Review Article

Innovations in Advanced Drug Delivery Devices: A Comprehensive Review

Abstract

Drug delivery systems are developed to maximize drug efficacy and minimize side effects. As drug delivery technologies improve, the drug becomes safer and more comfortable for patients to use. The study on advanced drug delivery systems aims to increase patient compliance, decrease adverse effects, and improve treatment efficacy. Furthermore, the goal of these systems is to deliver drugs to particular body tissues or cells in a targeted manner, which should enhance treatment outcomes. During the last seven decades, extraordinary progress has been made in drug delivery technologies, such as systems for long-term delivery for months and years, localized delivery, and targeted delivery. In this review, we explain the general principles of several advanced drug delivery systems, their introduction objective, components, mechanism, functioning principle, and application. Furthermore, the adoption of advanced drug delivery systems has demonstrated promising results in enhancing patient compliance and treatment outcomes. By increasing the bioavailability and pharmacokinetics of pharmaceuticals, these systems have the potential to transform the fields of drug delivery and personalized medicine. However, the field also faces challenges in overcoming physicochemical barriers and biological unknowns. To progress, the field should focus on translatable research ideas, develop realistic goals, and most importantly, diversify technologies. This emphasis on diversity will inspire new ideas and approaches, leading to the development of more effective, patient-friendly drug delivery systems.

Keywords: Advanced Drug Delivery Systems (ADDS), Targeted Drug Delivery, Controlled Release, Microneedles, Stimuli-Responsive Drug Delivery, Smart Drug Delivery Systems, Biodegradable Drug Carriers, Bioavailability Enhancement

1. Introduction

Drugs can enter the human body through a variety of anatomical pathways. Selecting the best possible administration route is crucial to achieving the intended therapeutic outcome. As a result, when administering a drug, a number of aspects need to be taken into account, including the drug's qualities, the illness that has to be treated, and the intended duration of therapy. The drugs might be administered systemically or directly to the intended tissue or organ. Over the last twenty years, novel methods and strategies have been developed to regulate many aspects that are considered crucial for augmenting therapy efficacy, including dosage, duration, and delivery targeting. This marked the start of the "drug delivery systems (DDS)."(Bae and Park 2020)

As previously mentioned, the main objective of employing a DDS is to maintain the drug's level in the body inside the therapeutic window in addition to delivering a biologically active chemical in a regulated manner (time period and releasing rate). Additionally, the drugs can be directed at a particular tissue or organ (targeted drug delivery). Drug carriers, often polymers (biopolymers or synthetic polymers) whose characteristics could be adjusted to increase DDS efficiency, were used to address the first two features(Paolino, Sinha et al. 2006).

As previously mentioned, the main objective of employing a DDS is to maintain the drug's level in the body inside the therapeutic window in addition to delivering a biologically active chemical in a regulated manner (time period and releasing rate). Additionally, the drugs can be directed at a particular tissue or organ (targeted drug delivery). Drug carriers, often polymers (biopolymers or synthetic polymers) whose characteristics could be adjusted to increase DDS efficiency, were used to address the first two features.(Coelho, Ferreira et al. 2010).

Drug delivery systems offer numerous benefits, such as reduced side effects and increased patient compliance, but also have drawbacks like final price. Despite these, their benefits often outweigh the costs, making them valuable in modern medicine. With continued research and development, drug delivery systems can target specific areas of the body, reducing medication needs and minimizing harm to healthy tissues. As technology advances, they become more sophisticated, efficient, and personalized, providing adequate care for various diseases. Their versatility allows for customization, enhancing therapeutic potential.(Coelho, Ferreira et al. 2010)The primary aim of this review is to provide a thorough analysis of the recent innovations and advancements in drug delivery devices, focusing on how these technologies are revolutionizing medicine by improving therapeutic efficacy, patient compliance, and targeted drug release.

2. Advanced Drug Delivery Devices

2.1 Implantable Polymeric Drug Delivery System

2.1.1 Introduction

Oral administration is the most common method of drug delivery, but it has disadvantages such as degradation, first-pass metabolism, and patient compliance issues. There are two options: intravenous (IV) and transdermal delivery, each with its own benefits and drawbacks. IV administration bypasses first-pass metabolism and ensures 100% bioavailability but requires skilled healthcare professionals. Transdermal delivery eliminates invasive procedures but has difficulties with accurate dosage and preservation. Implantable polymeric drug delivery systems are convenient and effective for long-term drug delivery, reducing frequent dosing and improving patient compliance. These systems can release drugs at a controlled rate, ensuring steady concentration, and can be used for localized treatment of specific conditions. Careful evaluation of these variables is crucial for maximizing pharmacological therapy and improving patient outcomes (Sershen and West 2002).

2.1.2 Objectives

The implantable polymeric drug delivery devices are made to slowly release a predetermined dosage of drugs over an extended period. This drug delivery system's objective is to improve treatment outcomes since it boosts patient compliance and ensures that the body receives a more consistent dosage. Through contraception, they offer reliable, long-lasting birth control. When treating cancer, they limit adverse effects and focus on malignancies. They minimize issues and promote healing in the setting of dentistry. These technologies mark a substantial development in the administration of drug technology and present opportunities for further innovation in patient care (Stewart et al., 2018)

2.1.3 Components

Active and passive implants are the two primary parts of implantable polymeric drug delivery systems. The category of passive implants comprises two main subtypes: implants that are biodegradable and can be broken down by biological processes and implants that are non-biodegradable and stay intact within the body(Stewart et al., 2018).

2.1.4 Types of Implantable Polymeric Devices

a) Non-Biodegradable

Implantable drug delivery systems are commonly prepared using non-biodegradable implants such as silicones poly(urethanes) and poly(acrylates). Because of being structurally durable and resilient throughout life, they have universal applications in contraceptives(Stewart et al., 2018).

b) Biodegradable

Materials that can gradually break down into smaller pieces are used to develop biodegradable polymer implants. Polymers, including polycaprolactone (PCL) polylactic acid (PLA) and poly (lactic-co-glycolic acid) (PLGA), make up these devices. The main advantage of these implants is that the patient's body breaks them down naturally, so there's no need to remove them after implantation. It is important to remember though, that the development of these particular devices is a more complex process than the non-biodegradable polymer(Stewart et al., 2018).

2.1.5 Working Principle

Implantable polymeric drug delivery systems contain a drug reservoir enclosed in a polymer or a mix of polymer and drug. The drug is released gradually into the specific area of the body as the polymer degrades at a controlled rate. Factors such as drug permeability, solubility in the polymer, and drug amount influence the release of medication. The drug's ability to pass through and dissolve in the polymer significantly impacts its effects. The system's drug amount also influences the drug's behavior. The polymer's degradation rate inside the body is crucial for drug release. Polymer degradation can occur through hydrolysis, enzyme degradation, and physical deterioration like mechanical wear and tear and oxidation (Govender, Choonara et al. 2017).

2.1.6 Mechanism:

Drugs released from the implanted device may achieve this through four different routes. Controlled swelling, matrix breakdown, passive diffusion, and osmotic pumping. In contrast to diffusion, controlled swelling occurs when a solvent seeps into the device's matrix, causing a slower rate of release. There are two methods for linear drug delivery: osmotic pumping and passive diffusion. Osmotic pumping uses water movement across a membrane to control drug delivery. Molecules diffuse spontaneously through barriers when a concentration gradient pushes them in that direction. Mainly influencing the release rate is the diffusants distribution or concentration gradient inside the diffusion barrier. Drug release in systems involving swelling osmotic pressure or passive diffusion is also influenced by variables such as drug quantity, drug solubility, diffusion coefficient in the polymer, and rate of polymer degradation in vivo(Govender, Choonara et al. 2017).

2.1.7Applications

I. Cancer

An emerging implantable drug administration device may modify chemotherapy. It delivers drugs directly to the tumor site and improves their efficacy. It is very useful for brain cancer as it passes over the blood-brain barrier (BBB) and easily releases drugs into the brain. With further studies, this device can improve cancer treatment as it will increase efficacy and decrease adverse drug reactions (ADRs) (Govender, Choonara et al. 2017).

II. Ocular

Research is focusing on silicone implants and membrane-controlled devices for improved drug delivery to eye tissues. These biodegradable implants release drugs slowly, reducing the need for regular administration and noncompliance. Consistent drug release from implantable infusion devices minimizes drug level fluctuations, minimizing negative effects and increasing efficacy. These implanted drug delivery techniques have the potential to enhance treatment results and ocular drug delivery (Govender, Choonara et al. 2017).

III.Dental

In dentistry, polymeric implants having continuous fluoride release show encouraging results. Placed on the surface of the tooth, these implants release fluoride slowly over time. Researchers perform this through the development of drug-releasing hydrogels or by injecting stannous fluoride to tooth cements. Providing that teeth are consistently exposed to the health-promoting benefits of fluoride(Govender, Choonara et al. 2017).

IV. Contraceptives

The FDA licenced Norplant, a long-term contraceptive subdermal implant that releases levonorgestrel. These capsules are placed under the skin on the upper or forearm in a fan-like configuration to guarantee the most effective delivery. Other polymer-based contraceptives are under investigation, which include an intrauterine device called Progestasert that delivers drug and a silicon rubber vaginal ring. Also being researched are injectable microspheres or rods made of biodegradable polymer. These innovations give women access to practical and efficient birth control methods, allowing them to make sensible choices about their reproductive health(Govender, Choonara et al. 2017).

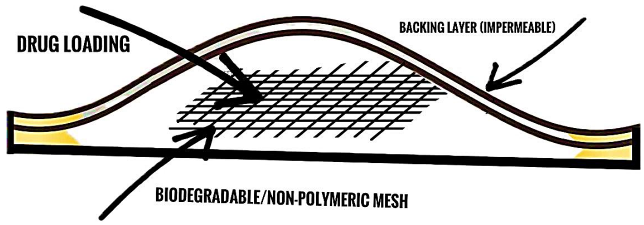

Figure 1. Diagrammatic Representation of Implantable Polymeric Drug Delivery System

2.2 Cardiac Pacemaker

2.2.1 Introduction

Piezoelectric nano-generators are used in implantable bioelectric devices like cardiac pacemakers, which regulate and maintain the heart's rhythm. These devices consist of a small battery-powered generator and thin wires implanted into the heart muscle or attached to its surface. The pacemaker monitors the heart's electrical activity and delivers impulses to stimulate the heart muscle when needed. Piezoelectric nano-generators could potentially provide a more sustainable and efficient power source for implantable bioelectric devices compared to traditional batteries (Azimi, Golabchi et al. 2021).

2.2.2 Objective

The primary objective of integrating a piezoelectric nano-generator into a cardiac pacemaker is to provide a self-powered and maintenance-free energy source. A pacemaker is an implantable device, and once implanted at its place, it has no physical contact with the outside environment under normal circumstances. Considering the fact that it is not possible to access a pacemaker at short intervals of time therefore by harnessing mechanical energy from cardiac movement's piezoelectric nano-generators eliminates the need for battery replacement surgeries, thus reducing risks and costs associated with device maintenance (Azimi, Golabchi et al. 2021).

2.2.3 Components

A cardiac pacemaker is mainly composed of some piezoelectric materials such as lead zirconate titanate or polyvinylidene fluoride that generate an electrical charge in response to mechanical deformation created by the ambient sources. There are also some supporting structures as well to the primary piezoelectric material. Piezoelectric nano-generators made for such purposes are typically constructed with a flexible and biocompatible substrate to ensure compatibility(Azimi, Golabchi et al. 2021).

2.2.4 Working Principle

Cardiac pacemakers regulate the heart's rhythm by sending electrical impulses with the assistance of piezoelectric nano-generators. These impulses cause the heart muscles to contract, maintaining a steady heartbeat. Modern pacemakers can monitor the heart's activity and change the pacing rate accordingly. This feature helps the heart maintain a healthy rhythm and adjust to changes in activity levels(Azimi, Golabchi et al. 2021).

2.2.5 Mechanism

A cardiac pacemaker is a bio-implantable bioelectric device that is integrated with a piezoelectric nano-generator. The process begins with a mechanical deformation as the heart contracts and expands during its natural rhythm, and the piezoelectric nano-generator experiences mechanical deformation. Then, this mechanical deformation of the piezoelectric material within the piezoelectric nano-generator generates an electrical charge proportional to the applied strain. As a result of there is electricity generation, and the electrical charge generated by the piezoelectric nano-generator is collected by the integrated electrodes and directed to the pacemaker's internal circuitry(Azimi, Golabchi et al. 2021).

2.2.6 Applications

Piezoelectric nano-generators find their applications in various devices and systems that are commonly used nowadays. They find great applications in the field of smart, self-sustainable wearable electronics. Piezoelectric-based energy harvesting systems can be integrated into wearable devices such as smartwatches, fitness trackers, and smart rings, as well as in health monitors to harvest electrical energy from the body's natural movement(Hu, Yao et al. 2019). This energy can power the device's sensors, display or communication modules.One of the significant applications of piezoelectric nano-generators is in biomedical self-sustaining implants. This piezoelectric-based energy harvesting system can power implantable biomedical devices such as cardiac pacemakers, neuro-stimulators, and drug delivery systems(Deng, Zhou et al. 2022).

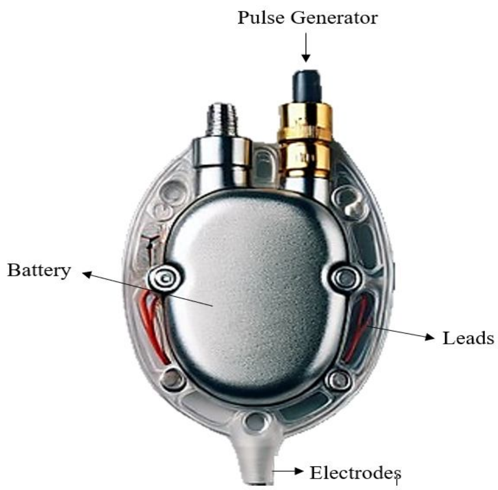

Figure 2. Diagrammatic representation of Cardiac Pacemaker

2.3 Prefilled Dual Chamber Device

2.3.1 Introduction

A prefilled dual-chamber dry powder inhaler that is used for the treatment of asthma and chronic obstructive pulmonary disease. It is a device meant to administer a combination of two drugs: formoterol, a long-acting beta-agonist that relaxes airway muscles, and budesonide, a corticosteroid that reduces inflammation. To give respiratory patients targeted relief, a prefilled dual chamber needs to be administered to the lungs using an appropriate method. Proper inhaler technique is crucial to ensure that the medication reaches the lungs effectively and provides optimal symptom relief. Patients should be educated on how to use the device correctly by their healthcare provider to maximize its benefits(van der Palen, Cerveri et al. 2020).

2.3.2 Objectives

Prefilled dual-chamber's objective is to provide symptom control for patients with asthma and Chronic obstructive pulmonary disease (COPD), including dyspnea, coughing, and wheezing. It prevents COPD and asthma attacks and is used as a maintenance drug. The easy-to-use device aims to increase medication compliance and adherence, ensuring patients receive the full benefits of their prescribed treatment regimen (van der Palen, Cerveri et al. 2020).

2.3.3 Components

The mechanism for delivering the powdered medication is contained in the main body of the inhaler, along with the dual chamber system. The prefilled dual-chamber consists of two distinct cavities, each designed for storing specific dosages of formoterol and budesonide powder. The mouthpiece, which delivers the medicated powder, is a component of the device designed to enhance comfort for the patient. Additionally, the device features a dose indicator on the side that shows the remaining number of doses. This allows the user to track how much medication is left in the inhaler easily. The prefilled dual-chamber is a convenient and user-friendly option for those needing a combination inhaler for their respiratory conditions(van der Palen, Cerveri et al. 2020).

2.3.4 Working Principle

The device works by mixing Formoterol and budesonide powder and inhaling them into the lungs to operate a prefilled dual-chamber.The dual chamber system of the inhaler releases a precisely measured dosage of medication when the patient winds the base. The powdered medication is then distributed into the airflow developed by the patient's inhalation, allowing it to be carried deep into the lungs, where it can exert its therapeutic effects (van der Palen, Cerveri et al. 2020).

2.3.5 Mechanism

Prefilled dual-chamber mainly consists of two medications, budesonide and formoterol. Budesonide is a corticosteroid.Budesonide primarily works by reducing inflammation in the airways, thus helping to prevent asthma attacks and COPD attacks. It acts locally in the lungs to inhibit the formation of inflammatory substances and reduce the swelling of the airway walls, which, as a result, improves airflow and reduces symptoms. On the other hand, formoterol is a long-acting beta-agonist that works by relaxing the muscles in the airways, thus making it easier to breathe. By binding to beta-adrenergic receptors in the lung, formoterol stimulates the production of cyclic AMP, which leads to bronchodilation and improved airflow(van der Palen, Cerveri et al. 2020).

2.3.6 Applications of prefilled dual chamber devices

Prefilled dual chamber devices are essential in various medical fields, particularly in respiratory diseases, where they allow direct administration of bronchodilators, corticosteroids, and other respiratory drugs. They also deliver biologic drugs like growth factors and monoclonal antibodies. These devices ensure stability and efficacy by handling complex drug formulations that require separate storage and mixing. Combination therapies are often used to treat hormonal imbalances and menopause symptoms, ensuring effective treatment and management of various medical conditions (Jezek, Darton et al. 2013).

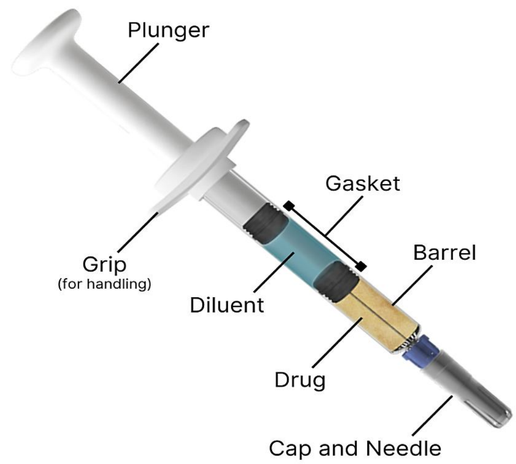

Figure 3. Diagrammatic representation of Prefilled Dual Chamber Devices

2.4 Closed Loop Insulin Delivery System

2.4.1 Introduction

The artificial pancreas, a closed-loop insulin delivery system, has revolutionized diabetes treatment by continuously monitoring blood glucose levels and automatically adjusting insulin delivery. This technology reduces the need for constant monitoring and manual injections, improving glucose control and quality of life for patients. The goal is to minimize blood glucose spikes and return them to normal levels, with ongoing research aiming to enhance the technology's accessibility further(Hovorka 2011).

2.4.2 Objective

The system monitors blood glucose levels and adjusts insulin delivery, providing precise control over diabetes management. It mimics the body's natural insulin regulation, enhancing the quality of life for diabetics through better blood sugar management, reduced complications risk, and increased convenience (Hovorka 2011).

2.4.3 Components

The artificial pancreas consists of three key components: continuous glucose monitoring, an insulin pump that regulates insulin doses based on glucose levels, and control algorithms (Renard, Costalat et al. 2006). Closed-loop insulin delivery systems, including continuous glucose monitoring, offer non-invasive glycemic variation and trend reporting, proving beneficial for diabetic patients (Thabit and Hovorka 2012). An insulin pump is a device that continuously monitors glucose levels and delivers a pre-determined amount of insulin when these levels are reached (Boughton, Allen et al. 2022). The control algorithms, the system's core, analyze large amounts of data from the continuous glucose sensor, calculate precise insulin doses, and deliver them to the patient (Bally, Thabit et al. 2018).

2.4.4 Working Principle

Closed-loop insulin uses continuous glucose monitoring (CGM) to estimate glucose levels in the interstitial fluid. The first continuous glucose monitoring device was introduced in early 2000, featuring a transcutaneous sensor and transmitter. The receiver displays updated glucose values every five minutes, with directional arrows indicating glycemic trends. Control algorithms process the data to calculate insulin doses for hypoglycemia and vice versa. The device was the first continuous glucose monitoring device available on the market (Efthymiadis, Bastounis et al. 2024).

2.4.5 Mechanism

The artificial pancreas works with a subcutaneously placed automated sensor that measures the interstitial glucose levels and checks them closely. It provides real-time data about the rate of change in glucose levels. Based on this data, the insulin doses are released through the insulin pump, delivering smaller amounts of drug into subcutaneous tissue, allowing greater flexibility of the doses in case of insulin sensitivity (Pickup and Keen 2002).

2.4.6 Applications

The closed-loop insulin system can enhance motivation and confidence in diabetic patients during exercise, though modifications like heart rate monitoring devices and motion senses may be necessary (van Bon, Verbitskiy et al. 2011). The future of artificial pancreas relies on patient compliance, which is crucial as it is patient-friendly and enhances their knowledge about the procedure. The closed-loop device is beneficial for patients unaware of their hypoglycemia, living alone, and the younger population, as they have higher non-compliance rates (Ringholm, Pedersen□Bjergaard et al. 2012). This system is easier and provides an efficient mode of delivery of insulin thus decreasing the requirement for stable and constant modification and monitoring of the patient (Benhamou, Franc et al. 2019)

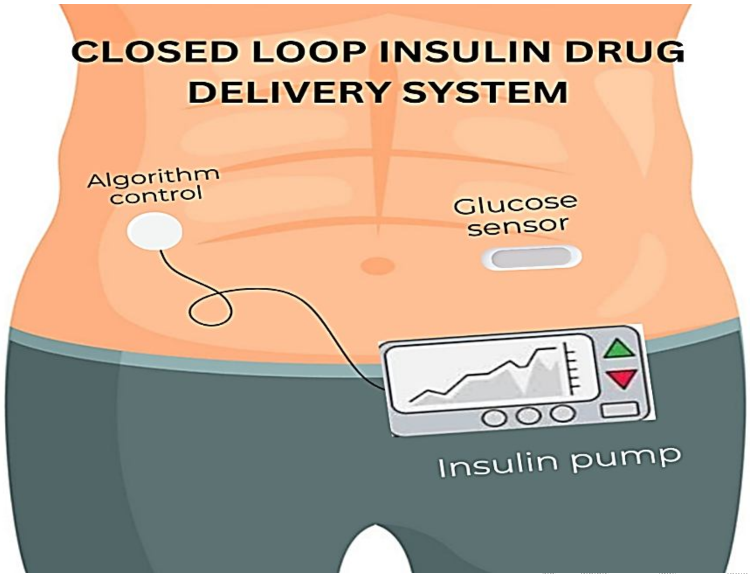

Figure 4. Diagrammatic representation of Closed-loop insulin drug delivery system

2.5 Hepatic infusion pumps

2.5.1 Introduction

Hepatic infusion pumps are increasingly being used globally for chemotherapy, specifically targeting hard-to-manage metastatic sites (Napier, Lidsky et al. 2021). This technique is increasingly used for treating unresectable liver metastases, enhancing long-term disease-free survival and potentially reducing rare resections compared to systemic chemotherapy(Sharib, Creasy et al. 2022). Hepatic artery infusion pump (HAIP) is a safe treatment for colorectal liver metastases and intrahepatic cholangiocarcinomas, delivering high chemotherapy doses directly to the liver via the hepatic arterial system (Callahan and Kemeny 2010).

2.5.2 Objectives

The objective of hepatic infusion pumps is to deliver high doses of chemotherapy directly to the liver while minimizing systemic side effects (Heggie, Lumicao et al. 1981). This targeted approach may lead to better tumour response rates and improved patient outcomes compared to traditional systemic chemotherapy alone (Kanat, Mari et al. 2012).

2.5.3 Components

The pump has been divided into **two chambers**, inner and outer.

a) Inner chamber

The pump's inner chamber ensures a uniform dosage due to its steady flow. The **reservoir** is filled with heparinized saline or chemotherapy via the septum and is located at the raised center.

The pump can only contain medicine for 14 days (about 2 weeks) and must be replenished on day 14. If not, the pump may run dry or get clogged. When not in use for chemotherapy, the pump is filled with glycerin, allowing for six-week refills(Lisa Parks MS and Meghan Routt 2015).

b) outer chamber

The outer chamber uses a propellantto push the contents of the inner chamber through the catheter to the delivery location when warmed by the body. The pump is gas-powered and requires no replacements(Lisa Parks MS and Meghan Routt 2015).

c) Pump catheters

Pump catheters are inserted directly in the hepatic or **gastroduodenal artery** (GDA). The pump is placed above the muscular layer in the lower right abdomen. If the patient is very obese, the pump might be positioned above the muscular layer near the ribs for easy access(Lisa Parks MS and Meghan Routt 2015).

2.5.4 Working principle

In hepatic arterial infusion (HAI) therapy, chemotherapy is delivered directly to the liver by a pump that is typically placed in the abdominal wall during hepatic arterial infusion (HAI) therapy. A catheter placed into the hepatic artery is connected to the pump. This configuration minimizes systemic toxicity while enabling high concentrations of chemotherapy drugs to target liver tumors specifically. High dosages of chemotherapy mostly stay in the liver which lessens the side effects that are frequently associated with systemic chemotherapy. By administering chemotherapy at concentrations up to 300-400 times higher than those administered intravenously this technique can increase the effectiveness of the treatment by reaching the liver tumors directly(Buisman, Grünhagen et al. 2019).

2.5.5 Mechanism

In a Hepatic arterial infusion pump (HAIP), a flexible tube is first inserted into the hepatic artery. Then a pump is surgically implanted in the abdominal wall as part of the HAIP procedure. With this approach, liver tumors like hepatocellular carcinoma and colorectal liver metastases can be directly targeted with high-dose chemotherapy. It is a specific method that maximizes the effectiveness of treatment while reducing systemic side effects.It is particularly helpful in cases where tumours are limited to the liver or when standard systemic chemotherapy is not effective enough.

2.5.6 Applications

I. Treatment for large hepatic cancer that can't be surgically removed

HAIP can be used for individuals with enormously large liver cancers that cannot be surgically removed or cannot be treated completely with Trans Arterial Chemoembolization (TACE)(He, Le et al. 2017).

II. Treatment for primary and secondary hepatic malignancies

Hepatic artery infusion pump (HAIP) chemotherapy is an advanced cancer treatment therapy for primary and secondary hepatic malignancies(Brajcich, Bentrem et al. 2020).

Hepatic arterial infusion (HAI) therapy is a treatment option available for patients with liver-dominant cancers, including those with multifocal/unresectable liver-only metastatic colorectal cancer that have already received systemic chemotherapy(Bonde, Fung et al. 2023).

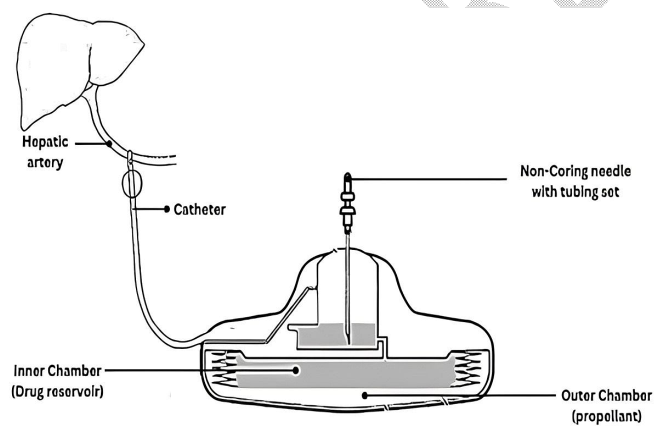

Figure 5. Diagrammatic representation of Hepatic Artery Infusion Pump

2.6 MEMS Devices

2.6.1 Introduction

MEMS technology is a significant innovation in the 21st century, focusing on creating compact, low-power integrated circuits for various industries. It is particularly useful in drug delivery systems, which use micropumps with piezoelectric actuators to deliver medicines through microneedles. These pumps can be mechanical or non-mechanical, with piezoelectric actuation being preferred due to its efficiency and lower frequency capability. MEMS drug delivery devices can be classified into passive diffusion osmotic devices, microneedles responsive hydrogels, and devices powered by fluorocarbon propellants (Lee, Choi et al. 2018).

2.6.2 Objectives

This study aims to explore how drug delivery systems can be improved using micro-electro-mechanical systems (MEMS) technology. The specific goal is to replace traditional drug delivery techniques with microtechnology-based systems like MEMS to overcome their shortcomings. It aims to highlight the benefits of MEMS technology in implantable device design and controlled drug delivery with minimal side effects. These benefits include high efficacy automation and precise control of parameters (Lee, Choi et al. 2018).

2.6.3 Components

a) Drug reservoirs: This is the location where prescriptions are held prior to delivery. It could be solid, liquid, or gel-like. Parts known as actuators are in charge of dispensing medication from the reserve. Their forms can include diffusion-based systems or mechanical pumps

b) Control systems: They regulate drug release according to physiological requirements. Sensors. Some modern drug delivery systems use sensors to precisely control the drug and track multiple parameters.

c) Power Sources: Drug delivery systems may require a power source based on their design to power the actuators and control systems. This could be an external power source or the battery of an energy-harvesting device.

d) Interfaces: these enable communication between the external devices and the body for the drug delivery system(Cobo, Sheybani et al. 2015).

2.6.4 Working Principle

The drug is transferred from the drug chamber to a designated site in the body by using different actuation mechanisms that can produce accuracy, reliability, and precision. These mechanisms include spring-loaded devices, pressurized gas systems, and electronic controls. The goal is to ensure that the drug is delivered safely and effectively to the targeted area within the body (Cobo, Sheybani et al. 2015).

2.6.5 Mechanism

Micropumps are systems that control drug dosage and delivery through fluid movement. They can be mechanical or non-mechanical, with mechanical micropumps using piezoelectric actuators to pump fluids. Mechanical micropumps use oscillating diaphragms, while non-mechanical micropumps use electrochemical forces. Piezoelectric materials like lead zirconate titanate (PZT) produce precise oscillations, allowing drug delivery through microneedles. These systems are ideal for long-term conditions like diabetes and cardiovascular diseases, as they offer precision and implantation-ready miniaturization, making them beneficial for long-term drug administration. The precision and miniaturization of these systems make them ideal for long-term use (Villarruel Mendoza, Scilletta et al. 2020).

2.6.6 Application

Mesh technology is utilized in Guided Tissue Regeneration (GTR) procedures for periodontal tissue repair and bone regeneration. It is also used for treating urinary incontinence and implantation of soft tissue reinforcement in cases of weakness in urological, gynecological, or gastroenterological anatomy. Mesh technology is also used to treat non-hyperkeratotic actinic keratoses in immunocompromised patients and improve luminal diameter in native coronary arteries. Additionally, an implantable polymer chip is used as a reservoir drug delivery device for sustained drug release (Staples, Daniel et al. 2006).

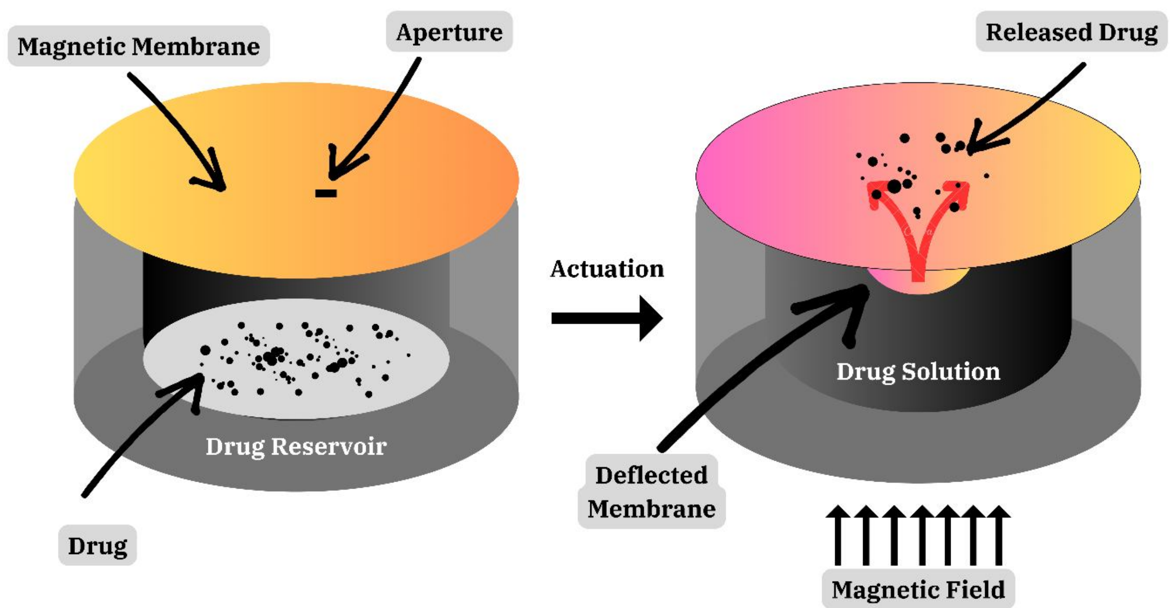

Figure 6. Diagrammatic Representation of MEMS Devices

2.7 Inhaled insulin device

2.7.1 Introduction

Subcutaneous insulin therapy, used since 1920, has faced resistance from patients due to concerns about hypoglycemia and needle pain. Alternative methods like oral, transdermal, buccal, and nasal have low bioavailability. New methods like lipid vesicles and iontophoresis improve insulin absorption and control hypoglycemia. Inhaled insulin, a non-invasive option, has shown promising results and high patient acceptance rates. These advancements in insulin delivery technology have transformed diabetes management by offering patients a variety of options to regulate blood sugar levels, improving their quality of life and enhancing their flexibility and convenience in managing their condition (Cavaiola and Edelman 2014).

2.7.2 Objective

The device offers a convenient subcutaneous method for diabetic patients to receive their medication, aiming to enhance their overall quality of life and adherence to their treatment regimen, thereby reducing the need for traditional injection techniques (Heinemann, Baughman et al. 2017).

2.7.3 Components

The inhaled insulin system has three components: human insulin inhalation powder, AIR Inhaler, and Directions for Use circular. The human insulin inhalation powder is pre-measured and placed into the AIR Inhaler for easy administration, while the Directions for Use circular provides step-by-step instructions on how to use the system properly(Muchmore, Silverman et al. 2007).

2.7.4 Working principle

An inhaled insulin device delivers insulin into the body by converting it into mist, which effectively controls sugar levels without injections, making it a convenient and less painful alternative for individuals with diabetes requiring insulin therapy (Muchmore, Silverman et al. 2007).

2.7.5 Mechanism

Human insulin powders are packed in blisters. Insulin packed in blisters is placed in chamber insulin disperse in chambers and form aerosols. Aerosols in the form of fine mist pass through the inhalers into the mouth when the inhaler is pressed down one time. The patient inhaled through the mouthpiece placed between lips and administer drug. Aerosols are made from nebulizers by using compressed air. First exhale fully to empty lungs then put inhaler into the mouth after removing the cap, take deep breath to inhale insulin. Insulin enters into the lungs in the form of aerosols. Each inhaler use for 15 days(Vargas, Martinez et al. 2013).

2.7.6 Applications

It is the most convenient method to deliver insulin because first-pass metabolism is avoided. Painless method people easily use don't feel reluctant. Inhalers are used in asthma and COPD and release inflammation(Heinemann, Baughman et al. 2017). They are also being studied for their potential use in delivering other medications, such as vaccines. Inhalers provide a quick and efficient way to administer medication directly to the lungs, where it can be rapidly absorbed into the bloodstream (Rashid, Absar et al. 2015).

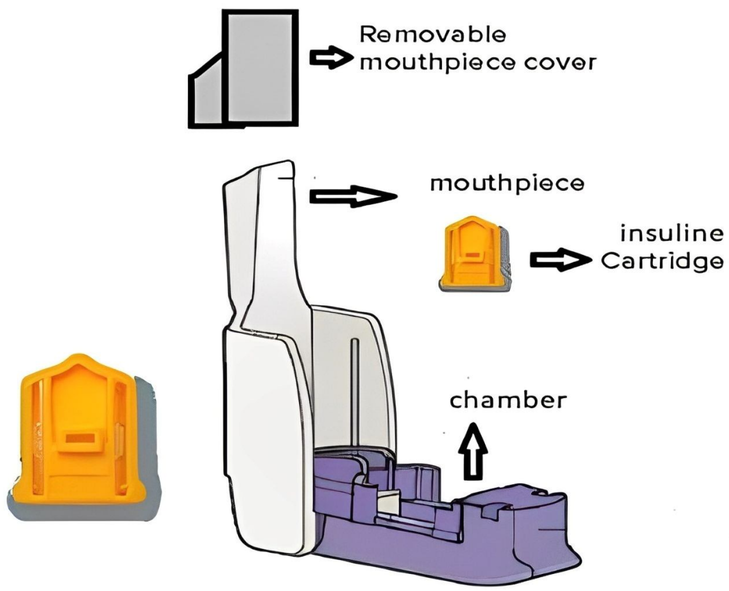

Figure 7. Diagrammatic representation of Insulin delivery devices

2.8 Hydrogels forming microneedles

2.8.1 Introduction

Hydrogels forming microneedles, developed in 2012, are a new type of microneedle made of swellable material. They swell rapidly when applied to the skin, making them useful for medicinal applications like interstitial fluid uptake in cells around tissue gaps. They can also be used as transdermal drug delivery systems by including pharmaceuticals into the polymer structure or loading them into reservoirs. These microneedles are minimally invasive, as they don't penetrate deep into the skin to interact with pain receptors. They can be easily made in various designs, making them more convenient to use. Additionally, they can be cleaned before application and are easier to remove from the skin, resulting in less harm to both the microneedles and the skin (Turner, White et al. 2021).

2.8.2Objectives

The study focuses on hydrogels for creating microneedles, aiming to enhance drug delivery and healthcare technologies by providing a painless, less invasive option and user-friendly system. It includes developing microneedle patches for chronic conditions and improving patient outcomes. Scientists are working on optimizing drug loading strategies, enhancing hydrogel stability, and refining microneedle fabrication processes (Lutton, Larrañeta et al. 2015).

2.8.3 Components

Hydrogels are made from polymers like PEG, PVA, PVP, PAA, PMVE, and PEO, which are derived from natural sources like cellulose, alginate, chitosan, hyaluronic acid, and gelatin. Crosslinking agents stabilize the hydrogel structure, and they can carry medication proteins, peptides, and other biomolecules to form microneedles. Some hydrogels can be mechanically and flexiblely enhanced with plasticizers like propylene glycol or glycerol, enhancing targeted delivery and encapsulation of medications (Turner, White et al. 2021).

2.8.4 Working Principle

Microneedles, small and sharp, are designed to cause minimal pain when piercing the stratum corneum, the outermost layer of skin. They use hydrogel components like gelMA, PVA, and MeHA to draw moisture from the skin, creating a gel-like substance upon insertion. The hydrogels' swelling can control or immediately release the drug payload, improving absorption and therapeutic efficacy by ensuring the medication passes through the stratum corneum barrier and reaches the systemic circulation or local tissues (Lutton, Larrañeta et al. 2015).

2.8.5 Mechanism

Hydrogel microneedles are made from hydrophilic and biocompatible polymer materials like PVA, MeHA, and GelMA. These materials are chosen for their swelling ability and mechanical durability, which are essential for medication delivery and skin penetration. The microneedles are designed to minimize pain and discomfort by being sharp enough to penetrate the skin's outermost layer but short enough to avoid deeper nerve-rich layers. The hydrogel material swells and changes from a solid to a gel-like state, enhancing drug interaction and diffusion within the tissue. Some designs allow for quick drug release when the hydrogel swells, while others allow for slower, more controlled release, offering versatility in drug delivery applications. This can be achieved by varying the hydrogel's crosslinking density or using distinct polymer compositions that alter the medication's diffusion out of the hydrogel as it swells(Donnelly, McCrudden et al. 2014).

Applications:

Hydrogel-forming microneedles are painless, painless alternatives to traditional hypodermic needles, providing a reliable method for delivering medication and controlled therapeutic agents. These needles are beneficial for drugs with steady absorption and long-lasting effects, especially for children and those with chronic conditions. They can also improve vaccination uptake by controlling release and enhancing interaction with skin-resident immune cells. Hydrogel-forming microneedles can also be used to apply growth factors and other medicinal agents directly to wounds, expediting healing and improving tissue regeneration. The moisturizing properties of hydrogels also contribute to a moist wound environment.

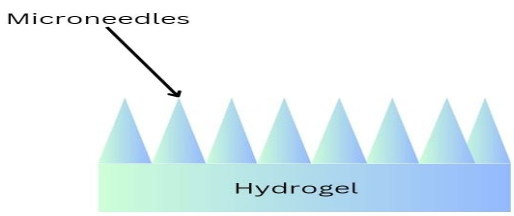

Figure 8. Diagrammatic representation of Hydrogels forming mirconeedle

Conclusion

Advanced drug delivery devices offer great promise in enhancing the effectiveness and safety of pharmaceutical treatments. Ongoing research and innovation in this area are essential for overcoming drug delivery challenges and improving patient outcomes. Overcoming challenges like poor solubility and limited bioavailability, these systems can revolutionize medication administration. With advancing technology, personalized and targeted drug delivery options will further expand. Since the introduction of the first drug delivery device, technological advancements have progressed continuously. Our advancements have transitioned from microtechnology to nanotechnology and from non-specific to targeted drug delivery. Future challenges involve scaling up procedures to introduce new therapies quickly and developing multifunctional devices to meet various biological and therapeutic requirements.

Disclaimer (Artificial intelligence)

Author(s) hereby declares that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of manuscripts.

Reference

Azimi, S., et al. (2021). "Self-powered cardiac pacemaker by piezoelectric polymer nanogenerator implant." Nano Energy**83**: 105781.

Bae, Y. H. and K. Park (2020). "Advanced drug delivery 2020 and beyond: Perspectives on the future." Advanced drug delivery reviews**158**: 4-16.

Bally, L., et al. (2018). "Closed-loop insulin delivery for glycemic control in noncritical care." New England Journal of Medicine**379**(6): 547-556.

Barold, S. S., et al. (2008). Cardiac Pacemakers step by step: An illustrated guide, John Wiley & Sons.

Benhamou, P.-Y., et al. (2019). "Closed-loop insulin delivery in adults with type 1 diabetes in real-life conditions: a 12-week multicentre, open-label randomised controlled crossover trial." The Lancet Digital Health**1**(1): e17-e25.

Bonde, A., et al. (2023). "Imaging of the hepatic arterial infusion pump: Primer for radiologists." Clinical Imaging: 110022.

Boughton, C. K., et al. (2022). "Closed-loop therapy and preservation of C-peptide secretion in type 1 diabetes." New England Journal of Medicine**387**(10): 882-893.

Brajcich, B. C., et al. (2020). "Short-term risk of performing concurrent procedures with hepatic artery infusion pump placement." Annals of surgical oncology**27**: 5098-5106.

Buisman, F. E., et al. (2019). "Adjuvant hepatic arterial infusion pump chemotherapy after resection of colorectal liver metastases: results of a safety and feasibility study in the Netherlands." Annals of surgical oncology**26**: 4599-4607.

Callahan, M. K. and N. E. Kemeny (2010). "Implanted hepatic arterial infusion pumps." The Cancer Journal**16**(2): 142-149.

Cavaiola, T. S. and S. Edelman (2014). "Inhaled insulin: a breath of fresh air? A review of inhaled insulin." Clinical therapeutics**36**(8): 1275-1289.

Cobo, A., et al. (2015). "MEMS: Enabled drug delivery systems." Advanced healthcare materials**4**(7): 969-982.

Coelho, J. F., et al. (2010). "Drug delivery systems: Advanced technologies potentially applicable in personalized treatments." EPMA journal**1**: 164-209.

Curley, S., et al. (1990). "Hepatic artery infusion pumps: cannulation techniques and other surgical considerations." Langenbecks Archiv fuer Chirurgie**375**: 119-124.

Deng, W., et al. (2022). "Piezoelectric nanogenerators for personalized healthcare." Chemical Society Reviews**51**(9): 3380-3435.

Donnelly, R. F., et al. (2014). "Hydrogel-forming microneedles prepared from “super swelling” polymers combined with lyophilised wafers for transdermal drug delivery." PloS one**9**(10): e111547.

Donnelly, R. F., et al. (2012). "Hydrogel□forming microneedle arrays for enhanced transdermal drug delivery." Advanced functional materials**22**(23): 4879-4890.

Efthymiadis, A., et al. (2024). "The impact of closed-loop automated insulin delivery systems on hypoglycaemia awareness in people living with type 1 diabetes: A systematic review and meta-analysis." Journal of Diabetes & Metabolic Disorders: 1-11.

Elleri, D., et al. (2011). "Closed-loop insulin delivery for treatment of type 1 diabetes." BMC medicine**9**: 1-9.

Franssen, S., et al. (2022). "Comparison of hepatic arterial infusion pump chemotherapy vs resection for patients with multifocal intrahepatic cholangiocarcinoma." JAMA surgery**157**(7): 590-596.

Govender, T., et al. (2017). "Implantable and transdermal polymeric drug delivery technologies for the treatment of central nervous system disorders." Pharmaceutical development and technology **22**(4): 476-486.

He, M.-K., et al. (2017). "Hepatic artery infusion chemotherapy using mFOLFOX versus transarterial chemoembolization for massive unresectable hepatocellular carcinoma: a prospective non-randomized study." Chinese Journal of Cancer **36**: 1-8.

Heggie, A. D., et al. (1981). "Chlamydia trachomatis infection in mothers and infants: A prospective study." American journal of diseases of children **135**(6): 507-511.

Heinemann, L., et al. (2017). "Pharmacokinetic and pharmacodynamic properties of a novel inhaled insulin." Journal of diabetes science and technology **11**(1): 148-156.

Hovorka, R. (2011). "Closed-loop insulin delivery: from bench to clinical practice." Nature Reviews Endocrinology **7**(7): 385-395.

Hu, D., et al. (2019). "Strategies to achieve high performance piezoelectric nanogenerators." Nano Energy **55**: 288-304.

Jezek, J., et al. (2013). "Biopharmaceutical formulations for pre-filled delivery devices." Expert opinion on drug delivery **10**(6): 811-828.

Kanat, M., et al. (2012). "Distinct β-cell defects in impaired fasting glucose and impaired glucose tolerance." Diabetes **61**(2): 447-453.

Lee, H. J., et al. (2018). "MEMS devices for drug delivery." Advanced drug delivery reviews **128**: 132-147.

Lisa Parks MS, C. and M. Meghan Routt (2015). "Hepatic artery infusion pump in the treatment of liver metastases." Clinical Journal of Oncology Nursing **19**(3): 316.

Lutton, R. E., et al. (2015). "A novel scalable manufacturing process for the production of hydrogel-forming microneedle arrays." International journal of pharmaceutics **494**(1): 417-429.

Lyshevski, S. E. (2018). MEMS and NEMS: systems, devices, and structures, CRC press.

Muchmore, D. B., et al. (2007). "The AIR® inhaled insulin system: system components and pharmacokinetic/glucodynamic data." Diabetes Technology & Therapeutics**9**(S1): S-41-S-47.

Napier, K. J., et al. (2021). "Hepatic arterial infusion pumps: what the radiologist needs to know." RadioGraphics**41**(3): 895-908.

Paolino, D., et al. (2006). "Drug delivery systems." Encyclopedia of medical devices and instrumentation.

Pickup, J. and H. Keen (2002). "Continuous subcutaneous insulin infusion at 25 years: evidence base for the expanding use of insulin pump therapy in type 1 diabetes." Diabetes care**25**(3): 593-598.

Rai, I., et al. (2021). "Recent advances in insulin delivery devices and modes of insulin therapy." Journal of Pharmaceutical Research International**33**(57B): 358-367.

Rashid, J., et al. (2015). "Newer devices and improved formulations of inhaled insulin." Expert opinion on drug delivery**12**(6): 917-928.

Renard, E., et al. (2006). "Closed loop insulin delivery using implanted insulin pumps and sensors in type 1 diabetic patients." Diabetes Research and Clinical Practice**74**: S173-S177.

Ringholm, L., et al. (2012). "Hypoglycaemia during pregnancy in women with Type 1 diabetes." Diabetic Medicine**29**(5): 558-566.

Sershen, S. and J. West (2002). "Implantable, polymeric systems for modulated drug delivery." Advanced drug delivery reviews**54**(9): 1225-1235.

Sharib, J. M., et al. (2022). "Hepatic artery infusion pumps: a surgical toolkit for intraoperative decision-making and management of hepatic artery infusion-specific complications." Annals of surgery**276**(6): 943-956.

Staples, M., et al. (2006). "Application of micro-and nano-electromechanical devices to drug delivery." Pharmaceutical research **23**: 847-863.

Teagarden, D. L., et al. (2010). "21 Practical Considerations for Freeze-Drying in Dual Chamber Package Systems." Freeze Drying/Lyophilization of Pharmaceutical and Biological Products: 494.

Thabit, H. and R. Hovorka (2012). "Closed-loop insulin delivery in type 1 diabetes." Endocrinology and Metabolism Clinics **41**(1): 105-117.

Turner, J. G., et al. (2021). "Hydrogel□forming microneedles: current advancements and future trends." Macromolecular Bioscience **21**(2): 2000307.

van Bon, A. C., et al. (2011). Exercise in closed-loop control: a major hurdle, SAGE Publications.

van der Palen, J., et al. (2020). "DuoResp® Spiromax® adherence, satisfaction and ease of use: findings from a multi-country observational study in patients with asthma and COPD in Europe (SPRINT)." Journal of Asthma **57**(10): 1110-1118.

Vargas, O., et al. (2013). "The use of metered-dose inhalers in hospital environments." Journal of aerosol medicine and pulmonary drug delivery **26**(5): 287-296.

Villarruel Mendoza, L. A., et al. (2020). "Recent advances in micro-electro-mechanical devices for controlled drug release applications." Frontiers in Bioengineering and Biotechnology **8**: 827.