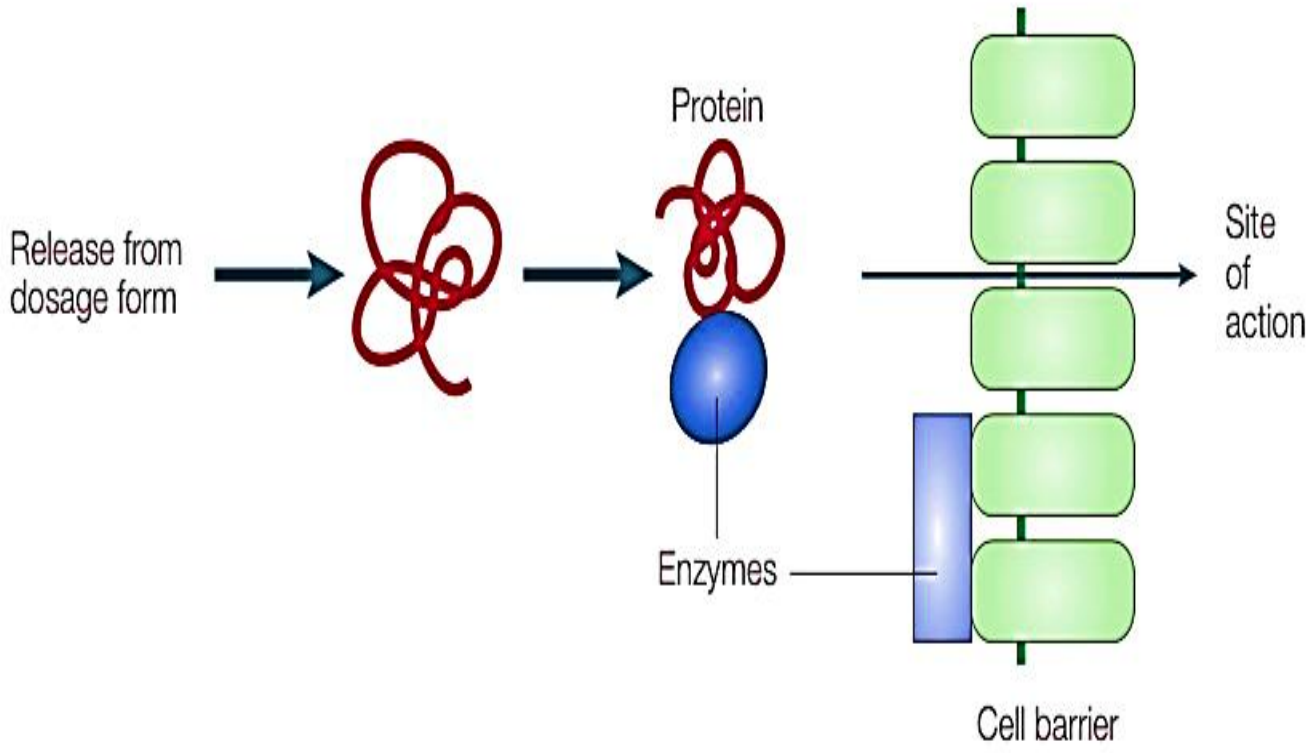

Figure 2.3: Barriers to bio macromolecular drug transport.

The primary challenges to effective transportation to the site of action include enzymatic degradation and the presence of biological membranes. It is also important to recognize that a biomaterial that may elicit an adverse reaction in one specific tissue type does not necessarily produce the same effect when applied in a different context or tissue type. Furthermore, from an interconnected viewpoint, the inherent properties of biomaterials alone do not dictate their biocompatibility. For example, PLGA nanoparticles, which are rapidly cleared from the body, typically do not lead to peritoneal adhesion, while PLGA microparticles, which remain in the peritoneal cavity for an extended period, are associated with the development of peritoneal adhesions. [47][49].

2.3.3 Applications in Chronic Disease Management

Smart transdermal drug delivery systems have emerged as a promising approach in chronic disease management, offering precise and controlled administration of medications through the skin. The integration of advanced technologies has expanded the applications of smart transdermal drug delivery systems in various chronic conditions, including[50].

1. Enhanced Therapeutic Efficacy
2. Reduced Side Effects
3. Personalized Medicine
4. Prolonged Drug Release
5. Improved Cancer Treatment
6. Advancements in Nanotechnology

7. Localized Drug Delivery

[51] The incorporation of smart features, such as real-time monitoring, feedback control, and connectivity to mobile health platforms, empowers these transdermal drug delivery systems to offer personalized, responsive, and efficient treatment options for individuals coping with chronic diseases. Furthermore, the potential for improved compliance, reduced systemic side effects, and optimized therapeutic outcomes underscores the value of smart transdermal drug delivery systems in chronic disease management [52].

2.3.3.1 Diabetes and Insulin Delivery Systems

Diabetes impacts a significant portion of the global population and has reached epidemic proportions[53]. The estimated global population of individuals with diabetes was 171.2 million, representing 2.8% of the total population, in the year 2000. This figure is projected to rise to 366.2 million, or 4.4%, by the year 2030[5] .The conventional and most reliable approach for insulin administration is through subcutaneous injections. However, this method can be painful, which may discourage patient adherence, particularly for individuals who need to administer multiple doses four times daily.

Current insulin delivery systems encompass insulin syringes, infusion pumps, jet injectors, and pens. Insulin pen devices are innovative as they integrate the insulin reservoir and syringe into a single, modular unit. This design alleviates the burden of transporting both insulin and syringes. The inaugural insulin pen, known as NovoPen®, was launched by Novo Nordisk in 1987. Since that time, a diverse array of pens has emerged, featuring various designs and functionalities. There are primarily two

categories of pens: reusable and prefilled. In the case of reusable pens, patients are required to insert an insulin cartridge before use. Regardless of the type, both pen variants accommodate cartridges containing between 1.5 ml and 3 ml of U100/ml insulin. The procedure for replacing an insulin cartridge in reusable pens differs among manufacturers. Prefilled devices are particularly favored for use in bedtime insulin regimens among type 2 diabetes patients. [59].

2.3.3.2 Controlled Release in Neurological Disorders

Neurological disorders encompass a range of conditions, including dementia types such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease, along with other related ailments. Cerebrovascular diseases, which include stroke, migraine, and various headache disorders, also fall under this category. Additionally, degenerative conditions like multiple sclerosis (MS), neuroinfections (whether viral, bacterial, or fungal), brain tumors (both malignant and benign), brain injuries, and other traumatic disorders of the nervous system are significant concerns. Mental disorders, often classified as psychiatric diseases, primarily manifest as disturbances in thought, emotion, or behavior, leading to distress or impairment.

These disorders are prevalent, particularly among the elderly population, and can have profound consequences. Genetic mutations inherited from parents can lead to abnormal development of the nervous system, neurodegenerative diseases, or neuronal dysfunction, resulting in a gradual decline in neuronal structure and/or function.

Furthermore, environmental factors may trigger genetic and epigenetic mutations, as well as inflammatory processes associated with diseases like Alzheimer's disease (AD).

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The clinical research comparing conventional and controlled-release (CR) dosage forms of medications utilized in neurology demonstrates the benefits of opting for CR formulations over traditional forms. Over the past twenty years, there has been a

significant increase in the availability of controlled-release formulations for various medications. These advanced delivery systems present several advantages over conventional dosage forms, such as a decrease in the frequency of doses required daily or weekly, minimized side effects, enhanced patient adherence, and greater convenience.[56]. CR products are designed to maintain constant therapeutic plasma concentration of the drug within the therapeutic range of the drug over prolonged periods[57]. Typically, all traditional dosage forms, with the exception of continuous intravenous infusion, release medications primarily through first-order kinetics. This mechanism leads to fluctuating high and low drug concentrations, with the ideal therapeutic level being maintained only for a short duration. Conversely, controlled release systems deliver the drug at a steady rate (zero order) or at a consistently decreasing rate (first order) over a specified time frame. This approach ensures a stable concentration of the drug in both plasma and tissue.[57]

2.3.3.3 Advancements in Cancer Therapeutics

Cancer, recognized as one of the most lethal diseases globally, represents a critical health challenge of the 21st century. It can initiate and disseminate throughout the body due to unchecked cell growth, which is often a consequence of a marked reduction in cellular apoptosis. Various treatment modalities are available, including surgical excision, chemotherapy, radiotherapy, and hormone therapy. Surgical intervention can yield favorable outcomes when addressing tumor tissue localized to a specific area. However, this approach is not appropriate for certain cancer types, such as leukemia or those that have metastasized across multiple regions.. [58]

Recent progress in our comprehension of the intricate mechanisms underlying tumorigenesis has revealed numerous obstacles encountered by existing systemic therapeutic approaches in cancer treatment. Drug delivery systems (DDS), particularly within the realm of nanomedicine, have shown exceptional potential in addressing many physiological hurdles related to the transport of hydrophobic chemotherapeutic agents to tumor locations, while simultaneously minimizing toxicity and preserving healthy tissues. The adaptable physicochemical properties of nanoparticles, including their shape, size, and functionalization, have facilitated the creation of "smart" nanoparticles that employ passive, active, and stimuli-responsive targeting methods to enhance the effectiveness of drug delivery.[59].

2.3.3.4 Opportunities for Intriguing Pharmaceuticals

The amendments made in 1962 to the Federal Food, Drug, and Cosmetic Act of 1938 initiated a transformative period in drug development within the United States. This legislation altered the competitive landscape for pharmaceutical companies, imposing heightened premarket regulatory obligations. Firms were now mandated to provide evidence of the efficacy of their new products, alongside obtaining a favorable review from the FDA for their marketing applications.

Between 1963 and 1999, pharmaceutical companies secured marketing approval for 691 New Chemical Entities (NCEs) in the United States. Following the implementation of the 1962 amendments, the approval rate for NCEs—defined as new molecular compounds that had not been previously authorized in the United States—experienced

a significant decline compared to the levels observed prior to the amendments. It is important to note that this definition excludes new salts and esters of existing compounds, surgical and diagnostic materials, vaccines, other biologics, and certain externally applied substances such as disinfectants, antiperspirants, and sunscreens.[60][61].Top 9 Innovations and Trends Coming in the Pharmaceutical Industry.

1- Precision Medicine and Personalized Therapies

2- Sustainability and Green Initiatives

3- Immunotherapy Advancements

4- Digital Therapeutics

5- Continuous Manufacturing

6- Nanotechnology in Drug Delivery

7- 3D Printing of pharmaceutical industry

8- Collaborations and Open Innovation

9- Regulatory Evolution

2.4 Technological Advancements in Transdermal Drug Delivery

Oral delivery systems present certain challenges, including inadequate drug stability within the gastrointestinal tract and vulnerability to first-pass metabolism. For example,

drugs may undergo degradation due to enzymatic reactions or the acidic conditions present in the stomach [62]. Additionally, the challenges related to the solubility of pharmaceuticals in intestinal fluid and their ability to permeate the intestinal membrane can serve as critical barriers to drug absorption, resulting in diminished bioavailability. Transdermal drug delivery systems utilize the skin as the site for drug administration. The drug introduced is absorbed into the systemic circulation through the blood vessels present in the skin, subsequently distributing throughout the body[63]. Transdermal drug delivery systems present several benefits for patients, including reduced invasiveness (with certain methods being completely noninvasive), avoidance of first-pass metabolism, simplicity in application and administration, elimination of the necessity for specialized personnel, and the possibility of decreasing the frequency of drug administration. Furthermore, this technology has been employed for the delivery of a wide range of pharmaceuticals, encompassing both hydrophilic and hydrophobic compounds. In this regard, the subsequent sections will be examined.

2.4.1 Microneedle Technology

Microneedles, which are a system of needles measuring in microns, are designed to penetrate the epidermal layer, thereby forming micro-channels in the skin while avoiding pain, bleeding, or the risk of infection. [64]. These channels facilitate the diffusion of therapeutic agents into the dermal layer, which is richly supplied with blood vessels. Microneedles (MNS) have been developed using a range of microfabrication techniques, resulting in diverse materials, shapes, and sizes (ranging from 50 to 900 μm in height and covering a surface area of 2000 mm^2). The microneedle drug delivery system addresses the limitations associated with conventional dosage forms. This

technology has been assessed for the delivery of not only small molecules but also a variety of macromolecules, cosmeceuticals, and micro/nano-particles. Recently, the use of both coated and dissolving microneedles has been investigated for noninvasive transdermal vaccination.[65].The research and development of microneedles have advanced to a point where large-scale manufacturing and commercialization are now feasible. These microneedles have been explored not only for transdermal drug delivery but also for applications in ocular treatments, diagnostic testing, and oral delivery. The technology surrounding microneedles is regarded as crucial for improving drug permeation.

2.4.1.1 Enhancement of Drug Permeation

The enhancement of drug delivery through solid removable microneedles operates by creating pores or openings in the stratum corneum (SC) either prior to or concurrently with the application of a drug on the skin's surface. These openings facilitate increased permeability of the SC, thereby enhancing the drug's flux. Numerous studies have been conducted to optimize transdermal skin permeation through various methods, including chemical, thermal, and physical enhancers. The ideal characteristics of penetration enhancers include being pharmacologically inert, non-allergenic, non-irritating, and non-toxic. Furthermore, they should ensure a rapid onset of action, as is required for the drug proposed in our project. It is essential that this process is compatible both chemically and physically with the delivery system, ensuring that viable cells remain unharmed. Finally, the utilization of cost-effective penetration enhancers is strongly advocated..[66]

2.4.1.2 Implementation in Smart Systems

This technology is utilized across a range of devices, including wearable and implantable options like infusion pumps, smart pens, inhalers, and auto-injectors. Nevertheless, the advancement and deployment of IoT-based drug delivery systems encounter numerous challenges, including the need to guarantee data security and privacy, adhere to regulatory standards, ensure compatibility, and maintain reliability. [67].

2.4.2 Nanotechnology in Transdermal Delivery

The term "nanoscale" denotes particle dimensions that span approximately 1 to 100 nanometers; however, in the context of drug delivery, nanoparticles measuring between 50 and 500 nanometers are deemed suitable, contingent upon the chosen route of administration. The delivery method of a drug can profoundly influence its effectiveness. Certain medications possess an ideal concentration range that maximizes their therapeutic benefits, while levels that exceed or fall short of this range may result in toxicity or lack of therapeutic effect. Nanotechnology is currently in vogue, as it appears to offer solutions for attaining objectives that were previously considered unattainable[68]. This encompasses the enhancement of human diagnostics and therapeutics. The primary challenge in creating such products, regardless of whether they

involve nanotechnology, lies in ensuring that any treatment administered to the human body is both effective and safe. Achieving these dual objectives necessitates a combination of exceptional engineering and formulation expertise alongside a comprehensive understanding of biological principles. Furthermore, it is essential to employ only bio-tolerable, if not biogenic, materials. An additional requirement for the development of small functional entities from biocompatible substances is the integration of (bio)chemical and (bio)physical principles. This section will delve into the exploration of the following subdivisions

2.4.2.1 Nanoparticle-Based Formulations

Nanoparticle technologies appear to offer promising prospects for the growth of the transdermal market. It is thought that the transdermal delivery of nanoparticles through the stratum corneum (SC) may take place through two potential pathways: one involving the skin appendages, such as hair follicles, pilosebaceous pores, and sweat gland openings, and the other through the intercellular spaces that exist between corneocytes (the bricks) and along the lipid matrix (the mortar)(Figure 2-6).

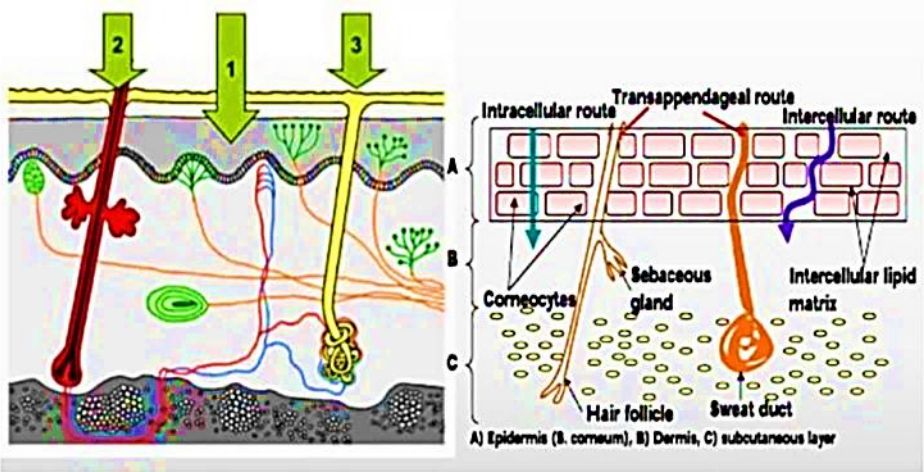


Figure 2. 4: Structure of skin showing routes of nanoparticle penetration: (1) across the intact horny layer, (2) through hair follicles with the associated sebaceous glands, or (3) via the sweat gland [69]

Nanoparticles (NPs) are internalized by cells through various mechanisms of endocytosis or pinocytosis, influenced by their surface properties, size, shape, and charge. This uptake can occur via non-specific interactions, such as membrane wrapping, or through specific interactions with cell surface receptors. After entering the cell, NPs are confined within vesicular structures known as endosomes, which possess distinct features, including both internal and external receptors. For effective functional delivery, it is crucial for most NPs to escape these compartments prior to their acidification. Responsive NPs, such as ionizable types that acquire a charge in acidic conditions, facilitate endosomal escape and enable intracellular delivery. In contrast, unresponsive NPs tend to remain sequestered and are often degraded by the acidic environment of lysosomes and the action of proteolytic enzymes.[70][71]

2.4.2.2 Integration with Controlled Release Mechanisms

Integration with controlled release mechanisms is a key consideration in the development of transdermal drug delivery systems, particularly for achieving sustained and predictable drug release profiles. Here are some important aspects to consider in this integration:

1. Matrix Systems
2. Rate-Limiting Membranes
3. Microneedle Arrays
4. Osmotic Systems
5. Feedback-Controlled Systems
6. Combination Systems[35]

By integrating these controlled release mechanisms into transdermal drug delivery systems, pharmaceutical developers can optimize therapeutic outcomes, minimize side effects, and enhance patient compliance through the consistent and predictable delivery of medications. It's important to consider the specific characteristics of the drug, the desired pharmacokinetic profile, and patient-specific needs when designing and implementing these integrated controlled release mechanisms.[43]

2.4.3 Wireless Connectivity and Monitoring

Wireless drug delivery, often referred to as wireless drug administration, is a technologically advanced approach for administering medications to patients without

the necessity of physical connections or wiring. This method can be achieved through the utilization of implantable devices, including pumps or ports, which are capable of receiving instructions from a remote control or other devices to release the correct dosage of medication. [72]. These devices present a viable approach to improving the operations of healthcare facilities by facilitating precise and prompt medication delivery, enabling ongoing patient monitoring, and enhancing overall patient outcomes.[73]. Healthcare technologies allow physicians to concentrate on essential responsibilities, offer crucial information for well-informed decision-making, and improve the overall quality of care.Within the confines of this section, we will navigate through the subsequent sections, such as.

2.4.3.1 Real-time Data Collection and Analysis

Wireless Sensor Network (WSN): Wireless sensor networks (WSNs) utilize compact, energy-efficient sensors equipped with wireless communication capabilities to gather environmental data. This system incorporates wearable or implanted sensors to monitor and collect real-time information regarding a patient's physiological parameters and clinical metrics. [74]. The information is transmitted wirelessly to a central monitoring unit, which processes the data and manages the drug delivery system from a distance, guaranteeing that patients obtain the necessary medication in the appropriate dosage and at the correct time. Wireless Body Area Networks (WBANs) offer several advantages in drug delivery, such as enhanced patient adherence, lower healthcare expenses, and greater access to medical services. Nevertheless, the deployment of these systems faces obstacles, including concerns related to security, privacy, and interoperability.

2.4.3.2 Patient Engagement and Adherence

Improved patient involvement facilitated by mobile applications, wearable technology, and interactive platforms enables individuals to take an active role in their healthcare, resulting in better self-management and enhanced treatment results.[75].The scalability and interoperability of IoT infrastructure facilitate the smooth integration with current healthcare systems, permitting smart drug delivery systems to adjust to changing requirements. Predictive maintenance and data-driven insights enhance system reliability, optimize resource allocation, and improve workflow efficiency.

2.5 Challenges and innovations in Transdermal Delivery

Transdermal drug delivery offers several benefits. This method allows for the avoidance of pain and pre-systemic metabolism. Furthermore, it provides a more consistent pharmacokinetic profile for the drug, resulting in reduced peaks and troughs. Nonetheless, the stratum corneum, which is the outermost layer of the skin, presents a significant barrier that hinders the permeation of substances at clinically effective rates. To date, approximately 35 transdermal products have received approval from regulatory bodies, with around 19 drugs successfully formulated into transdermal patches and authorized by the Food and Drug Administration[76] The primary difficulty resides in the incorporation of macromolecules—such as proteins, small interfering RNA, and various biotechnological products—into transdermal delivery systems. This issue is being addressed through methods including microneedles, iontophoresis, sonophoresis, and electroporation.

2.6 Amphetamines for ADHD and Dictation Treatment

Methamphetamines, or amphetamines, treat stimulant-related illnesses. Under medical supervision, amphetamines can help addicts recover. Amphetamines modify dopamine and norepinephrine to reduce withdrawal, cravings, and cognitive performance. Addiction therapy patients can get motivation, attention, and energy from amphetamines. Amphetamines can aid in holistic addiction rehabilitation methods that include behavioral therapy, psychotherapy, and support groups. Medical professionals should strictly manage amphetamine use in addiction rehabilitation to reduce overuse, dependence, and negative effects. Responsible amphetamine use in addiction therapy requires ethical considerations for patient safety and regulatory compliance. In addition, it is widely recognized for its effectiveness in treating attention deficit hyperactivity disorder (ADHD). By increasing the levels of neurotransmitters like dopamine and norepinephrine in the brain, amphetamines help regulate attention, focus, and impulse control—core symptoms of ADHD. This pharmacological action improves cognitive function and behavioral regulation in individuals with ADHD, enhancing their ability to concentrate, organize tasks, and manage impulses [77][78].

2.6.1 Available Formulations of Amphetamine:

Approximately 30 distinct formulations of amphetamine (AMPH) are available in the market, encompassing both immediate-release and extended-release compounds. These formulations feature a range of ratios between the immediate-release and extended-release components. affecting the pharmacokinetic profile. The choice of stimulant medication depends on factors such as symptom severity, timing of impairing symptoms, and individual preferences [79]. All available formulations are orally administrated. Due to amphetamines play a crucial role in ADHD and addiction treatment, smart transdermal device that have designed in this project offer a promising avenue for enhancing adherence and overall patient well-being.

Chapter Three

Design and components of the smart transdermal drug delivery system for the suggested drug

3.1 Materials and Methodology

3.1.1. The Amphetamines as a Suggested Pharmaceutical Formula

Amphetamines, including dextroamphetamine and methamphetamine, exert their effects by enhancing the release of neurotransmitters such as dopamine and norepinephrine. Traditionally, oral formulations have been preferred due to ease of administration and established pharmacokinetics. However, recent interest in transdermal drug delivery has prompted investigations into the feasibility of administering amphetamines through the skin.

In terms of lipophilicity, Amphetamines are lipophilic (soluble in fat), which enhance their ability to penetrate the skin barrier. Accordingly, developing an effective transdermal formulation is possible due to this property [80].

Innovatively, we can suggest the pharmaceutical substance amphetamines, as its working principle applies to our designed circuit. Amphetamines are a type of central nervous system stimulant that can increase alertness, attention, and energy. They are often used to treat conditions like attention deficit hyperactivity disorder (ADHD) and narcolepsy. However, they are also commonly misused as recreational drugs due to their potential for abuse and addiction. It's important to note that amphetamines should only be used as prescribed by a healthcare professional and under their supervision to avoid potential health risks.[81]

3.1.2 Transdermal drug delivery system fundamentals

Transdermal drug delivery systems are designed to deliver medication through the skin and into the bloodstream. Smart transdermal systems incorporate advanced technology to enhance drug delivery, improve efficacy, and provide real-time monitoring of drug release and patient response. These systems typically use innovative materials, microelectronics, and sensors to optimize drug delivery and ensure safety.

The fundamentals of a smart transdermal system include the following:

1- Feedback Mechanisms
2- Controlled drug release

3- Microelectronics and sensor technology
4- Advanced Materials [82]

We've selected Transdermal Drug Delivery (TDD) due to its nearly painless systemic drug delivery through intact skin, providing non-invasiveness and placement flexibility. The drug initially penetrates through the SC and then passes through the deeper epidermis and dermis without drug accumulation in the dermal layer. When a drug reaches the dermal layer, it becomes available for systemic absorption via the dermal microcirculation [83]. TDD has many advantages over other conventional routes of drug delivery. It can provide a non-invasive alternative to parenteral routes, thus circumventing issues such as needle phobia. A large surface area of skin and ease of access allow many placement options on the skin for transdermal absorption [84].

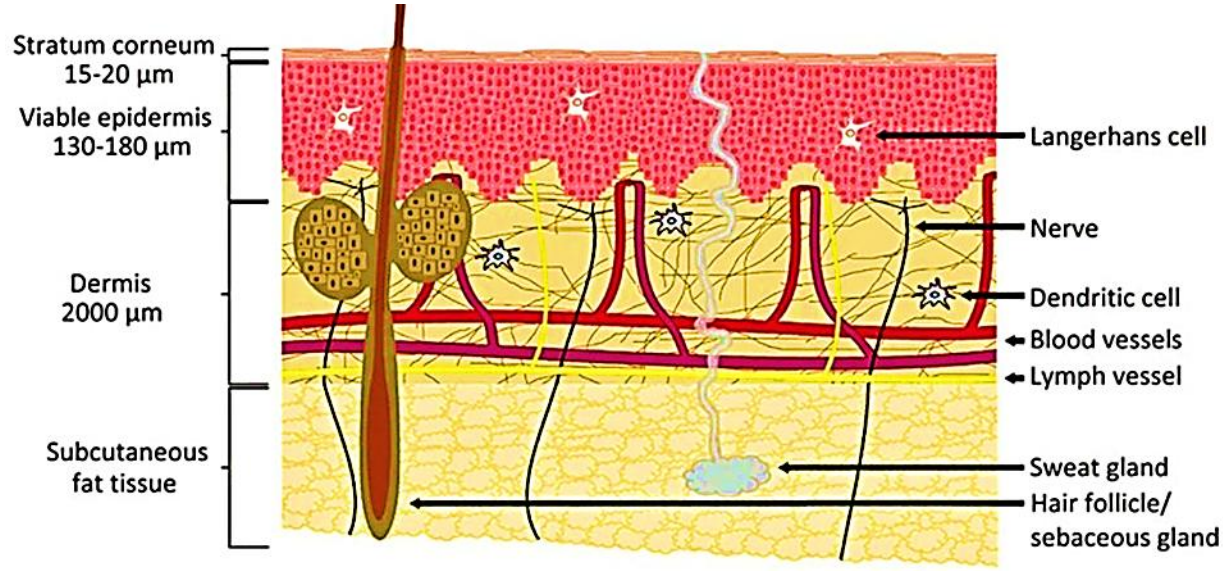


Figure 3.1 Anatomy of the skin [85]

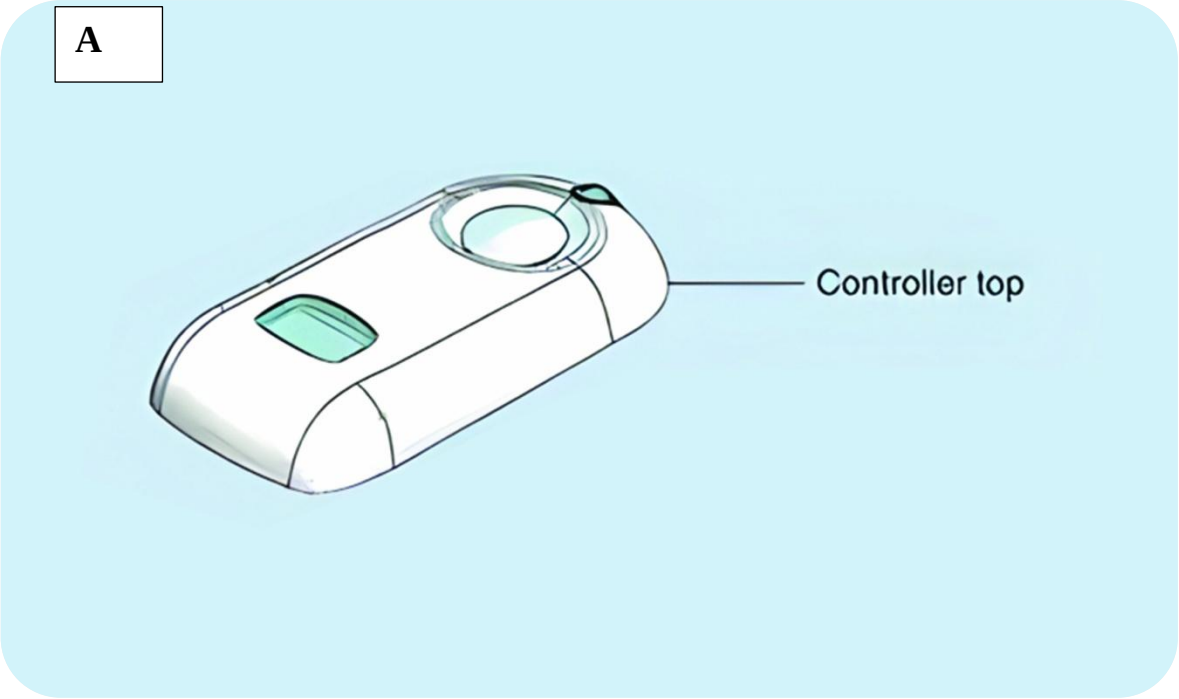
3.2 Smart System Components

Smart wearable patch systems typically consist of supporting substrates, adhesive layers, flexible circuitry, thin-film sensor technologies, actuator elements, therapeutic mechanisms, data communication systems, power sources, and/or energy-harvesting technologies[86]. When these systems are utilized on the skin, the sensor elements are capable of detecting and monitoring a range of physical and biochemical parameters, including blood pressure and glucose levels derived from sweat. The data generated by the sensors can be transmitted wirelessly, allowing for real-time viewing on a mobile

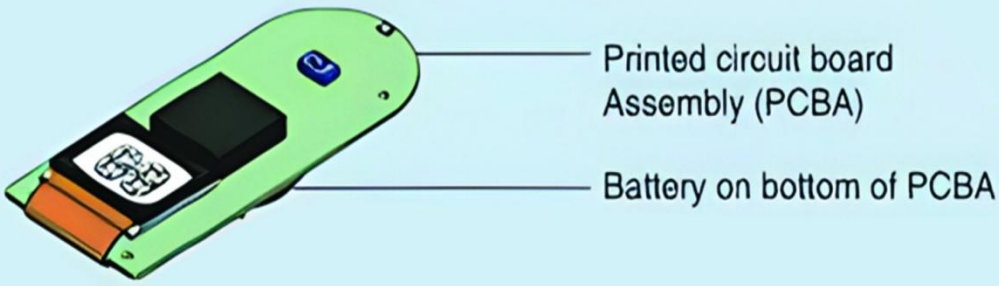
device or computer. Furthermore, actuator components can produce electric, thermal, or vibrational energy in response to signals that fall outside of normal ranges. This energy transfer serves as a stimulus for therapeutic systems, potentially triggering or enhancing drug delivery mechanisms[87]

Therapeutic agents may be integrated directly into the substrates, or alternatively, micro- or nanoparticles can be embedded within various delivery systems, including hydrogels or microneedles.

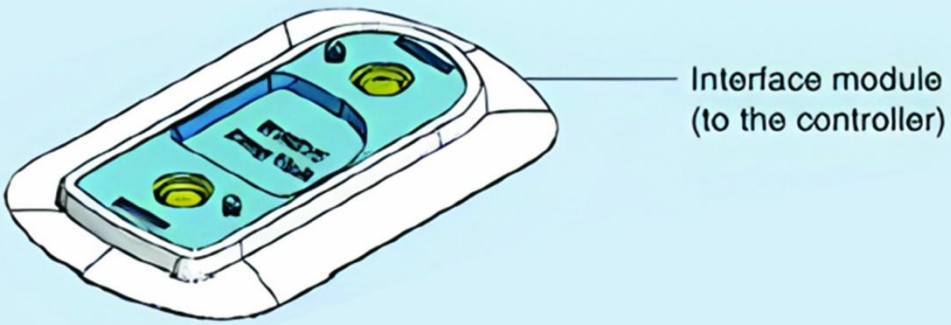
This theme will be explored further in the figure 3.3 a,b,c,d,e,f and in the following sections.



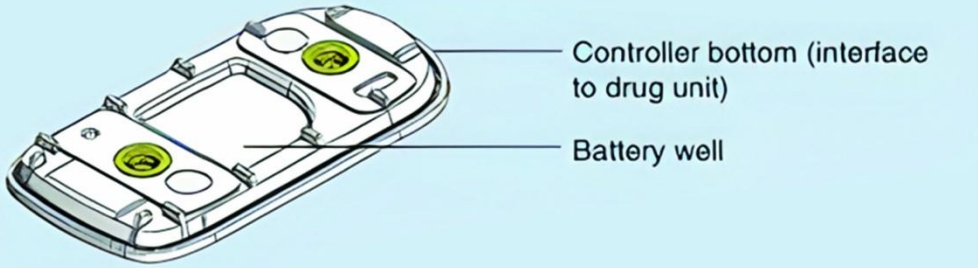
B


Printed circuit board
Assembly (PCBA)
Battery on bottom of PCBA

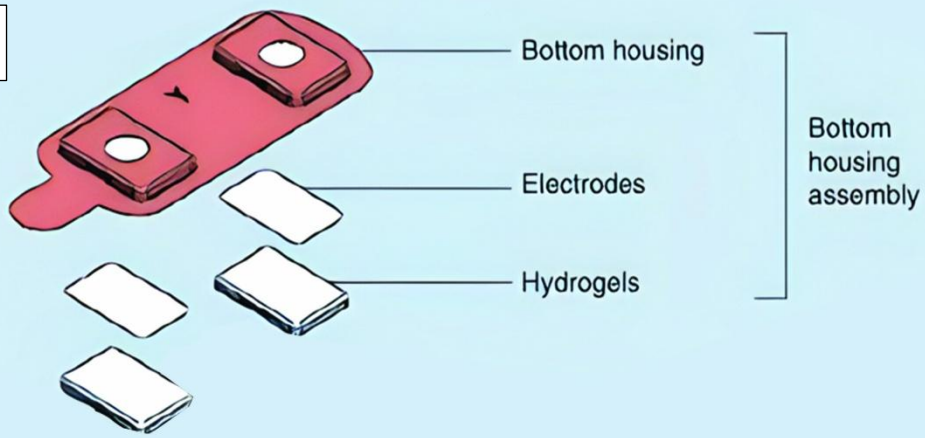
C


Interface module
(to the controller)

D


Controller bottom (interface to drug unit)
Battery well

E


Bottom housing
Electrodes
Hydrogels
Bottom housing assembly

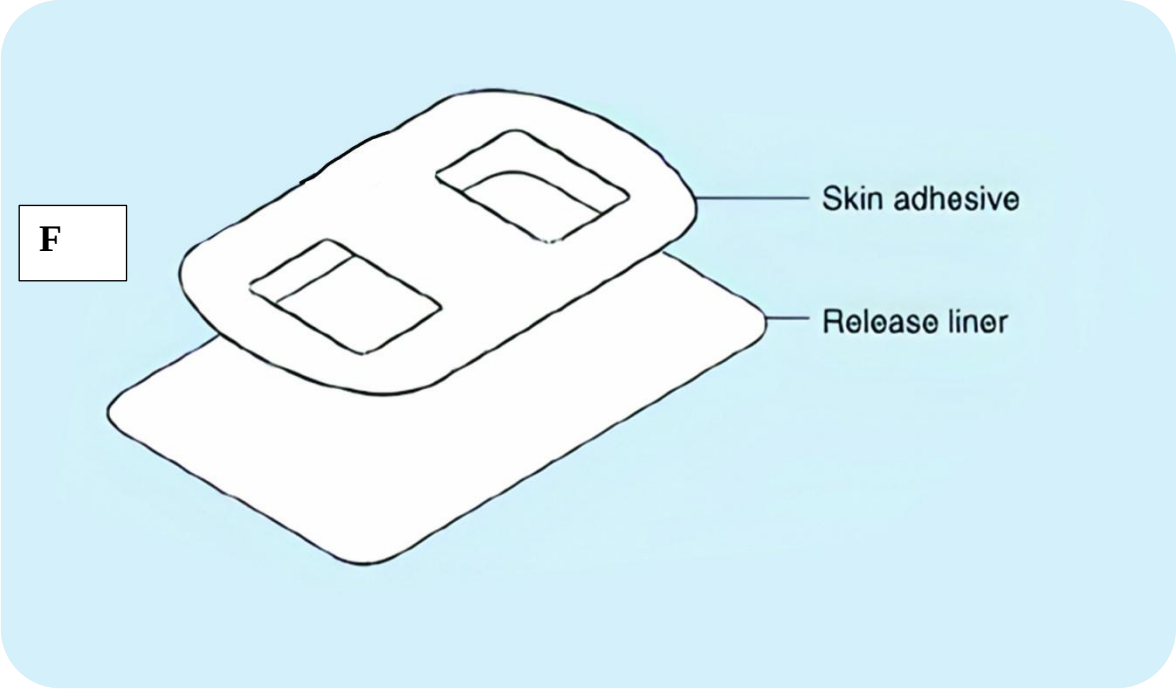


Figure 3.3: Layered Components of the Smart Transdermal Patch

3.2.1 Sensors for Real-Time Monitoring

A sensor for real-time monitoring in a drug delivery system would need to be able to track various parameters related to the delivery of the drug. Some potential parameters to monitor could include:

1. Flow rate or pressure of the drug being delivered

2. Temperature to ensure the drug is not exposed to extreme conditions

3. pH level to monitor the stability of the drug

4. Presence of the drug in the delivery system

5. Battery level or power source status for the delivery system [88]

The specific type of sensor needed would depend on the requirements of the drug delivery system and the properties of the drug being administered. For example, if the drug is sensitive to temperature, a temperature sensor would be essential. If precise measurement of drug volume is critical, a flow sensor might be required.

It's important to consider factors such as accuracy, reliability, and compatibility with the drug and the delivery system when selecting a sensor for real-time monitoring in a drug delivery system.

3.2.2 Microprocessors for Intelligent Control

In a SDDS, microprocessors play a crucial role in enabling intelligent control and automation. Here are some key considerations when selecting microprocessors for this purpose:

1. Processing Power: Choose a microprocessor with sufficient processing power to handle the complex algorithms for precise drug delivery control.

2. Connectivity: Consider microprocessors that support various communication interfaces such as USB, Wi-Fi, Bluetooth, or other wireless protocols.

3- Low Power Consumption: In portable or battery-powered drug delivery systems, choose microprocessors with low power consumption to maximize battery life and minimize heat generation.

4-Security: to protect sensitive patient data and ensure the integrity of the drug delivery system.

5- Development Tools and Support: Ensure that the chosen microprocessor platform provides comprehensive development tools, software libraries, and technical support to facilitate the implementation of intelligent control algorithms and interfaces.[89]

3.2.3 Drug carriers and Release Mechanisms

Targeted delivery necessitates the use of specialized carrier systems. A TDD carrier refers to a unique molecule, particle, composite, or system capable of retaining the drug either within or on its surface, achieved through encapsulation and/or the use of a separator.

Drug delivery vehicles are required to fulfill a number of essential criteria:

1- They must be able to pass through hard-to-reach places, such as the blood-brain barrier.

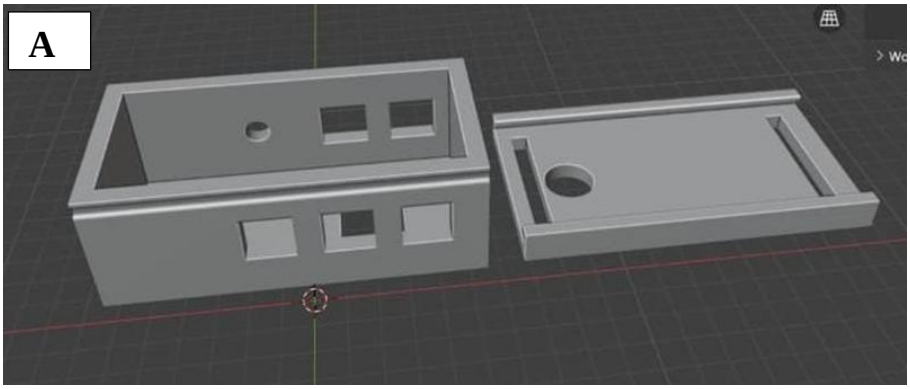
2- The drug vehicle used must be non-toxic and non-immunogenic.
3- Proper, controlled release rate of drug molecules to achieve an effective local concentration.

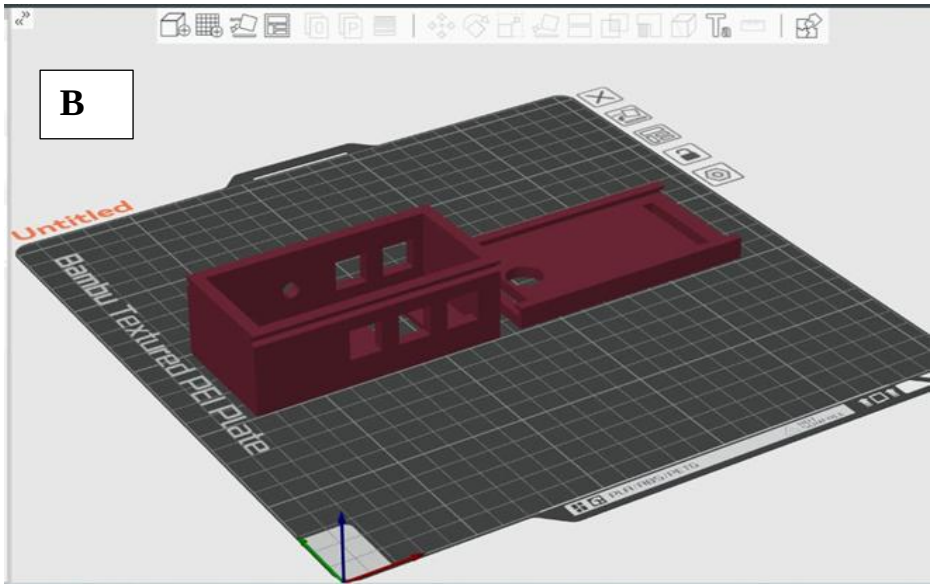
Currently, research into nanotechnology-based drug delivery systems has gained momentum owing to advancements in the development and fabrication of diverse nanostructures. These nanoparticles or structures possess the ability to penetrate tissues more effectively, with their absorption rates being approximately 15 to 250 times greater than those of microparticles. Furthermore, they provide a protective barrier for drugs against degradation by various gastrointestinal enzymes, thereby facilitating the safe transport of the drug to its intended target. [90]

3.2.4 Device electronic circuit designing

In the previous context, an electronic circuit to inject the medicinal substance into the body was designed. The circuit contains an Arduino Nano, a variable resistance that controls the degree of drug, a tank to store the medicinal substance, a screen display type 128x64 put on, connecting wires, a micro needle, and a tourniquet.

A 3D cover was designed to contain the electrical circuit using blender program.


A


B
Untitled
Bambu Textured PEI Plate

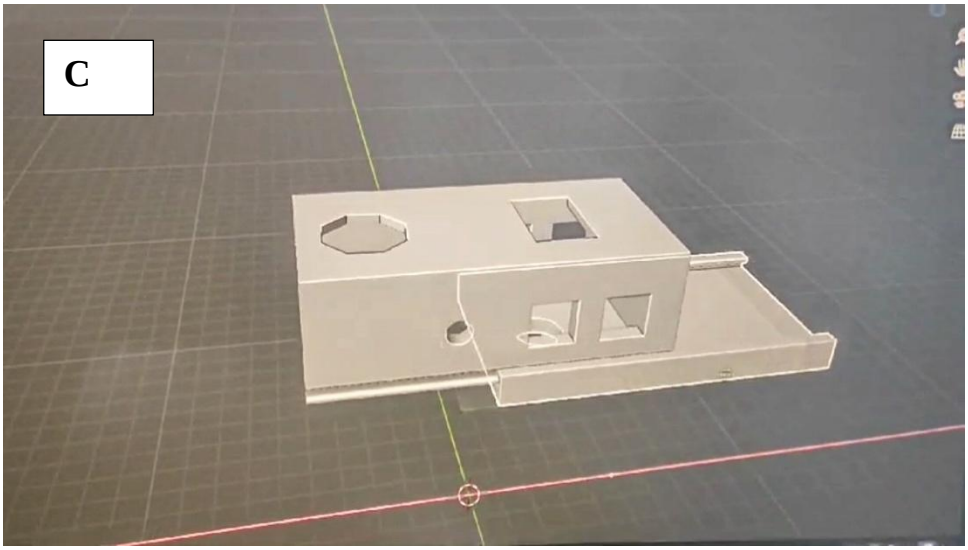


Figure 3.4 a, b, c: Design 3d cover of transdermal device by using a program blender

3.2.5 The working principle of the Electrical Circuit

We used Arduino programming to write a code. The purpose of the code is to program the electrical circuit through which we release the drug into the body. The code contains four times to organize giving drug

Positively charged drug is placed under the anode. Positively charged drug is placed under the cathode. To release the drug from the opposite direction. The circuit contains a salt solution to close the electrical circuit. The cathode contains a negative charge because it contains a salt such as cl^-.The anode usually contains a silver ion Ag+.

Underneath there is a tank with drug solution gel with the medicinal substance.

The drug substance is charged with a positive charge, and the anode is charged with a positive charge. When the electrical circuit is closed and the electric current flows, the anode charge moves, and repulsion occurs between the existing electrode, which expels the drug substance (cation).

The anode expels the substance with the same charge carried on the shoulders of the negative ions. The medicinal substance goes into the bloodstream and the negative ions return to restart the work again.

Chapter Four: Results and Discussion

4.1 Results and Discussion

4.1.1. The Suggested Drug Formula Utilizing Adherence-Enhancing Agents

4.1.1.1. Addiction Treatment

Research suggests that individuals struggling with addiction may face barriers to seeking traditional treatment. Medication nonadherence, Stigma, financial constraints, and geographical limitations often deter them from accessing help [80]. In such cases, the designed smart transdermal drug administration could offer a promising alternative. By delivering medications through patches applied directly to the skin, we can bypass the need for frequent oral dosing. This approach may reduce the risk of misuse and enhance treatment adherence. For those battling addiction, transdermal formulations could address both physical and psychological aspects, promoting a holistic recovery journey.

Amphetamines are central nervous system stimulants that boost specific brain functions, resulting in feelings of energy, attention, and confidence. They can also induce euphoria.

Accordingly, they serve an important role in addiction treatment, especially when dealing with stimulant-related substance use disorders.

Amphetamines are abused by swallowing pills, crushing them for snorting, or dissolving them in water for injection. Injecting amphetamines provide due to rapid brain delivery

[91]. That's why; the suggested formula and designed device can be suggested utilized for addiction therapy, as transdermal amphetamine formulations may give benefits such as:

1- Improving Adherence: Patches provide continuous release, minimizing the need for frequent doses.

2- Reducing stigma and misuse. Transdermal delivery prevents oral stigma and possible misuse.

4.1.1.2 The Suggested Drug Formula (Amphetamines) ***for ADHD Treatment or Controlling Adherence***

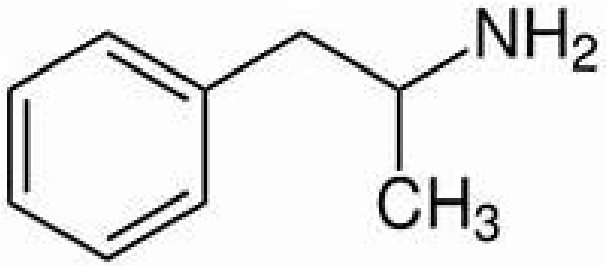


Figure 4.1: Molecular Structure of Amphetamines

ADHD is the most common youth psychiatric disorder in the US. Approximately 3.8 million U.S. children aged 2-17 with ADHD were medicated in 2016. Drugs like amphetamines are significant. are stimulants. Novel ADHD treatments include immediate-release and extended-release drugs with varying component ratios. Patient

preferences and symptom severity at specific times of day affect stimulant medication selection[77].

4.1.1. Design and Fabrication of Smart Transdermal System:

The design and fabrication of a smart transdermal drug delivery system using advanced technologies such as microelectronics, sensors, and responsive materials. The integration of these components enables real-time monitoring and triggered drug release based on physiological signals or external stimuli have been conducted in this project as in the Figure 4.1,2,3,4 that show the device from deferent sides.

Figure 4.3: Control Panel with On/Off Buttons (Side view)

Figure 4.5: Micro Needles for Drug Delivery (Pottom view)

4.1.2 Characterization of the designed unit:

The properties of the smart transdermal system, including size, shape, surface morphology, drug loading capacity, and response kinetics. Analysis of sensor sensitivity, drug release profiles, and system compatibility with skin tissues provides critical insights into its performance.

Challenges related to patient compliance and treatment adherence by offering convenient, non-invasive drug delivery, automated dosing schedules, and reminder functionalities. By integrating smart features, the system promotes patient engagement and therapy monitoring.

At the beginning of the code, define the offices on the screen to display the names, commands to display the name of the university, the name of the college, the name of the department, the name of the supervising and the name of the students, between each name and the name dely, with a duration of either two seconds or one second.In void loop l, there is a loop that repeats itself, displaying the value of the variable resistance, meaning the drug value and the dose concentration.

Special commands witch

(switch1) applies the time for duration

(switch 2) time for 6 hours

(switch 3) Duration: 12 hours

(Switch 4) is direct. Simply clicking on it will download the drug directly without a timer. The code contains a manual control and a timer becauseif the drug is pain reliever.The patient can take it as needed It may be a timer according to the doctor's prescription.

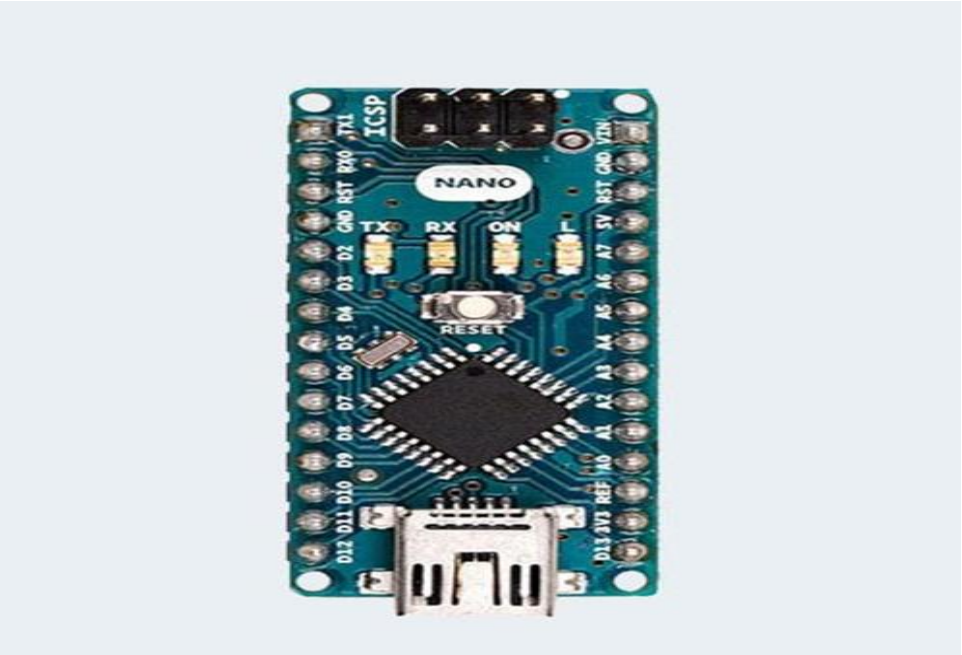


Figure 4.6 Arduino type Nano

Figure 4.7: Variable resistance that controls the degree of drug

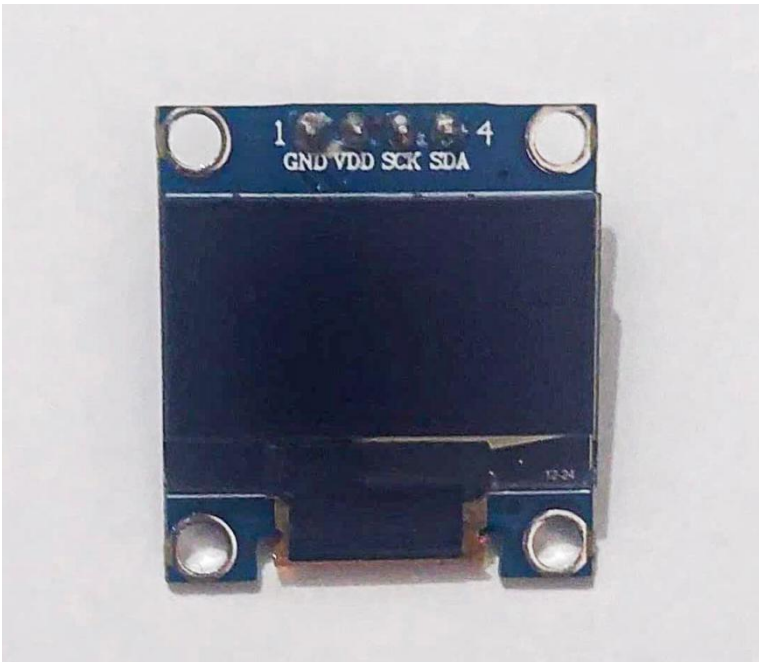


Figure 12 Screen display type 128x64

Figure 5 **Put-on**

Figure 4.9: Microneedle

Figure 4.10 Connecting Wires

```
#include <Wire.h>
#include <Adafruit_GFX.h>
#include <Adafruit_SSD1306.h>
Adafruit_SSD1306 display(128,64,&Wire,-1);
int ControlOUT = 7;
int ControlIN = A2;
int readControlIN;
int newRead;
int b1;
int b2;
int b3,b4;
void setup() {
pinMode(ControlOUT,OUTPUT);
pinMode(ControlIN,INPUT);
pinMode(2,INPUT_PULLUP);
pinMode(3,INPUT_PULLUP);
pinMode(4,INPUT_PULLUP);
pinMode(5,INPUT_PULLUP);
display.begin(SSD1306_SWITCHCAPVCC,0x3C);
display.clearDisplay();
display.setTextSize(1);
display.setTextColor(WHITE);
display.setCursor(10,30);
display.println("Dhi Qar University");
display.display();
delay(1000);
display.clearDisplay();
display.setTextSize(1);
display.setTextColor(WHITE);
display.setCursor(10,30);
display.println("College of Engineering");
display.display();
delay(1000);
display.clearDisplay();
display.setTextSize(1);
display.setTextColor(WHITE);
display.setCursor(20,30);
display.println("  Department of");
display.display();
display.clearDisplay();
display.setTextSize(1);
display.setTextColor(WHITE);
display.setCursor(30,20);
display.println(" .Biomedical Engineering" );
display.display();
delay(1000);
display.clearDisplay();
display.setTextSize(1);
display.setTextColor(WHITE);
display.setCursor(20,30);
display.println("Made by");
display.display();
delay(1500);
display.clearDisplay();
display.setTextSize(1);
display.setTextColor(WHITE);
display.setCursor(30,20);
display.println("Rosil gabbar");
display.display();
display.setTextSize(1);
display.setTextColor(WHITE);
display.setCursor(20,30);
display.println("  Maktoof" );
display.display();
delay(2000);
display.clearDisplay();
display.setTextSize(1);
display.setTextColor(WHITE);
```

```
  display.setCursor(30,20);
 display.println("Alaq Talal ");
      display.display();
  display.setTextSize(1);
 display.setTextColor(WHITE);
  display.setCursor(20,30);
  display.println(" Sameer" );
      display.display();
         delay(2000);
    display.clearDisplay();
    display.setTextSize(1);
  display.setTextColor(WHITE);
   display.setCursor(20,30);
 display.println("Supervisor");
      display.display();
         delay(1000);
    display.clearDisplay();
    display.setTextSize(1);
 display.setTextColor(WHITE);
   display.setCursor(30,20);
display.println("Lecturer. Zahraa ");
      display.display();

    display.setTextSize(1);
 display.setTextColor(WHITE);
  display.setCursor(20,30);
.splay.println("   Abdulhussein Mousa" ),
      display.display();
         delay(2000);
               }
          void loop() {
   display.clearDisplay();
   display.setTextSize(1);
 display.setTextColor(WHITE);
```

```
 display.setTextColor(WHITE);
  display.setCursor(30,30);
  display.println(newRead);
    display.display();
  display.setTextSize(1);
display.setTextColor(WHITE);
  display.setCursor(8,30);
  display.println("drg=");
    display.display();
 display.setTextSize(1);
display.setTextColor(WHITE);
 display.setCursor(48,30);
  display.println("%");
   display.display();

readControlIN = analogRead(ControlIN);
newRead=map(readControlIN,0,650,0,100);
      b1=digitalRead(2);
      b2=digitalRead(3);
      b3=digitalRead(4);
      b4=digitalRead(5);

         if(b1==0){

  display.setTextSize(1);
display.setTextColor(WHITE);
  display.setCursor(68,20);
display.println("Mode one");
     display.display();
  display.setTextSize(1);
display.setTextColor(WHITE);
  display.setCursor(68,35);
display.println("Time=3h");
     display.display();
```

```
analogWrite(ControlOUT,newRead);
          delay(10000);
               }
        else if(b2==0)
               {
      display.setTextSize(1);
    display.setTextColor(WHITE);
     display.setCursor(68,20);
   display.println("Mode two");
        display.display();
     display.setTextSize(1);
   display.setTextColor(WHITE);
     display.setCursor(68,35);
    display.println("Time=6h");
        display.display();
analogWrite(ControlOUT,newRead);
          delay(10000);
               }
        else if (b3==0){
     display.setTextSize(1);
   display.setTextColor(WHITE);
    display.setCursor(68,20);
  display.println("Mode three");
        display.display();
    display.setTextSize(1);
  display.setTextColor(WHITE);
   display.setCursor(68,35);
  display.println("Time=12h");
        display.display();
analogWrite(ControlOUT,newRead);
          delay(10000);}
        else if (b4==0){
     display.setTextSize(1);
  display.setTextColor(WHITE);
    display.setCursor(20,50);
display.println("OUTPUT LIVE");
       display.display();
analogWrite(ControlOUT,newRead);
          delay(1000);
               }
```

Figure 4.11: Arduino Code for Operating the Smart Transdermal Drug Delivery Device

Chapter Five: Conclusion

5.1 Conclusion:

While orally administered amphetamines remain an important part of ADHD and addiction treatment, smart transdermal device that have designed in this project shed light on a bright future. These formulations not only have the potential to increase adherence, but they also serve as beacons pointing us towards improved patient well-being.

The development of a smart transdermal drug delivery system for administering amphetamines represents a significant advancement in healthcare technology with potential implications for addiction treatment and ADHD management. Through the integration of advanced materials, microelectronics, and sensor technologies, the project has achieved its objectives in designing a versatile and effective drug delivery platform**.**

The feasibility assessment conducted in this project has demonstrated the potential of transdermal delivery for amphetamines, offering benefits such as continuous release, improved adherence, and reduced risk of misuse. By optimizing drug release mechanisms and incorporating real-time monitoring capabilities, the system holds promise in addressing the complex healthcare needs of individuals with addiction and ADHD**.**

Furthermore, the project has underscored the importance of patient-centric design, safety considerations, and regulatory compliance in the development of medical devices. Collaboration with healthcare professionals and regulatory authorities has facilitated the validation of clinical applications and paved the way for future implementation in medical practice.

In conclusion, the smart transdermal drug delivery system represents a transformative approach to drug administration, offering enhanced therapeutic outcomes, improved patient experiences, and opportunities for personalized medicine. By harnessing the power of technology, innovation, and interdisciplinary collaboration, this project lays the foundation for advancing drug delivery technologies and improving healthcare delivery for individuals with addiction and ADHD.

5.2 Potential Advantages of Transdermal Amphetamine Delivery:

1. **Steady Drug Release:** Transdermal systems allow for controlled and gradual drug release over an extended period. By maintaining consistent plasma concentrations, this sustained delivery may enhance patient compliance and improve therapeutic efficacy.
2. **Avoidance of First-Pass Metabolism:** Unlike oral administration, which subjects drugs to hepatic metabolism during their first pass through the liver, transdermal delivery bypasses this process. Consequently, amphetamines enter the systemic circulation directly, potentially reducing fluctuations in plasma levels.
3. **Minimized Gastrointestinal Side Effects:** Transdermal formulations can mitigate gastrointestinal disturbances associated with oral amphetamine use.

Patients may experience fewer adverse effects when receiving amphetamines through the skin.

5.3 Challenges in Developing Transdermal Amphetamine Systems:

1- **Stability**: Ensuring stability and consistent drug release from the patch is crucial.
2- **Skin Permeability:** The stratum corneum, the outermost layer of the skin, acts as a barrier. Ensuring adequate permeability of amphetamines through this layer is crucial for successful transdermal delivery.
3- **Ionization State:** Active amphetamines typically exist as positively charged ions (cations). Their interactions with skin transporters and receptors depend on this charge. Designing a transdermal system that allows skin penetration while retaining the positive charge remains challenging.
4- **Adhesive Matrix Design:** Creating an adhesive matrix that adheres comfortably to the skin and ensures consistent drug release is essential. Balancing adhesion, comfort, and drug diffusion poses difficulties.

5.4 Ethical and governmental issues in clinical trials:

The development of a smart transdermal drug delivery system for administering amphetamines holds immense promise for revolutionizing healthcare delivery in addiction treatment and ADHD management. However, despite the significant advancements made in designing and optimizing the drug delivery platform, ethical and governmental obstacles present formidable challenges to conducting clinical experimental work.

Ethical considerations surrounding the use of controlled substances, such as amphetamines, in clinical trials require meticulous adherence to regulatory guidelines and ethical principles. Concerns about patient safety, potential misuse, and regulatory compliance necessitate thorough scrutiny and approval processes, which can significantly delay or impede the progression of clinical trials.

Moreover, governmental regulations and policies governing the use of controlled substances further exacerbate the challenges faced in conducting clinical experimental work. Stringent regulatory frameworks, licensing requirements, and bureaucratic hurdles pose formidable barriers to obtaining the necessary approvals and permits for conducting clinical trials involving amphetamines.

Despite these obstacles, it is imperative to continue advocating for the advancement of research and innovation in drug delivery technologies. Collaborative efforts between researchers, healthcare professionals, regulatory authorities, and policymakers are essential for navigating the complex landscape of ethical and governmental considerations and facilitating the progression of clinical trials.

To sum up, while ethical and governmental obstacles present significant challenges to conducting clinical experimental work, perseverance, advocacy, and collaboration remain paramount in overcoming these barriers. By addressing these challenges and advancing research in smart transdermal drug delivery systems, we can unlock new opportunities for improving patient care and treatment outcomes in addiction treatment and ADHD management.

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