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Review

The Evolution of Transdermal Drug Delivery: from Patches to Smart Microneedle-Biosensor Systems

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Abstract

Transdermal drug delivery systems offer a novel approach to administering medications through the skin, ensuring controlled and sustainable drug release. This is an important tool because it allows the drugs to bypass the gastrointestinal tract, avoiding any reduced effectiveness due to digestive enzymes. Such systems are widely used to administer painkillers and hormone replacement therapy via patches. Cardiovascular diseases like angina and hypertension can also be treated. One of the most promising advancements in drug delivery systems has been that of microneedles which provides a pain-free method to administer drugs with the same efficacy of injections. This makes them a versatile tool in the medical field. The integration of biosensors adds on to their advantages. Biosensors can monitor various physiological factors and patient responses, allowing continuous observations. Consequently, a lot of valuable data will be collected. Biosensors can also improve safety by ensuring appropriate dosage and detecting any anomalous behaviors. This review looks into these factors and some others in detail.

Keywords

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1. Introduction

Drug delivery systems are devices that transport pharmaceutical compounds into the body to achieve their desired therapeutic effect. Over the years the drug delivery system has evolved, beginning with the development of oral and injectable methods. While it offers a lot, these traditional drug delivery systems often face challenges such as the degradation of drugs in the gastrointestinal tract, first-pass metabolism in the liver, and patient discomfort with injections and so with these limitations coming with the drug delivery system there is a search for an alternative method that can improve drug bioavailability, efficacy, and patient compliance. That was where transdermal drug delivery systems (TDDS) emerged. TDDS offers several advantages over the traditional drug delivery system, including improved bioavailability, reduced side effects, and the ability to maintain steady drug levels over extended periods of time [1].

The first generation of TDDS significantly transformed medical treatment, starting with the introduction of the nicotine patch for smoking cessation therapy. The second generation of TDDS emerged as researchers sought to overcome the limitations of passive diffusion. This generation employed active techniques such as iontophoresis, which utilizes electrical currents to enhance drug penetration through the skin [2]. Commercially available products like the LidoSite Topical System and SYNERA exemplified these innovative approaches. The third generation of TDDS aims to further redefine drug delivery methodologies by specifically targeting the stratum corneum, the outermost layer of the epidermis. This approach seeks to achieve more efficient and enhanced transdermal drug delivery by disrupting or bypassing the stratum corneum barrier. These advancements in TDDS technology have significantly expanded the range of drugs that can be delivered transdermally and improved the efficacy of existing transdermal formulations [3].

With recent developments microneedle Transdermal Drug Delivery Systems (MTDDS) represent a novel method for administering drugs through the skin, avoiding the gastrointestinal system and the liver's first-pass metabolism. The primary goal of MTDDS research is to enhance the effectiveness and uniformity of medication penetration through the stratum corneum—the outermost layer of skin that acts as a strong barrier to drug entry. MTDDS holds promise for the painless, beneficial, and patient-friendly administration of medications in the future [4]. Unlike conventional hypodermic needles, microneedles are designed to be minimally invasive, delivering medication directly into the dermal microcirculation by typically penetrating only the stratum corneum. This invention addresses several issues associated with conventional drug administration techniques, including injection-related discomfort and anxiety, oral medication annoyance, and irregular drug absorption due to gastrointestinal factors. MTDDS is composed of tiny needles made of metals, polymers, and ceramics designed to dissolve, break off, or remain in place inside the skin. These devices are capable of effectively delivering a variety of therapies, from small-molecule medications to large macromolecules such as peptides, hormones, and vaccines [5]. The ability of MTDDS to provide controlled and prolonged release profiles that enhance therapeutic efficacy and patient compliance makes them particularly useful for managing pain, diabetes, and vaccine administration. Highly integrated microfluidic systems could combine sample preparation, pathogen sensing, and drug delivery functions on a single chip that interfaces with the skin [6]. Looking ahead, continued research and development into enhancing production procedures, optimizing medication formulation compatibility, and optimizing needle design are bolstering the prospects of MTDDS. Innovations such as biodegradable microneedles, smart microneedles with sensors for real-time monitoring, and individually tailored microneedle patches could broaden therapeutic options and improve patient outcomes. Additionally, the convenience of self-administration offered by MTDDS provides a significant opportunity to enhance access to essential pharmaceuticals, particularly in remote and underserved regions. As technology advances, MTDDS has the potential to revolutionize the pharmaceutical sector by offering a groundbreaking method of drug administration aligned with the growing focus on patient-centered care and personalized medicine [7]. The paper discusses the historical development of drug delivery methods, from traditional oral and injectable approaches to the emergence of TDDS including the types of microneedles that are commonly used in TDDS. It will explore the limitations of conventional systems and how TDDS addresses these challenges.

2. Discussion

2.1. Principle of transdermal drug delivery system

The human skin acts as a complex barrier and interface between the body and the external environment. Its structure is designed to protect the body from external physical and chemical harm while also providing homeostasis for the body to regulate the body temperature, water loss, etc. So with many functions, the skin is divided into three main layers: (1) The Epidermis: It is the outermost layer of the skin, it contains the stratum corneum(SC) [2], the topmost layer of the epidermis. It gives the TDDS its significance due to the formidable barrier properties with the presence of dead keratinocytes (corneocytes) being planted in the lipid matrix, which blocks the process of drug permeation. (2) The Dermis: The dermis layer is below the epidermis and serves as a place where drug diffusion takes place into the body circulation, as it contains a high amount of vascular tissue which is critical for the absorption of the drug delivery system to deliver drugs into the bloodstream of the patient. (3) The Hypodermis: This is the layer of skin where there are connective fibers and tissue. This layer is not directly in contact with the TDDS, yet it has influences over TDDS in the overall pharmacokinetics functioning as a storage for the drug [8].

The gradients that convey the drug from the higher concentration in the TDDS to the lower concentration in the dermal layers constitute the primary cause of passive diffusion [9]. Drug permeation involves multiple transport mechanisms in addition to diffusion. Drugs that go through the transcellular pathway pass directly through the stratum corneum (SC), progressively making their way through lipid bilayers and watery environments within cells. The intercellular route, which lipophilic medicines frequently prefer, entails drug diffusion via the lipid matrix between SC cells [10]. The appendageal route makes utilization of anatomy characteristics including sweat ducts, sebaceous glands, and hair follicles. To prevent the SC, which can be vital in formulations administered to high follicular density areas. To minimize adverse effects, minimize overdosing or underdosing, and ensure stable drug release over extended periods, controlled release mechanisms in TDDS are essential. To achieve controlled release, methods like polymer matrices—where the drug is uniformly dispersed within a polymeric matrix—reservoir systems, that utilize a rate-controlling membrane to separate the drug from the skin, and colloidal systems, such as microemulsions and nanoemulsions, which enhance drug solubility and stability—are utilized. Of these, MTDDS have proven to possess the most effectiveness, outperforming other TDDS approaches in an array of sectors such as offering improved drug penetration along with precisely guided release.

2.2. Microneedle Transdermal Drug Delivery System

While Transdermal administration of drugs can be done through various methods such as hypodermic needles, topical creams, and transdermal patches, microneedles are the most effective method as it is capable of delivering the drug while overcoming problems posed by other methods of Transdermal drug delivery, such as slow administration, low permeability, and excessive pain. Microneedles merely penetrate the SC which results in the drug being administered without pain.

2.2.1. Types of Microneedles

Solid microneedles are mostly used to form pores in the skin to allow the penetration of drugs into the dermis. This works by allowing the pointed tips of the needles to penetrate into the skin, creating micron-sized channels, through which the drug enters directly into the skin's layers, improving permeability. Solid microneedles deliver the drug with passive diffusion to skin layers. This type of microneedle lasts longer and possesses a more robust antibody response, making it suitable for delivery of vaccines. They are also easy to manufacture, have superior mechanical properties, and sharper tips [11]. Solid microneedles are usually fabricated from silicon, metals, and polymers by molding, photolithography, dry-etching, and wet-etching.

The microneedles have hollow spaces inside, which are filled with the drug solution, and a hole on the tip. This microneedle allows for the delivery of a large amount of drug solution which ranges from a few microliters to hundreds of microliters and compounds of higher molecular weight such as proteins, vaccines, and oligonucleotides [11]. However, this microneedle is relatively weaker, the design is more complex and insertion requires much more care. This needle type may also suffer from leakage and clogging during administration. Hollow microneedles are usually made by photolithography, wet chemical etching, and micro-fabrication.

These microneedles are solid and surrounded by the drug solution. The drug is delivered very quickly in a minimally invasive manner and the amount of drug delivered depends

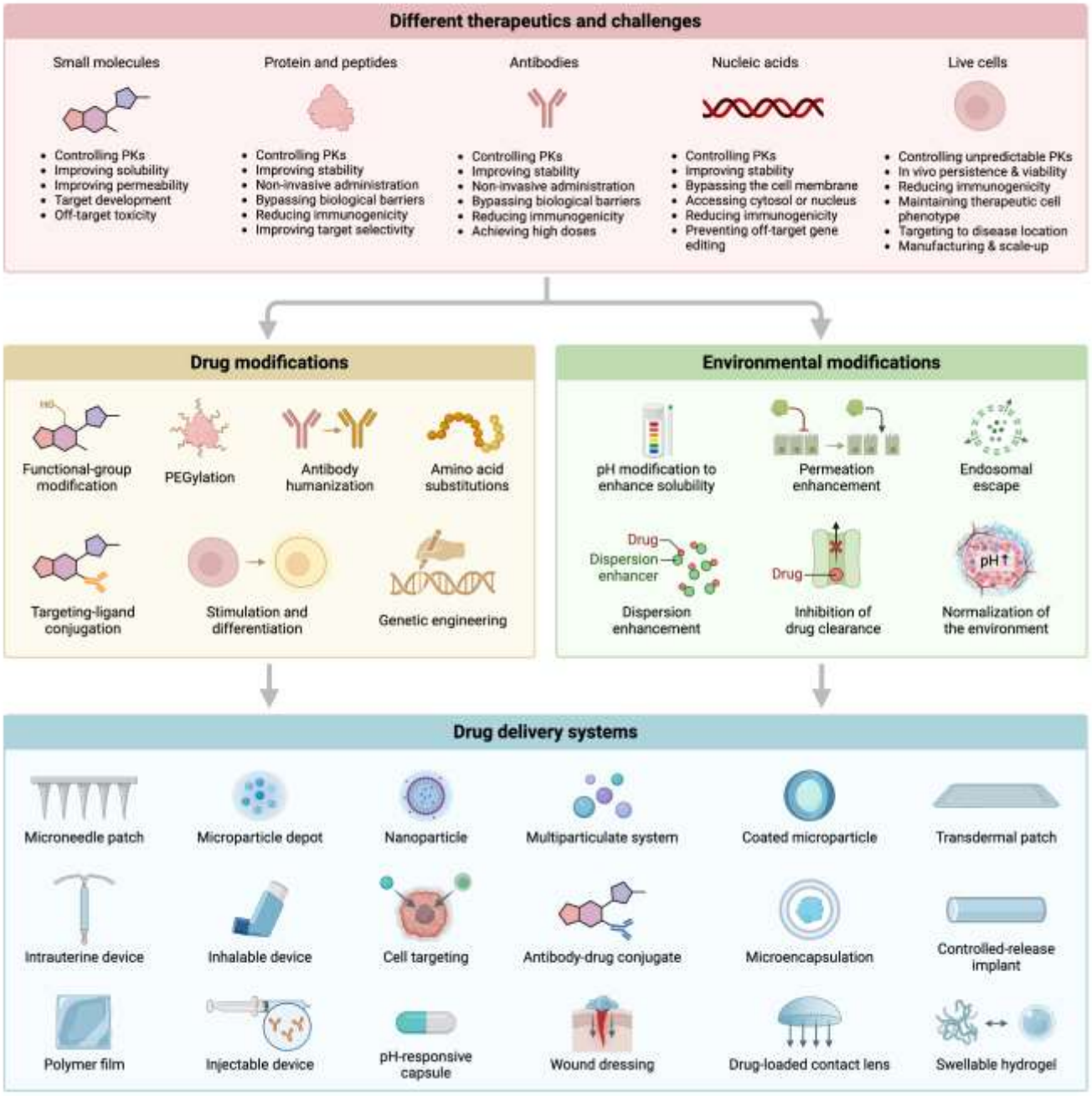

Figure 1. *Commercial Drug Delivery Technologies. Created with BioRender.com*

on the needle thickness and size. However, on average it can administer a smaller amount of drugs. However, the remnant drug at the tip of the needle may infect other patients if proper care is not taken. Materials used to fabricate this type of microneedle include silicon and polymer. Considered superior to others for long-term therapy. Upon insertion, the drug-load releases and diffuses easily followed by dissolution of the needle. Water-soluble drugs are easily delivered by this method. It is fabricated by the micro-mold method using silicon and other metals. However, designing these needles is a complex process and this type of MN requires complete insertion which is often difficult to accomplish [11].

This type of microneedle is a recent development. It is made using super-swelling polymers. These polymers are hydrophilic and swell when inserted into the skin due to the intestinal fluid present and form a 3D network. This helps create a channel for the delivery of drugs in a controlled manner. Upon removal of the needle, no residue is left. There is improved

permeation and bioavailability of the drug. These needles work by initially disrupting the skin barrier and later behaving as a rate-controlling membrane. The easy sterilization and intact removal are advantages of this microneedle type [12].

2.2.1. Delivery Mechanisms

There are various methods to deliver the drug using microneedles. One approach is to poke the skin and place a drug-containing patch or a coating of the drug over the area using solid microneedles. This method allows for direct release of the drug into the system. One may also dip the microneedles into the solution containing the drug and scrape the needles on the skin such that the drug remains in the abrasions. The microneedles mentioned above may also be used to deliver the drug [13]. The limited amount of drugs that can be transmitted transdermally is a major issue. Microneedles mainly increase skin permeability to small molecules, proteins, and nano-particles [14]. Only drugs with specific physicochemical properties, i.e. molecular weight < 500 Da, adequate lipophilicity, and low melting point can be administered transdermally. There is difficulty in Transdermally delivering hydrophilic drugs and large compounds, including peptides, DNA, and small interfering RNA. Drug transport also depends on the properties of the needle, such as height, density, aspect ratio, type of material, patch size, and duration of application. Research has been done on the effect of these variables on skin permeability. Skin thickness was also found to strongly affect the skin's permeability for different skin types (e.g. different race, sex, age, and anatomical regions) [15]. Recently, research has been done to examine the influence of different variables related to the microneedles affecting drug delivery. The microneedle's mask shape, the microneedle hole's location, the microneedle tip radius, etc. have all been looked into. Researchers have concluded that the square mask shape has the optimum shape, optimum locations and the microneedle tip radius has been looked into by Qallaf B. et. al., 2008 [16].

2.3. Biosensors for TDDS

Electrochemical biosensors, detect the analytes and translate biological events into electrical signals. Quantitative analysis is made possible when biological receptors attach to targets and cause detectable changes in conductivity, voltage, or current. Electrochemical biosensors are further classified based on detection methods: (a) Conductometric sensors measure changes in the conductivity of a medium as a result of an enzyme reaction that changes its ionic composition. (b) Amperometric sensors: these measure the electric current associated with electron flow resulting from the redox reaction. (c) Potentiometric sensors: these are ion-selective electrodes to determine changes in the concentration of the chosen ions. Electrochemical biosensors are used to monitor the activities of living cells or enzymes. Water Quality Testing: Detects contaminants like heavy metals, pesticides, and pathogens. Air Quality Monitoring: Measure pollutants such as carbon monoxide, sulfur, and nitrogen oxides. Pathogen Detection: Identify bacterial contamination in food products [17].

Optical biosensors employ microfluidics in conjunction with immobilized protein bio-receptors on transducers to introduce analytes and segregate molecules that are not bound. Optical biosensors are classified based on their working principle: (a) Surface Plasmon Resonance (SPR) uses polarized light on a metal film to excite surface plasmons via the Kretschmann configuration. By monitoring resonance angle shifts, researchers can study molecular binding events and kinetics label-free [18]. (b) Fiber optical biosensor: Fiber optic biosensors use a fiber optic transducer to generate signals proportional to chemical concentrations, based on Total Internal Reflection. (c) Absorbance-based: consists of Colorimetric test strips, these are Cellulose pads embedded with enzymes and reagents. (d) Luminescence-based: Luminescence-light that is not primarily generated from heat. But from a biochemical reaction. It can be used in the detection of bacteria. Optical biosensors are mainly used in medical telesensors, used to measure oxygen levels in the blood, in optical biopsy sensors used to detect esophageal cancers, and in the test for tuberculosis [19].

The purpose of microneedle-based biosensors is to continuously and minimally invasively monitor analytes in the interstitial fluid beneath the skin. They are often constructed of silicon, metals, polymers, or ceramics and range in length from tens to hundreds of micrometers. The procedure is painless since these needles pass through the SC without hitting any pain receptors. Enzymes and antibodies are examples of sensing components that are attached to or integrated into microneedles. Biochemical interactions are transformed into optical, electrochemical, or piezoelectric signals via the transducer. Optical sensors that detect changes in light properties and electrochemical sensors that measure changes in current or voltage are examples of common transducers. Skin-implanted microneedles interact with biomarkers found in interstitial fluid. Target analytes attach to biological receptors, changing characteristics measured by the transducer. The transducer then translates interactions into signals for quantitative measurements that can be made in real-time [21]. Microneedle biosensors are used in continuous glucose monitors for diabetes management, lactate monitoring for athletes to monitor fatigue and performance, therapeutic drug monitoring to ensure optimal dosing, wearable health devices for fitness

trackers related to exercise and recovery and chronic disease management [21].

2.3.1. Glucose Monitoring with Biosensors

Diabetes is a disease causing high blood glucose levels. About 422 million people over the world are diagnosed with diabetes and access to medical treatment and monitoring is key [22]. Continuous monitoring glucose monitors (CGM) constantly measure and report the blood glucose levels of the patient. The finger-pricking test is most commonly used to measure glucose levels but is unreliable and painful. CGMs provide a non-invasive and efficient method to monitor glucose levels. Some of the body fluids can be used to determine blood glucose levels [23]. Urine tests prove to be very useful for the diagnosis of prediabetes and are non-invasive. Nowadays, urine test strips are the most widely used technique to measure urine glucose levels. However, this test is subjective and depends on the user's perception of color and can hence give inaccurate results. Recently developed cylinder sensors, which use microbial fuel cells as a tool, provide an attractive alternative to test strips. These cylinder sensors have a wide range of sensing and are highly accurate [24]. Studies show that salivary glucose levels can strongly indicate blood glucose levels. This serves as an advantage for children, old, and critically ill patients. However, more study needs to be done on a larger scale to ensure accurate results as common medications can alter the glucose levels in saliva [25]. The glucose levels in tears are representative of the blood glucose levels to some extent. However, there are a few factors that may affect the results and reduce the reliability of the test include contamination by blood, method of tear collection, and the stimulant for the production of tears- calling for a non-invasive technique to measure blood glucose levels. Transdermal insulin delivery systems, including iontophoretic and microneedle patches, are being developed as alternatives to injections [26].

2.3.2. Characteristics of Biosensors

The efficiency of a biosensor is determined by its attributes such as selectivity, sensitivity, reproducibility, stability, and linearity. This will help identify the most suitable type of biosensor for the particular cause [27]. Sensitivity, the most important characteristic of a biosensor, is its ability to detect and measure the change in the concentration of the analyte. High-quality biosensors can detect even the slightest changes in the concentration of the analyte [28]. Selectivity is the ability of the biosensor to detect only the desired analyte amongst other molecules. This is very important in the clinical applications of these devices. When a biosensor fails to do this, a false result is obtained [29]. Reproducibility, the ability of biosensors to produce the same results in identical experimental conditions. A biosensor can maintain its working even when there are changes in external factors. High stability is associated with a high tendency of the analyte to bind with the bioreceptor in the sensor [27].

2.4. Clinical Applications of TDDS

The development of microneedles can be traced through three generations so far. The early primitive usage was in the form of a patch called "Transdermal Scop" which was used to treat motion sickness. This was later followed by estradiol, nitroglycerin, fentanyl, nicotine, testosterone, and many more transdermal systems. The first generation of transdermal drug delivery systems includes small lipophilic low-dose drug administration. The second generation was however an advanced one that included iontophoresis, non-cavitational ultrasound, chemical enhancers, etc. The third generation consists of electroporation, microneedle, thermal ablation, microdermabrasion, etc. These systems are now even progressing through clinical trials for the delivery of macromolecules and vaccines, such as insulin, parathyroid hormone, and influenza vaccine. Widely utilized Food and Drug Administration (FDA)-approved transdermal drugs (*with the year of approval*) and their clinical usage is elaborated in Table 1 [2]. Transdermal patches containing opioids like fentanyl and buprenorphine are widely used for chronic pain relief. Recent developments include abuse-deterrent formulations and patches with advanced rate-controlling membranes for improved safety and efficacy [30]. Nitroglycerin patches for angina and clonidine patches for hypertension remain important. Recent research focuses on improving patch adhesion and drug stability [x]. Rivastigmine patches for Alzheimer's disease and rotigotine patches for Parkinson's disease provide steady drug levels. Ongoing studies explore transdermal delivery of other CNS-active drugs [31]. Methylphenidate patches like Daytrana provide controlled release for managing ADHD symptoms. A new amphetamine patch (Xelstrym) was recently approved, expanding options [32].

Name of the Drug	Year of Approval	Clinical Usage
Transdermal Scop/Scopolamine	1979	Treatment of motion sickness

Nitroglycerin	1981	Vasodilatory drug primarily used for anginal chest pain (Angina pectoris) relief
Clonidine/Catapres-TTS	1984	Treatment of hypertension
Estradiol/Estraderm	1986	Estrogen steroid hormone that is used to treat Menopausal symptoms
Fentanyl/Duragesic	1990	Chronic pain to manage the pain in cancer patients and those recovering from painful surgeries
Nicotine/Nicoderm	1991	Stimulant drug (speeds up the messages traveling between the brain and the body) utilized for smoking cessation
Testosterone/Testoderm	1993	Steroid hormone that is used to treat Testosterone deficiency
Lidocaine with epinephrine	1995	Treatment of local dermal analgesia
Estradiol with norethindrone	1998	Treatment of menopausal symptoms
Lidocaine/Lidoderm	1999	Treatment of post-herpetic neuralgia pain
Ethinyl estradiol with norelgestromin	2001	Contraception
Estradiol with levonorgestrel	2003	Treatment of menopausal symptoms
Oxybutynin	2003	Treatment of overactive bladder
Lidocaine (ultrasound)	2004	Treatment of local dermal anesthesia
Lidocaine with tetracaine	2005	Treatment of local dermal analgesia
Fentanyl HCl (iontophoresis)	2006	Treatment of acute postoperative pain
Methylphenidate	2006	Correcting attention deficit hyperactivity disorder
Selegiline	2006	Treatment of major depressive disorder
Rotigotine	2007	Used in Parkinson's disease
Rivastigmine	2007	Used in dementia

Table 1. *FDA approved drugs currently being used on-market commercially.*

3. Conclusion

MTTDS, these days, is gaining an increasing amount of traction with its benefits that include reduced pain, avoidance of hepatic first-pass metabolism, maintenance of steady plasma concentration, safety, and compliance over oral or parenteral pathways [33]. Attempts have been made to integrate Microneedles with biosensors to monitor patients and increase compatibility effectively. Microneedle-based biosensors, while currently being used only in Glucose Monitoring, Lactate Monitoring, Drug Monitoring, Wearable Health Devices such as Fitness Trackers, and also in Chronic Disease

Management, are believed to have many more uses in the future. MTTDS at the moment has very limited applications, which are mentioned above, this study has gone over them. However, its usage in monitoring specific diseases such as cancer, thyroid-related diseases, single cell genomics, AI based technologies and more is yet to be explored [34] [35]. In the future, it is important to study further applications of this technology, specifically, explore its usage in treating and monitoring various diseases as mentioned above and chronic illnesses, and how to further improve patient compatibility with microneedles.

Author Contributions

H.H.W., K.D., S.V. conceptualization. D.M. and T.N. abstract. A.D, O.S introduction. O.S. 'Principle of Transdermal Drug Delivery System'. A.R. 'Microneedle Transdermal Drug Delivery System'. T.N. and A.D. 'Biosensor Technologies for Integration'. D.M. 'Clinical Applications'. N.C.K. 'Advantages and limitations of MTDDS'. A.R conclusion. K.D. and S.V. figure 1. A.R., H.H.W., K.D., S.V. reviewing and editing.

Conflicts of Interest

The authors declare no competing financial interests or conflicts of interest.

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