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ADVANCEMENTS IN TARGET DRUG DELIVERY: ROLE OF TRANSDERMAL PATCHES IN PRECISION MEDICINE

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ABSTRACT
Modern pharmacotherapy has undergone a radical change thanks to targeted drug delivery systems (TDDS), which maximize treatment efficacy while reducing systemic side effects. By delivering active medicinal ingredients straight to particular cells, tissues, or organs, these methods increase bioavailability and decrease off-target interactions. Transdermal patches have been a popular non-invasive, patient-friendly platform among TDDS techniques that may sustain regulated drug delivery for prolonged periods of time. The basic ideas and categories of targeted drug delivery are examined in this study, including stimuli-responsive carriers, ligand-receptor-mediated targeting, and nanotechnology-based strategies including liposomes, dendrimers, and nanoparticles. To enhance drug penetration and site-specific action, particular attention is paid to the creation and improvement of transdermal patches that incorporate smart polymers, nanocarriers, and microneedles.

KEYWORDS: Target delivery, controlled release, nanocarriers, nanoparticles, microneedles.

INTRODUCTION

A technique for giving a patient medication that is more concentrated in some parts of their body than others is called targeted drug administration, or smart drug delivery. This delivery strategy, which is primarily based on nanomedicine, aims to overcome the drawbacks of conventional drug delivery techniques by employing drug administration mediated by nanoparticles.[1] To enhance regeneration processes, targeted drug delivery devices have been developed. The foundation of the system is a technique for gradually administering a certain dosage of a medicinal substance to a diseased area of the body. Because of its high level of integration, the drug delivery system necessitates collaboration between chemists, biologists, and engineers in order to be optimized.[2]

The ideal features of a targeted drug delivery system[3]

Targeted drug delivery system must have certain properties which include:

1. It should be stable, safe (non-toxic), compatible with body fluid and biodegradable.
2. Deliver the drug only to the target site.
3. Control the drug release at a predetermined rate.
4. The rate of drug release not affecting the pharmacological effect.
5. Minimum leakage of the drug during transportation to the target site.
6. Using an inert, biodegradable, or easily eliminated carrier.
7. The preparation process of the drug delivery system should be simple, easy and costless.

Fundamentals of target drug delivery

CARRIER SYSTEM

LIPOSOMES

Liposomes are tiny, naturally occurring phospholipid-based vesicles with a bilayer structure.[4] They have the ability to capture both lipophilic and hydrophilic medications in phospholipid or watery bilayers.[5–6] The physical and chemical characteristics of the medication, along with its lipid composition, affect the percentage of entrapped drug.[7] Huwyler et al. looked at using liposomal antitumor drugs to target tumors.[8]

NIOSOMES

Drugs that are hydrophilic or lipophilic can be contained in niosomes, which are non-ionic surfactant vesicles. Because of the intrinsic properties of phospholipid, niosomes are more stable than liposomes.[9–11] Niosomes

have demonstrated efficacy in targeting antiviral, antibacterial, antifungal, anti-inflammatory, and antitumor medications.[12] A novel daunorubicin (DNR) niosomal administration method was created and evaluated by Liu et al. to treat acute myeloid leukemia.[13] Piroxicam niosomes were developed by Ahmed et al. to target the pain location for analgesic and anti-inflammatory actions.[14]

NANOPARTICLES[15-16]

Nanoparticles have the potential to be effective drug transporters, and when paired with targeted ligands, they may resemble a "magic bullet." In the late 1960s, Professor Speiser created the first nanoparticles for drug administration and vaccination. Tetanus and diphtheria infections require multiple injections to reach appropriate antibody levels in the body. The goal was to develop extended medicine release from Nano capsules that may circulate in the bloodstream after intravenous injection.

MICROSPHEREs[17]

Microspheres are free-flowing powders composed of biodegradable proteins or synthetic polymers with particle sizes below 200 μm. A well-designed controlled drug delivery system can overcome some of the concerns with traditional therapy while also boosting the therapeutic efficacy of a specific medicament. There are numerous methods for delivering a therapeutic chemical to the target area in a sustained controlled release way. One option is to use microspheres as drug carriers. It is a dependable means of delivering medicine to the target location with specificity, if adjusted, and maintaining the desired concentration at the point of interest without side effects.

AQUASOME[18-19]

Aquasomes are nanoparticulate carrier systems, however instead of simple nanoparticles, they are three-layered self-assembled structures composed of a solid phase nanocrystalline core coated with an oligomeric film onto which biochemically active molecules are adsorbed, with or without modification. Aquasomes are sometimes known as "bodies of water" due to their water-like qualities, which protect and preserve delicate biological molecules. This ability to preserve structural integrity, as well as a high level of surface exposure, is employed to direct bioactive substances such as peptide and protein hormones, antigens, and genes to specified regions. These carbohydrate-stabilized ceramic nanoparticles, known as "aquasomes," were first developed by Nir Kossovsky.

TRANSDERMAL PATCHES

The transdermal patch is a transdermal carrier system that delivers medications directly into the bloodstream via the skin, allowing for precise treatment administration. Because the patch can manage drug release, it has the potential to lessen systemic side effects while boosting treatment efficacy. This is one advantage of this route over other methods of administering medication, such as oral, intravenous, and intramuscular. The primary goal of the transdermal drug delivery system is to transport the medicine into the systemic circulation via the skin at a predefined rate, with little fluctuation between patients.[20]

Advantages[21-22]

a) Due to the continual advancements in innovation plus the capability to deliver the medication to the site of action without disrupting the skin, transdermal delivery is becoming one of the foremost acknowledged methods of drug delivery.
b) Escaping drug exposure to the gastrointestinal tract (GIT), hepatic first-pass metabolism, enzymatic breakdown, and gastrointestinal discomfort.
c) Improves drug absorption and maintains a constant drug concentration in blood for a predefined duration.
d) Easy to scale up. Several drugs are commercially available as transdermal patches.
e) Improves patient compliance.
f) Reduced inter and intra-patient variability.
g) Decreases dose to be administered.
h) Minimizes gastrointestinal (GI) side effects.
i) It is easy to discontinue the treatment in case of toxicity or side effects.
j) Drug administration is possible in the case of unconscious patients.
k) Having a relatively large area of application compared to the buccal or nasal cavity.

Disadvantages[23]

a) Transdermal drug delivery systems are incapable of conveying ionic medications/drugs.
b) Drugs with a size greater than 500 Daltons are not appropriate for transdermal delivery.
c) It is not capable of reaching elevated drug levels in blood/plasma.
d) Possibility of skin irritation, erythema, and itching.
e) It cannot transmit drugs in a pulsatile fashion.
f) Long-term adherence causes discomfort to the patient.
g) Drugs with low or high partition coefficients cannot enter the bloodstream.
h) Lesser dose candidates are preferred for this type of drug delivery system.

TYPES OF PATCHES

1. Single-layer Drug in Adhesive

In this sort of patch, the adhesive layer adheres the numerous layers and the entire system to the skin while also responsible for medication release. The adhesive layer is protected by a temporary liner and backing.[24]

2. Multi-layer Drug in Adhesive

This type of patch is comparable to a single-layer patch in that both sticky layers contribute to medication release. However, in this system, another layer adheres to the drug and is normally separated by a membrane (although not always). This patch also has temporary and permanent liner layers.[25]

3. Reservoir
In this method, a drug reservoir is placed between the support layer and the rate-control membrane, and the drug is released via the micropore rate-controlled membrane. In the reservoir compartment, the medicine may be in the form of a solution, suspension, gel, or disseminated in a solid polymer matrix.

4. Matrix
The matrix system's two primary components are the adhesive and backing material, with the backing layer acting as the formulation's outer layer. Drugs and other additives, such as polymers and enhancers, are mixed together to generate an adhesive solution, which is then evaporated to form a matrix film. Following that, the matrix film and adhesive are placed to the backing film. The matrix patch is the most common form of transdermal patch on the market. One advantage of this matrix approach is that the patch produces a thin and elegant preparation, making it easier to use, and the production process is simple, rapid, and cost-effective.[26]

METHODS OF PREPERATION[27]
Solvent Casting/Evaporation Method
In solvent casting method, all the ingredients including polymer, copolymer and plasticizer are mixed together in a certain temperature. The drug containing solution is then added to the above mixture and stirred well. After all homogenization, the mixture is transferred into a Petri dish and is allowed to cool in room temperature leading to formation of a drug loaded transdermal patch.

Mercury substrate method
This approach is comparable to the solvent casting method. All of the materials, including polymer, copolymer, and plasticizer, are combined at a specific temperature. The drug-containing solution is then added to the aforesaid mixture and thoroughly mixed. The difference between the two procedures is that the mixture of polymer, drug, and plasticizer is poured over a mercury surface and covered with an inverted funnel to control solvent evaporation.

COMPONENTS
1. Polymer matrix/drug reservoir
The polymer in TDDS regulates drug release from the patch. As a result, the polymers utilized in TDDS must be both biocompatible and chemically compatible with medications and other system components including penetration enhancers and PSA. Aside from that, polymers must ensure consistent and effective medication delivery. Polymers are classified into two types depending on their source: natural polymers and synthetic polymers. The table below shows examples of polymers commonly used in transdermal preparations.

2. Membrane
The membrane controls drug release from the reservoir in a multilayer patch. The diffusion properties of the membrane are used to control the availability of drugs and/or excipients in the skin. For instance, ethylene vinyl acetate, silicone rubber, and polyurethane. These are used as a membrane to regulate drug release.

3. Drugs
The success of TDDS development is also determined by the drug to be used. For example, transdermal patches offer many advantages for drugs that undergo extensive firstpass metabolism, drugs with a narrow therapeutic window or drugs with short half-lives, leading to no adherence due to frequent dosing.

4. Permeation enhancer
Enhancers function to increase skin permeability to reach the desired therapeutic level. The ideal properties of enhancers are non-toxic, non-allergic, non-irritating, controlled and reversible enhancing action, pharmacological inertness, ability to act specifically for the predictable duration, chemical and physical compatibility with drugs and other pharmaceutical excipients, odourless and colourless.

5. Pressure-sensitive adhesives (PSA)
PSA is a material that adheres to the substrate, in this case, is leather, with a light force application and leaves no residue when removed. PSA polymers widely used in TDDS are polyacrylate, polyacrylate, polyisobutylene, and silicon-based adhesives.

6. Backing film
Backing films are selected for their appearance, flexibility, and the need for occlusion. Therefore, when designing a backing layer, it is of utmost importance to consider the material's chemical resistance. In addition, excipient compatibility should also be considered because prolonged contact between the backing layer and the excipient may cause the additives to detach from the backing layer or cause diffusion of the excipient, drug or enhancer penetration through the layer. These materials include vinyl, polyethylene, polyester, aluminium, and polyolefin films.

7. Other excipients such as plasticizers or solvents
a) Solvents: chloroform, methanol, acetone, isopropanol, and dichloromethane are used to manufacture drug reservoirs.
b) Plasticizers: dibutyl phthalate, triethyl citrate, polyethylene glycol, and propylene glycol are also added to provide plasticity to the transdermal patch.

ANALYSIS PARAMETERS
1. Organoleptic observations
Organoleptic patches can be observed visually, including colour, odour, flexibility and surface texture.[27]

2. Thickness test
The thickness of the patch can be measured using a calliper by dividing the five areas to be measured. Then the thickness of each side of the section is measured, and the average is determined.[28]

3. Weight uniformity test
This test is performed by weighing each patch on a digital scale and then determining the average value.[29]

4. Moisture content (%)
For 24 hours in a desiccator filled with calcium chloride, fabric patches have been produced, weighed, and stored at room temperature. The patch was weighed again after 24 hours in order to calculate its moisture content % using the formula:[30]
%moisture content= [Initial weight – final weight / Final weight] × 100.

5. Drug content
The drug content of the patch preparation was measured by dissolving a predefined amount of patch preparation in phosphate buffer saline (pH 7.4 0.05). A filter was placed over the solution, and the drug content was measured using UV or HPLC spectroscopy, respectively.[31-35]

6. Folding endurance
A film was folded and unfolded repeatedly at an identical location till it broke. The number of times the film was bent over on itself at a particular position without breaking was recorded as folding endurance. The experiment suggests the extent of flexibility or brittleness of the film.

MECHANISM OF ACTION
The greatest challenge for transdermal drug delivery is diffusing active substances through the barrier formed by the many layers of the skin. The outermost (and thickest) layer of the skin, the stratum corneum, contains numerous layers of keratin-heavy corneocytes. Additionally, the stratum corneum consists of 2 chemically different regions that must be accounted for when creating transdermal drugs. There is an aqueous region at the outer surface of the keratin filaments and a lipid matrix between the filaments that active medications must diffuse through to be effective.[36]

However, recent advancements have been made in the development of enhancement delivery methods for active drugs through the transdermal route. These methods are listed below.

- Microneedles: These are tiny needles that are either hollow or solid and filled with the desired drug. The microneedles pierce through the stratum corneum without causing a painful sensation. This method's advantages include painless delivery and delivering compounds with a higher molecular weight.[37-38]
- Iontophoresis: This method uses electrical driving force to drive charged particles across the stratum corneum via electrophoresis. Through this process, a persistent low-voltage current enables the diffusion of substances across the stratum corneum. An electrical current can control the drug delivery rate under the control of a preprogrammed microprocessor unit or the patient.
- Thermal portion: Applying heat to the skin creates small pores that allow the easy diffusion of molecular substances across the stratum corneum.
- Electroporation: Applying a high electrical voltage to the stratum corneum also creates small pores through which molecular substances can diffuse.
- Conventional enhancers: A chemical substance applied first to the skin to increase the stratum corneum's permeability or change the active drug's thermodynamics.
- Ultrasound: The application of sound waves to disrupt the stratum corneum and increase its permeability.[39-40]

RECENT ADVANCEMENT OF TRANSDERMAL PATCH
Traditional transdermal patches serve only two purposes: storage and release of drugs. While this method has some advantages, traditional patching has many challenges and drawbacks, for example limited dosage or low release. To date, there have been several advances in the field of transdermal drug delivery. These include the design of novel patches, which include the ability to sense and release drugs accurately, higher loading, and enhanced penetration and release of drugs. Overall, the field of transdermal drug delivery is an active area of research and development, with many exciting new developments on the horizon, as discussed below

SMART PATCHES: are equipped with sensors and other technologies that can monitor patient conditions and adjust drug delivery accordingly. In 2014, a group of researchers developed a microneedle-based smart patch sensor platform for painless and continuous intradermal glucose measurement for diabetics. This patch uses a conducting polymer such as poly (3, 4-ethylenedioxythiophene) (PEDOT) as an electrical mediator for glucose detection and as an immobilizing agent for the glucose-specific c-enzyme glucose oxidase (GOx).[41] Smart patches are also used to deliver natural compounds such as curcumin. The material consists of paraffin wax and polypropylene glycol as a phase change material (PCM). PCM was combined with graphene-based heating elements obtained by the laser scribing of polyimide films. This arrangement offers a new approach to smart patches whose release can be electronically controlled, and which allows repeated dosing. Emission is induced and terminated by controlled heating of the PCM rather than relying on passive diffusion, and permeation only occurs when the PCM transitions from solid to liquid. Curcumin delivery yields were found to be good and satisfactory.[42]

DISSOLVING/DEGRADABLE PATCHES
These patches are designed to dissolve on the skin and do not need to be removed and discarded. In general, these patches are made from biodegradable materials that are absorbed by the body after use. In a proof-of-concept paper published in 2019, researchers successfully administered the antibiotic gentamicin via a dissolving

patch in a mouse model of bacterial infection.[43] The results showed that a gentamicin-dissolving microarray patch applied to mouse ears could control Klebsiella pneumoniae infection. In addition, mice treated with lysing patches had reduced bacterial burden in nose-associated lymphoid tissue and lungs compared with untreated control. Medicina 2023, 59, x FOR PEER REVIEW 8 of 22 dissolving microarray patch applied to mouse ears could control Klebsiella pneumoniae infection. In addition, mice treated with lysing patches had reduced bacterial burden in nose-associated lymphoid tissue and lung compared with untreated control.

THREE-DIMENSIONAL (3D)-PRINTED PATCHES

Researchers are using 3D printing technology to create customized transdermal patches that can be tailored to the individual needs of each patient.[44] One good example is the use of a 3D-printed patch for wound healing. In a study by Jang et al., gelatin methacrylate (GelMA) was tested as a viable option with tunable physical properties. GelMA hydrogel incorporating a vascular endothelial growth factor (VEGF)-mimicking peptide was successfully printed using a 3D bio-printer owing to the shear-thinning properties of hydrogel inks. The 3D structure of the hydrogel patch had high porosity and water absorption properties. VEGF peptide, which is slowly released from hydrogel patches, can promote cell viability, proliferation, and tubular structure formation, indicating that the 3D Gel-MA-VEGF hydrogel patch can be used for wound dressing.[45]

APPLICATION IN DISEASE MANAGEMENT

Mental disorders

Mental disorder studies associated with transdermal patches include cases from schizophrenia, obesity, attention deficit disorder and substance abuse. Anxiety, depression and sleep disorders represent the majority of the studies. The addition of a new FDA-approved[46] transdermal patch (Secuado) to treat schizophrenia is an exciting addition to the TDD repertoire, as experts predict that it may raise the likelihood of treatment adherence for individuals detesting pills or invasive injections, while leading to fewer side effects since it bypasses the gut. The patch would also give experts assurance that patients are taking their medications.[47]

Cancer

Many trials are currently underway or have been executed to study the use of transdermal oestrogen in metastatic prostate cancer, fentanyl, buprenorphine and morphine patches to relieve cancer pain, and granisetron and other antiemetic drugs to help prevent nausea and vomiting associated with chemotherapy. Other studies include methylphenidate patches and their effect on fatigue caused by cancer and its treatment, nitroglycerin patches added to chemotherapy and radiation therapy treatments in order to improve progression-free survival in patients with metastatic non-squamous non-small-cell lung cancer (NSCLC), and rectal cancer, in addition to pilot studies that model the location on the body to place patches to test uniformity of TDD. Reviews have been undertaken to further understand the comparative efficacy of transdermal buprenorphine and fentanyl patches. Treatment of cancer pain, while still maintaining quality of life with minimization of adverse effects (nausea, diarrhoea, constipation, etc.), and avoidance of aberrant drug taking have been a long time goal of the World Health Organization (WHO), European Association for Palliative Care (EAPC) and the European Society for Medical Oncology (ESMO).[48]

Alzheimer's Disease (AD)

Rivastigmine, galantamine and donepezil represent the most common cholinesterase inhibitors that are used to treat senile dementia associated with Alzheimer's disease. The sustained-release and transdermal formulations are favoured over orally disintegrating tablets due to their rapid absorption through the gastrointestinal wall. Donepezil is considered to be a molecule with favourable physicochemical properties (MW of 379.5, Log P of 3.08–4.11), as well as Rivastigmine (MW of ~ 250 Da, and Log P of 2.1) for TDD. Donepezil patches were compared to pills (Aricept) taken daily in clinical trials, and a clinical study to evaluate the pharmacokinetics (PK) of Corplex^{TM} Donepezil TDS applied to different body locations have been completed. This resulted in Corium International, Inc. announcing a new key patent related to their once-weekly patch that delivers safe, effective and sustained delivery of the drug.[49-51]

CONCLUSION

Transdermal drug delivery systems (TDDS) have evolved significantly, offering a promising alternative to conventional drug administration routes by enhancing patient compliance, minimizing systemic side effects, and providing controlled drug release. The integration of innovative carrier systems—such as liposomes, ethosomes, solid lipid nanoparticles, and polymeric nanoparticles—has further improved drug permeability, stability, and bioavailability across the skin barrier. These carriers play a pivotal role in overcoming the stratum corneum’s restrictive nature, enabling the effective transdermal delivery of both hydrophilic and large-molecular-weight drugs. As research progresses, the convergence of nanotechnology, biomaterials, and pharmaceutical sciences is expected to yield next-generation transdermal systems that are safer, more efficient, and customizable to individual patient needs. Continued interdisciplinary collaboration will be essential to translate these advancements into widely accessible clinical applications, shaping the future of non-invasive therapeutic strategies.

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