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EXPLORING THE EVOLUTION OF PATCHES AND IMPACT OF SMART PATCHES ON DRUG DELIVERY: A COMPREHENSIVE REVIEW

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ABSTRACT: This comprehensive review investigates the evolution of patches and the transformative impact of smart patches on drug delivery. Beginning with a historical overview of patches, the review examines the advancements that led to the development of smart patches. It explores the design principles, functionalities and applications of smart patches in drug delivery, highlighting their potential to revolutionize medication administration and patient care. Additionally, challenges and future directions in the field are discussed, providing insights into the ongoing innovation and development of smart patch technology.

INTRODUCTION: Patches have indeed revolutionized drug delivery, transitioning from basic transdermal systems to sophisticated smart patches, ushering in a new era of efficiency and efficacy. Initially, transdermal patches like the nicotine patch were a breakthrough, providing a convenient and non-invasive method for drug administration [1]. These patches slowly released drugs through the skin, offering advantages such as steady plasma drug levels and reduced dosing frequency. As technology advanced, smart patches emerged, incorporating innovative features to enhance drug delivery. One example is the insulin patch for diabetes management. These patches not only deliver insulin but also monitor blood glucose levels in real-time, adjusting insulin release accordingly.

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This closed-loop system improves glycemic control and reduces the risk of hypoglycaemia [2]. Another notable advancement is the use of microneedle patches. These patches contain tiny needles that painlessly penetrate the skin's surface, enabling precise drug delivery to targeted layers of tissue. Microneedle patches have been developed for various applications, including vaccination, hormone delivery, and pain management [3].

Furthermore, smart patches equipped with sensors and wireless connectivity enable remote monitoring and personalized treatment. For instance, wearable patches for cardiovascular conditions can monitor vital signs like heart rate and blood pressure, providing continuous health monitoring and timely intervention [4]. Moreover, patches incorporating microfluidic systems offer precise control over drug release kinetics. These patches can deliver multiple drugs simultaneously or adjust drug release rates based on physiological changes, optimizing therapeutic outcomes [5]. In summary, the evolution of patches from simple transdermal systems to smart, technologically advanced platforms has significantly improved drug delivery efficiency and patient outcomes. These innovations showcase the potential of smart patches to revolutionize healthcare delivery by providing personalized, targeted therapy with minimal intervention. The integration of nanotechnology into patch development has further enhanced drug delivery capabilities. Nanoparticles can be embedded within patches to encapsulate drugs, allowing for controlled release and targeted delivery to specific tissues or cells. This approach minimizes systemic side effects and maximizes therapeutic efficacy [6]. For example, cancer therapy patches loaded with chemotherapy nanoparticles can selectively target tumor cells while sparing healthy tissue, reducing toxicity and improving patient tolerance to treatment.

Furthermore, the advent of flexible electronics and biocompatible materials has enabled the development of wearable patches with enhanced functionality and comfort [7]. These patches conform to the body's contours, ensuring continuous drug delivery without impeding daily activities. Advanced materials such as hydrogels and biodegradable polymers contribute to the flexibility and biocompatibility of these patches, making them suitable for long-term use. Moreover, the incorporation of artificial intelligence (AI) algorithms into smart patches holds promise for optimizing drug delivery regimens. AI can analyze patient data in real-time, such as physiological parameters and drug response patterns, to tailor treatment protocols and dosage adjustments dynamically. This personalized approach maximizes therapeutic efficacy while minimizing adverse effects, improving patient outcomes and quality of life [8]. Furthermore, the potential for self-administration and remote monitoring offered by smart patches enhances patient autonomy and compliance with treatment regimens. Patients can easily apply and remove patches at home, reducing the need for frequent clinic visits and improving convenience. Remote monitoring capabilities allow healthcare providers to track patient progress and intervene promptly if necessary, promoting proactive disease management and reducing healthcare costs.

The evolution of patches from conventional transdermal systems to smart, technologically advanced platforms represents a paradigm shift in drug delivery. These innovative solutions offer precise control over drug release, personalized therapy, and enhanced patient convenience, ultimately improving therapeutic outcomes and revolutionizing healthcare delivery [9].

Functionality and Applications of Smart Patches in Drug Delivery: Smart patches offer a range of functionalities that enable optimized drug delivery strategies. These patches can monitor physiological parameters such as glucose levels, pH, and temperature, providing feedback for adaptive drug dosing [10]. Additionally, smart patches can deliver drugs in response to specific triggers or stimuli, such as changes in biomarkers or patient behaviour [11]. Applications of smart patches in drug delivery span diverse therapeutic areas, including diabetes management, pain relief, and personalized medicine.

FIG. 1: DIFFERENT APPLICATIONS OF SMART PATCHES

Some of the Different Types of Patches commonly found in Markets:

Transdermal Drug Delivery Patches [12]:

Nicotine patches: Used for smoking cessation by delivering nicotine through the skin.

Hormonal Patches: Deliver hormones like estrogen and progestin for birth control or hormone replacement therapy.

Pain Relief Patches: Contain analgesic medications such as lidocaine or diclofenac for localized pain relief.

Motion Sickness Patches: Administer medications like scopolamine to prevent motion sickness.

Topical Medication Patches [13]:

Lidocaine Patches: Provide localized pain relief for conditions like neuropathic pain or post-herpetic neuralgia.

Fentanyl Patches: Deliver the potent opioid fentanyl for managing chronic pain.

Smart Patches:

Glucose Monitoring Patches: Continuous glucose monitoring (CGM) systems use sensor patches to monitor blood sugar levels in diabetic patients.

Wearable Health Monitoring Patches: Track various physiological parameters such as heart rate, temperature, and activity levels.

Drug Delivery Monitoring Patches: Incorporate sensors to monitor drug levels in the body and adjust drug delivery accordingly.

Cosmetic Patches [14]:

Anti-aging Patches: Contain ingredients like retinol or hyaluronic acid to reduce wrinkles or hydrate the skin.

Acne Patches: Hydrocolloid patches that absorb excess oil and pus from acne lesions, promoting healing and reducing inflammation.

Nutritional Patches [15]:

Vitamin Patches: Deliver vitamins and minerals directly through the skin for nutritional supplementation.

Energy Patches: Contain ingredients like caffeine or B-vitamins to boost energy levels.

Herbal and Natural Patches [16]:

Herbal Pain Relief Patches: Utilize natural ingredients like menthol, eucalyptus, or capsaicin for pain relief.

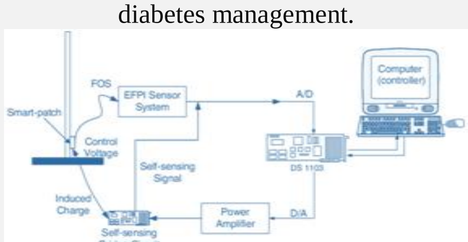
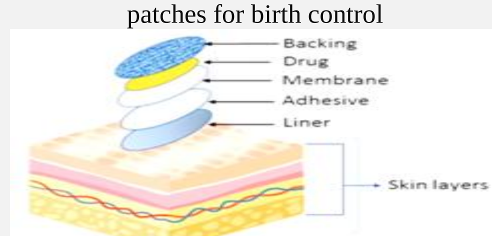
Detox Patches: Claimed to remove toxins from the body through the skin, often containing herbal ingredients like bamboo vinegar or tourmaline.

Wearable Technology Patches [17]:

Fitness Monitoring Patches: Track physical activity, calories burned, and other fitness metrics.

Posture Correction Patches: Provide feedback on posture and help correct poor posture habits.

TABLE 1: DIFFERENCES BETWEEN SMART PATCHES AND CONVENTIONAL PATCHES [18]

Feature	Smart Patches	Conventional Patches
Functionality	Monitor physiological parameters, provide feedback, adjust drug delivery.	Passive delivery of medications or substances
Technology	Incorporate sensors, microelectronics, microprocessors.	Simple adhesive layer containing drug/substance
Drug Delivery	Dynamic, adjusts based on real-time data.	Passive, follows predetermined release rate
Applications	Health monitoring, personalized medicine, disease management.	Drug delivery for various conditions (e.g., nicotine, hormones)
Personalization	Highly personalized, adapts to individual physiology.	Limited personalization, fixed release profile
Feedback	Provides real-time feedback based on sensor data.	No feedback capability
Examples	Glucose monitoring and insulin delivery patches for diabetes management.	Nicotine patches for smoking cessation, hormonal patches for birth control
Figure	 Smart PatchesSchematic-diagram	 Transdermal Patches

Historical Evolution of Patches: The history of patches dates back centuries, with early examples including poultices and plasters used for medicinal purposes. The advent of modern transdermal patches in the 20th century marked a significant milestone, enabling controlled release of drugs through the skin for systemic delivery. Over time, innovations in patch design and formulation have expanded their applications across various therapeutic areas, including pain management, hormone replacement therapy, and smoking cessation.

These are just a few examples of the diverse range of patches available in markets today. With advancements in technology and formulation, the patch market continues to expand, offering innovative solutions for various health and wellness needs [19].

The historical evolution of patches is a fascinating journey that spans centuries and encompasses various cultures and technological advancements. Here's a brief overview:

Ancient Times:

- Patches have been used for medicinal purposes since ancient times. Early examples include poultices and plasters made from natural materials such as herbs, leaves, and animal fats. These were applied directly to the skin to treat wounds, infections, and other ailments.

Middle Ages and Renaissance:

- During the Middle Ages and Renaissance period, herbal plasters became more sophisticated. Pharmacists and healers developed formulas containing a wider range of ingredients, including resins, oils, and powdered minerals. These plasters were applied topically and held in place with bandages or cloth.

19th Century:

- The 19th century brought significant advancements in patch technology. In 1845, Dr. George F. Lyon invented the first adhesive bandage, consisting of a simple adhesive plaster with a fabric backing. This innovation revolutionized wound care and paved the way for modern adhesive patches.
- During this time, patches were primarily used for wound dressing and as topical treatments for various skin conditions.

20th Century:

1. The 20th century saw the commercialization and widespread use of adhesive patches for various purposes. In the 1920s, nicotine patches were introduced as a method for smoking cessation, although they didn't gain popularity until later decades.
2. Hormonal patches for birth control and hormone replacement therapy were developed in the latter half of the 20th century, providing an alternative to oral medications.
3. Transdermal patches for drug delivery became increasingly common, offering a non-invasive way to administer medications through the skin directly into the bloodstream. These patches provided sustained release of drugs over an extended period.

21st Century:

- The 21st century has seen further advancements in patch technology, including the development of smart patches. These patches incorporate advanced sensors, microelectronics, and microfluidics to monitor physiological parameters, provide real-time feedback, and adjust drug delivery accordingly.
- Smart patches are being developed for a wide range of applications, including continuous health monitoring, personalized medicine, and disease management.

Throughout history, patches have evolved from simple poultices and plasters to sophisticated transdermal delivery systems capable of precise drug administration and real-time monitoring.

They have become an integral part of modern healthcare, offering convenience, effectiveness, and versatility in various medical and wellness applications.

TABLE 2: MARKETED TRANSDERMAL PATCHES [20]

Transdermal Patch	Drug	Company
Fentanyl Transdermal Patch	Fentanyl	Duragesic-100 (Generic name: fentanyl transdermal)
Catapres®	Clonidine	ALZA (Mountain View, California, USA)
Transderm-Scop®	Scopolamine	Vyteris (Fair Lawn, New Jersey, USA)
Transderm-Nitro®	Nitroglycerin	Empi (St. Paul, Minnesota, USA)
Nicotine Replacement Patch (NicoTouch)	Nicotine	Sparsha Pharma International Pvt. Ltd. (India)

TABLE 3: MARKETED SMART PATCHES [21]

Smart Patch	Technology used	Company
Disposable Patch	Various sensors	Covestro AG (in collaboration with accensors)
ReUse Patch	Electronics	Covestro AG (in collaboration with accensors)
Second generation devices	Power paper technology	ALZA, Vyteris, Empi, Power Paper
MEDICSEN Smartpatch	Needle-free drug delivery	Medicsen (based on patented skin permeabilization technology)

Smart Patches in Drug Delivery: Smart patches in drug delivery are meticulously designed to achieve precise control over medication administration while ensuring patient comfort and convenience. These patches typically consist of multiple layers, including a drug reservoir, a membrane for controlled release, and a backing layer for adhesion to the skin. Advanced materials such as hydrogels, microneedles, and biocompatible polymers are employed to optimize drug stability and enhance skin permeability. The design also incorporates microelectronics, sensors, and communication modules for real-time monitoring and feedback [22].

Smart patches offer a range of functionalities that enable tailored drug delivery strategies. They can deliver medications in response to specific physiological cues or external triggers, such as changes in biomarker levels, body temperature, or patient activity. Adaptive dosing algorithms integrated into the patch software enable personalized medication regimens based on individual patient characteristics and treatment goals. Additionally, some smart patches incorporate feedback mechanisms to adjust drug release rates dynamically, ensuring optimal therapeutic outcomes while minimizing side effects. Smart patches have diverse applications in drug delivery across various therapeutic areas. In diabetes management, for example, smart patches equipped with glucose sensors and insulin delivery systems offer continuous monitoring and automatic insulin administration, reducing the need for frequent injections and improving glycemic control. In pain management, transdermal patches deliver analgesic medications directly to the site of pain, providing targeted relief with minimal systemic side effects. Moreover, smart patches are utilized in hormone replacement therapy, smoking cessation, and contraception, offering convenient and discreet delivery of medications [22]. The design principles, functionalities, and applications of smart patches in drug delivery represent a significant advancement in medication administration technology. By combining precision dosing with real-time monitoring capabilities, smart patches offer personalized and adaptive drug delivery solutions that enhance therapeutic efficacy and patient adherence. As research and development in this field continue to progress, smart patches hold promise for revolutionizing drug delivery across a wide range of clinical settings, ultimately improving patient outcomes and quality of life [23].

Principle of a Smart Patch: The working principle of a smart patch involves a combination of advanced materials, sensors, and microelectronics to achieve precise drug delivery and real-time monitoring capabilities [24]. The mechanism of action varies depending on the specific design and functionality of the smart patch, but generally follows several key steps:

Drug Encapsulation: The smart patch contains a reservoir or compartment where the drug of interest is stored. The drug may be in the form of a liquid, gel, or solid formulation, depending on its properties and the desired release profile [25].

Controlled Release: The smart patch is designed to release the drug in a controlled manner over a predetermined period. This can be achieved through various mechanisms, including diffusion, osmosis, or external stimuli such as temperature, pH, or electrical signals.

For example, stimuli-responsive materials or coatings may change their permeability in response to specific environmental cues, triggering drug release when needed [26].

1. **Sensing and Monitoring:** Smart patches are equipped with sensors capable of monitoring relevant physiological parameters or environmental conditions. These sensors may include biosensors for detecting biomarkers, temperature sensors, accelerometers, or pH sensors. The data collected by the sensors provide real-time feedback on the patient's health status, medication response, or environmental factors[27].

2. **Feedback and Control:** Based on the information gathered by the sensors, the smart patch may adjust its drug release rate or dosage in response to changing conditions. This feedback loop allows for personalized and adaptive drug delivery tailored to the individual patient's needs. For example, in a glucose-responsive insulin patch for diabetes management, the patch may release insulin in response to elevated blood glucose levels, helping to maintain glycemic control [28].

3. **Communication and Connectivity:** Some smart patches are equipped with wireless communication capabilities, allowing them to transmit data to external devices such as smartphones, tablets, or cloud-based platforms. This enables healthcare providers to remotely monitor patients' health status, track medication adherence, and adjust treatment regimens as needed. Additionally, patients may receive alerts or notifications on their devices based on the data collected by the smart patch [29].

Overall, the working mechanism of a smart patch involves a dynamic interplay between drug delivery, sensing, feedback, and communication components to achieve precise and personalized healthcare interventions.

By harnessing the power of advanced materials and electronics, smart patches offer innovative solutions for drug delivery, diagnostics, and monitoring, with the potential to improve patient outcomes and quality of life.

Smart Patch Design: Materials Used and Emerging Methods

Materials Used:

Hydrogels: Hydrogels are widely employed in smart patch design due to their biocompatibility, flexibility, and ability to retain moisture. These materials can absorb and release drugs in response to external stimuli such as temperature, pH, or electric fields, making them ideal for controlled drug delivery applications. Additionally, hydrogels can incorporate drug reservoirs and sensors, enabling real-time monitoring and feedback within the patch [30].

Biodegradable Polymers: Biodegradable polymers offer the advantage of controlled degradation over time, allowing for sustained drug release while minimizing tissue irritation and foreign body reactions. Polymers such as polylactic acid (PLA), poly (lactic-co-glycolic acid) (PLGA), and polyethylene glycol (PEG) are commonly used in smart patch formulations. These materials can be tailored to achieve desired drug release profiles and mechanical properties, making them suitable for various drug delivery applications [31].

Conductive Materials: Conductive materials such as graphene, carbon nanotubes, and conductive polymers are integrated into smart patches to enable electrical sensing and stimulation capabilities. These materials facilitate the detection of physiological signals such as heart rate, muscle activity, and skin impedance, allowing for real-time monitoring of health parameters. Additionally, conductive materials can be used to deliver electrical stimuli for therapeutic purposes, such as neuromodulation and wound healing [32].

Microfabricated Structures: Microfabrication techniques are utilized to create precise and reproducible structures within smart patches, such as microneedles for transdermal drug delivery or microfluidic channels for on-chip drug synthesis and analysis. These microstructured features enhance the performance and functionality of smart patches by improving drug delivery efficiency, sensor sensitivity, and device integration[33].

Emerging Methods:

Nanotechnology: Nanotechnology holds promise for revolutionizing smart patch design by enabling precise control over drug encapsulation, release kinetics, and targeting capabilities. Nanoparticles, liposomes, and nanofibers can be incorporated into smart patches to encapsulate drugs, enhance skin penetration, and achieve sustained release profiles. Furthermore, nanomaterials can be functionalized with targeting ligands or stimuli-responsive coatings to achieve site-specific drug delivery and on-demand release [34, 35].

3D Printing: 3D printing technology offers a versatile and customizable approach to smart patch fabrication, allowing for rapid prototyping and personalized device manufacturing. By layering biocompatible materials in precise geometries, 3D printing enables the creation of complex structures within smart patches, such as drug reservoirs, microfluidic channels, and sensor arrays. Moreover, 3D printing enables the incorporation of patient-specific features, such as customized drug doses and anatomically conformable patch shapes [36].

Biosensing Technologies: Advances in biosensing technologies, such as wearable biosensors and implantable microdevices, are driving innovation in smart patch design. These technologies enable real-time monitoring of biomarkers, metabolites, and physiological signals, providing valuable insights into disease progression, medication response, and overall health status. By integrating biosensors into smart patches, healthcare providers can deliver personalized and timely interventions based on actionable data collected from the patient's body [36].

Bioinspired Design: Bioinspired design principles draw inspiration from nature to create smart patches with enhanced functionality and biocompatibility. For example, biomimetic materials such as silk proteins and extracellular matrices can be used to mimic the structure and properties of native tissues, promoting tissue integration and wound healing. Similarly, bioengineered systems inspired by biological organisms, such as microalgae-based photosynthetic patches or bacterial biofilms for drug production, offer novel approaches to sustainable and self-sustaining drug delivery platforms [37]. In smart patch design continues to evolve with the integration of advanced materials and emerging fabrication methods.

By leveraging these innovations, smart patches hold promise for revolutionizing drug delivery, diagnostics, and therapeutics, offering personalized and precision healthcare solutions for improved patient outcomes.

Advancements Leading to Smart Patches: The transition from conventional patches to smart patches has been driven by advancements in microelectronics, materials science, and biomedical engineering. Smart patches incorporate sensors, microprocessors, and drug delivery systems, allowing for personalized and targeted drug administration. By integrating real-time monitoring capabilities with drug delivery functionality, smart patches offer unprecedented control and precision in medication dosing and timing [38].

Global Connected Smart Drug Delivery System:

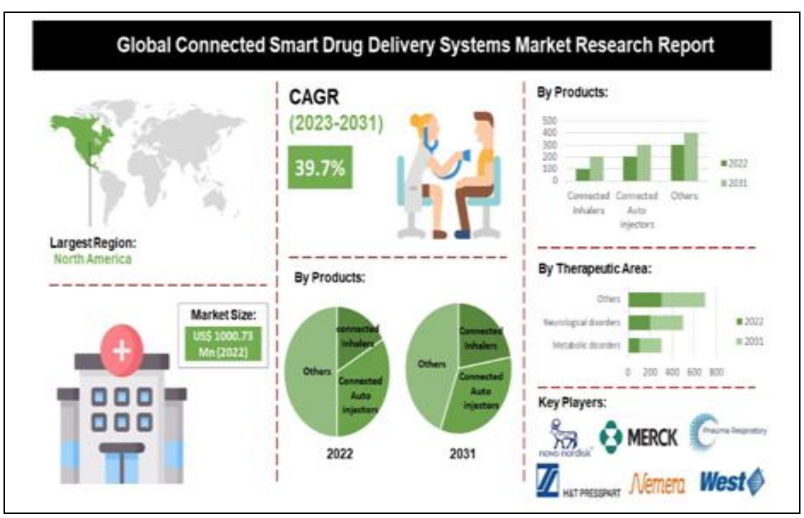


FIG. 2: STATUS OF GLOBAL CONNECTED SMART DRUG DELIVERY SYSTEMS

Global Connected Smart Drug Delivery Systems Market Research Report [39]:

CAGR: The projected compound annual growth rate (CAGR) from 2023 to 2031 is 39.7%.

Largest Market: North America is identified as the largest region in this market.

Market Growth: The market size is expected to grow from US$ 1002.8 million in 2022 to a higher value in 2023.

Product Trends: Significant growth is expected in connected inhalers and auto injectors, with other products also showing an increase.

Therapeutic Areas: Neurological and metabolic disorders are anticipated to see increased use of smart drug delivery systems.

Key Players: Notable companies in the market include Novartis, MERCK, HT Presspart, Nemera, and West. This data reflects the market trends and potential areas of interest for stakeholders in the connected smart drug delivery systems industry.

Challenges and Considerations: Despite their potential, smart patches face challenges related to regulatory approval, scalability, and user acceptance. Ensuring the safety, efficacy, and reliability of smart patch technology requires rigorous testing and validation processes [40].

Moreover, addressing concerns regarding data privacy and security is essential to maintain patient trust and compliance. Collaboration between stakeholders across academia, industry, and regulatory agencies is needed to overcome these challenges and facilitate the widespread adoption of smart patches in drug delivery.

Future Directions: The future of smart patches in drug delivery holds promise for continued innovation and advancement. Emerging technologies such as nanomedicine, microfluidics, and wearable sensors are expected to further enhance the capabilities of smart patches, enabling personalized and targeted drug delivery strategies. Additionally, advances in data analytics and artificial intelligence will enable smart patches to generate actionable insights for precision medicine and improved patient outcomes.

CONCLUSION: In conclusion, the evolution of patches from simple transdermal systems to smart patches represents a significant advancement in drug delivery technology. Smart patches have the potential to revolutionize medication administration by offering personalized, precise, and adaptable drug delivery solutions. While challenges remain, ongoing innovation and collaboration are driving the development of smart patch technology, paving the way for a future where drug delivery is safer, more effective, and more patient-centric.

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CONFLICT OF INTEREST: Nil

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