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REVIEW ARTICLE

Advanced Analgesic Drug Delivery and Nanobiotechnology

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Abstract Transdermal administration of analgesic medications offers several benefits over alternative routes of administration, including a decreased systemic drug load with fewer side effects, and avoidance of drug degradation by the gastrointestinal tract. Transdermal administration also offers a convenient mode of drug administration over an extended period of time, particularly desirable in pain medicine. A transdermal administration route may also offer increased safety for drugs with a narrow therapeutic window. The primary barrier to transdermal drug absorption is the skin itself. Transdermal nanotechnology offers a novel method of achieving enhanced dermal penetration with an extended delivery profile for analgesic drugs, due to their small size and relatively large surface area. Several materials have been used to enhance drug duration and transdermal penetration. The application of nanotechnology in transdermal delivery of analgesics has raised new questions regarding safety and ethical issues. The small molecular size of nanoparticles enables drug delivery to previously inaccessible body sites. To ensure safety, the interaction of nanoparticles with the human body requires further investigation on an individual drug basis, since different formulations have unique properties and side effects.

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Key Points
Nanoparticles enable targeted drug delivery to the desired destination, reducing systemic toxicity and side effects.
Nanoparticles allow drug delivery to previously inaccessible body sites.
Nanostructures include nanosuspensions, spontaneously emulsifying systems, solid lipid nanoparticles and nanostructured lipid carriers, polymeric nanocarriers (e.g. dendrimers), inorganic nanoparticles, and hybrid carriers.
Our article discusses nanoparticles as enabling delivery of anti-inflammatories, analgesics, and local anesthetics.

1 Introduction

Transdermal analgesic medications delivery offers several benefits over alternative routes of administration, including the prevention of significant drug degradation by the gastrointestinal (GI) tract, resulting in a decreased required systemic drug load with fewer side effects. The transdermal route also offers a convenient mode of drug administration over an extended period of time, particularly in pain medicine, with an increased safety profile for drugs with a narrow therapeutic window [1, 2]. The primary goal of

transdermal drug administration is to overcome the skin absorption barrier [3]. Nanotechnology offers a novel method of enhanced dermal penetration for small-size molecules conferring a large specific delivery profile [2].

The first nanoparticles were initially developed at the end of the 20th century to serve as carriers for vaccines and cancer chemotherapeutic agents [4–6]. Over the past decade, nanotechnology has impacted the way drug delivery systems are developed, and nanoparticles are now approved by the US FDA for several indications [7, 8]. The National Nanotechnology Initiative defines nanoparticles as stable, solid colloidal particles, chiefly composed of biodegradable polymer or lipid materials, ranging in size from 10 to 100 nm [9]; however, this definition remains controversial considering size limits, with some scientists proposing nanoparticles as large as 1000 nm [8, 9]. A drug is absorbed into the nanoparticle by attachment to its surface, entrapment within the polymer/lipid, or dissolution into the particle matrix [10]. Drugs can be targeted to a specific site of action by conjugation with a tissue- or cell-specific ligand, or by coupling to macromolecules destined for the target organ [11].

A number of FDA-approved nano-analgesics are currently available. Exparel® (Pacira Pharmaceuticals, Inc., San Diego, CA, USA) is a liposome-based (DepoFoam®) bupivacaine topical formulation currently approved for use in adults [12]. DepoDur® (Pacira Pharmaceuticals, Inc.), approved by the FDA in 2004, offers an extended-release, liposomal formulation of morphine sulfate for use in postoperative pain management. The extended-release injectable formulation is supposed to provide 48-h pain relief after epidural administration; however, several adverse events have been reported, such as decreased oxygen saturation, vomiting, constipation, anemia, pyrexia, and pruritus. The FDA approval and marketing process for nanotechnology-based topical analgesic products is estimated to be expensive ($1 billion per new drug) and takes up to 15 years to be completed [13, 14].

Although nanomedicine addresses many of the challenges of drug delivery by improved drug stability, increased bioavailability, and decreased toxicity and side effects, the search for the perfect nanoparticle continues [15].

2 Nanoparticle Use in Transdermal Drug Delivery

2.1 Pharmacokinetics and Dynamics

Pharmaceutical companies have recently focused on improving the bioavailability of existing therapeutic agents while exploiting more selective methods of delivery in an effort to reduce systemic side effects [16].

At this time, biopharmaceutical and biotechnological drugs must be differentiated. According to the FDA, the former are derived from recombinant proteins, monoclonal antibodies, and nucleic acid-based products. In contrast, biotechnological drugs originate through processes such as fermentation, enzymatic processes, hybridomas, tissue and cell culture technology, and genetic engineering [17].

Factors that may affect the bioavailability of oral therapeutic agents include digestive mechanisms, including pH variability throughout the GI tract and permeability of cell membranes [16, 18]. The amplified hepatic metabolism of some drugs must also be considered [16, 18]. Chemical features contribute to the determination of drug bioavailability; therefore, drug delivery is dependent on hydrophilicity, solubility and intrinsic dissolution rate, described as the mass of drug dissolved per time unit and area of absorption [19]. In contrast, transdermal drug delivery faces relatively little degradation before reaching the target since first-pass metabolism is avoided [19].

The components of the skin (stratum corneum, epidermis, and dermis) provide a natural barrier to infections and unwanted chemicals, but also to beneficial therapeutic agents. Nanoencapsulation can assist therapeutic drugs in penetrating the skin, and the small size of nanoparticles facilitates the diffusion of drugs across the skin. Variables that may be improved by nanoencapsulation include drug efficiency, specificity and tolerability. Biodegradable nanoparticles are a focus of ongoing research [20].

2.2 Types of Nanostructures Used in Drug Delivery

Several materials have been used to enhance drug duration and transdermal penetration [19]. These nanostructures include nanosuspensions, spontaneously emulsifying systems (SESs), solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), polymeric nanocarriers (e.g. dendrimers), inorganic nanoparticles, and hybrid carriers [17, 19].

2.2.1 Solid Lipid Nanoparticles and Nanostructured Lipid Carriers

SLNs are composed of solid lipids, while NLCs are composed of both liquid and sold lipids. SLNs are accepted as one of the most suitable nanocarriers, presenting numerous advantages (Table 1) [21].

zur Müehlen et al. assessed the possibly of prolonged release of tetracaine, etomidate, and prednisolone incorporated in SLN carriers. The nanoencapsulation of the anesthetic drugs tetracaine and etomidate resulted in a rapid and high-yield burst of drug release, explained by a large specific surface area and a drug-enriched outer layer. The authors also demonstrated that prednisolone

Table 1 Advantages of solid lipid nanoparticles

Possibility of controlled drug release and targeting
Increased molecular stability
High drug payload
Incorporation of lipophilic and hydrophilic drugs
Nontoxic carrier
No organic solvents used to produce them
Large-scale production and sterilization

incorporated in the lipid matrix of SLN carriers had a greater stability compared with the free drug molecules due to its interaction with the matrix. Ultimately, the prolonged release of prednisolone SLNs demonstrated the suitability of SLNs as prolonged-release drug carriers [22].

Akbari et al. studied the skin permeation of naproxen-loaded SLNs, prepared by a probe ultrasonication method. The study demonstrated high concentrations of naproxen within the skin layers, and limited systemic absorption. The results indicate that naproxen SLNs can accomplish the local analgesic goals and avoid the possible systemic side effect of non-steroidal anti-inflammatory drugs (NSAIDs) [23].

Wang et al. studied in vivo the analgesic effects of lidocaine NLC gel versus standard lidocaine hydrochloride (HCl) solution. The study concluded that lidocaine NLC gel presented better penetrative qualities, enhancing drug delivery through the skin and increasing the pain threshold when compared with the lidocaine HCl solution (38.55 ± 9.38% vs. 19.05 ± 5.23% permeation) [24].

Basha et al. concluded that benzocaine-loaded SLN hydrogel was more effective than benzocaine hydrogel when considering the intensity and duration of anesthetic effect [25].

2.2.2 Polymeric Structures

Polymeric nanoparticles are solid colloidal particles with diameters of up to 1000 nm, with spherical, branched, or shell-shaped configurations [26]. These structures exhibit several favorable properties, including biocompatibility, biodegradability, and wide functional capabilities, which make them desirable for drug delivery. Drugs are encapsulated within the polymers, allowing better pharmacokinetic control of the active drug molecule and a zero-order kinetic profile, maintaining steady levels of the drug at the delivery site compared with standard drug delivery routes (first-order kinetics) [27, 28].

2.2.3 Dendrimers

Dendrimers are highly branched nanostructures produced from large molecules, with an inner core and size range

between 1 and 100 nm [11, 27]. It is the number of branches, well-defined molecular weight, stability, and globular structure that make these particles effective carriers for drug delivery. Dendrimers are typically composed of one or more of the following polymers: polyamidoamine (PANAM), polypropylenimine, and polyaryl ether [29–32]. Drugs in dendrimers are either incorporated into or attached to the surface of the nanostructure [33].

PAMAM dendrimers have been shown to successfully deliver NSAIDs such as indomethacin, diflunisal, and ketoprofen. Compared with pure drug suspension administration, transdermal PAMAM dendrimer use in rat models showed significantly greater bioavailability [34, 35]. Administration of PAMAM dendrimers with surface amino groups loaded with indomethacin resulted in 1.6-fold greater bioavailability than a free indomethacin suspension [34]. Likewise, drug bioavailability was 2.73-fold greater for a ketoprofen-loaded PAMAM dendrimer complex than a free ketoprofen suspension, and 2.48-fold greater for a diflunisal-loaded PAMAM dendrimer complex than a free diflunisal suspension [35].

2.2.4 Liposomes

Liposomes were first described in 1961 by Alec D. Bangham, and remain among the most widely used nano-sized drug carrier aggregates [36, 37]. They are small, artificial vesicles composed of natural or synthetic phospholipids designed to be phagocytized to prevent drug degradation, increase target specificity, and reduce side effects. On average, liposomes have a diameter of approximately 75 nm in order to provide ideal encapsulation volumes [37]. Applications of liposomes include transdermal drug delivery, reduced-toxicity antibiotic delivery, ophthalmic delivery, and treatment of parasitic infections [8, 11]. Liposomes are considered reliable drug carriers due to a number of advantages (Table 2) [3].

The success of liposomes as agents for transdermal drug delivery is owed to their interaction with the stratum corneum skin layer. Liposomes establish a retention effect in the stratum corneum and enhance their penetration at this

Table 2 Advantages of liposomes

No biotoxicity reported
Biocompatibility and biodegradability
Easy to prepare
Minimal loss of encapsulated drug volume
Sensitivity to pH and temperature
Hydrophobic and hydrophilic elements that interact with lipophilic and amphiphilic drugs

skin layer by altering the structure of the intercellular lipid lamellae [38, 39].

A major advantage of liposomal formulations of local anesthetics is the slow release and subsequent prolonged analgesic effect, while also keeping anesthetic serum levels nontoxic [3, 40]. A number of clinical studies have been conducted to compare free drug solutions with liposomal formulations of local anesthetics. Liposomal formulations of lidocaine or tetracaine were proved to exert a longer and more powerful effect than nonvesicular eutectic mixtures of local anesthetics (EMLAs) [41–44].

2.2.5 Carbon Nanomaterials

These are carbon-based, cage-like particles called nanotubes or fullerenes. Fullerenes are made up of 60 or more carbon bases with a polygonal configuration [27]. These particles have shown tissue-selective targeting and intracellular targeting of the mitochondria [45, 46]. Nanotubes and fullerenes exhibit properties that include low cytotoxicity and high biocompatibility, making them an excellent system for targeted drug delivery. Nevertheless carbon nanotubes may cause inflammation and fibrosis [47–49].

2.2.6 Metallic Nanoparticles

Metallic nanoparticles are a biomolecular conjugation of metals such as gold, silver, platinum, and palladium. This conjugation can be achieved with bifunctional linkages, lipophilic interaction, silanization (self-assembly with organofunctional alkoxysilane molecules), electrostatic attraction, and nanobead interactions [50]. They remain active for a long period of time and are mechanically durable [37]. Metallic particles are able to incorporate high drug loads due to a wide surface area; however, the use of those particles has been limited by their toxicity [11, 37, 50, 51].

2.2.7 Nanofibers

These particles are manufactured in different shapes, but are commonly assembled into membrane or tube shapes. Biodegradable, transmucosal polycaprolactone nanofiber patches delivering diclofenac sodium to treat tooth pain were successfully developed in 2012 by Grewal et al. These patches have demonstrated superiority in regard to patient compliance, safety, and therapeutic efficacy [52]. Transdermal drug delivery systems have demonstrated the ability to avoid hepatic first-pass metabolism, thus maintaining constant serum drug levels for a longer duration of time, with fewer side effects and increased compliance [53]. Nevertheless, slow-onset kinetics, delayed absorption after patch removal, lengthy half-life, and slow offset,

make such patches inappropriate for acute pain management [54–56].

2.2.8 Polymers

The flexible hydrophobic surface of polymers allows them to intercalate between the stratum corneum cells, causing a disruption in lipids, and facilitating drug passage through the skin [3]. Biodegradable polymers release drugs either by erosion or diffusion. During the release process, nanofibers act as sponge-like membranes due to the high osmotic pressure. The polymer matrix breaks down to form 'pores' for drug release. Polymer breakdown begins when its molecular weight decreases sufficiently, releasing drug as the matrix continues to dissolve [53].

Poly-lactic acid, poly-glycolic acid, and their poly-lactic-co-glycolic copolymers are among the most studied polymers for transdermal analgesic delivery. Nanospheres and nanocapsules (160–300 nm) obtained from poly-lactic-co-glycolic copolymers with and without oily cores were successfully tested for ropivacaine, benzocaine, and bupivacaine delivery [57–59]. The encapsulation efficiency was very low for ropivacaine (3.8%), and significantly greater for benzocaine (60%) and bupivacaine (75%), due to differences in charge and water solubility characteristics of this drug. However, the nanoencapsulation of ropivacaine significantly decreased its systemic toxicity. The composition of the oily core is an important factor in boosting the analgesia efficiency, per De Melo et al. [60].

In 2012, Karthikeyan et al. developed hybrid aceclofenac-loaded zein nanofiber/pantoprazole-loaded nanofibers, combining the advantages of protein materials and electrospun structures for dual drug delivery applications [61].

2.3 Nanotechnology for Transdermal Analgesic Drug Delivery

2.3.1 Nanotechnology for Wound and Burn Care

Wound healing is a process of tissue repair after injury and involves various phases, including hemostasis, inflammation, proliferation, and maturation [62]. A wound dressing ideally allows exudate absorption and maintains oxygen permeability, providing an optimal healing environment [29, 63]. Nanofibers exhibit properties including a wide surface area and open porous structure. Extracellular matrix structures also release components such as collagen and cytokines necessary for the repair of damaged tissues. These properties guide cellular drug uptake, promote healing, and reduce pain. Multiple drugs, including antibiotics, analgesics, and anti-inflammatory agents can be incorporated within nanofibers. Chen et al. investigated the in vitro release of vancomycin, gentamicin, and lidocaine

from novel electrospun sandwich-structured polylactide–polyglycolide (PLGA)/collagen nanofibrous membranes. The in vitro concentrations of vancomycin, gentamicin, and lidocaine released by these membranes was maintained 'well above the minimum inhibition concentration' for 4, 3 and 2 weeks, with bioactivity ranging from 30 to 100% for vancomycin and gentamicin, and 37 to 100% for lidocaine [64].

2.3.2 Tramadol Hydrochloride

Tramadol was first produced and marketed in the 1970s in Germany, intended for oral, rectal, intramuscular, intravenous, and subcutaneous administration. Currently, no transdermal via nanoparticles delivery has been reported. The FDA approved tramadol hydrochloride (TrHC) in 1995 as a treatment option for patients with moderate to severe pain. Tramadol is known to present a 'complex pharmacology', and its effects are mainly exerted in the central nervous system, demonstrating an agonist action in μ receptors, with a weaker effect in δ and κ receptors. In addition, it also exerts some action on monoamine receptors, affecting pain transmission through the spinal cord by decreasing the reuptake of norepinephrine and serotonin [65].

Advances in nanobiotechnology increased the efficacy of tramadol due to the introduction of new drug delivery systems. Less plasma variation and a long duration of action offer therapeutic improvements and better outcomes. Among the types of nanoparticles containing tramadol, different combinations have been described, such as those with chitosan-graft-poly (2-hydroxyethyl methacrylate-co-itaconic acid), hydrogels, microsphere, and PLGA, most of which have been used in vivo with promising results [66].

2.3.3 Nonsteroidal Anti-Inflammatory Drugs

NSAIDs are well-known for their association with GI toxicity (e.g. gastric irritation, abdominal pain and ulcers) and bleeding disorders [67]. Control of drug release and GI mucosa bypass seem to play an important role in avoiding NSAID-related GI toxicity [68]. Thus, transdermal NSAID administration through nanobiotechnology may offer both targeted therapy and a significantly improved drug safety profile.

Dias et al. used nanoprecipitation and dialysis methods to obtain acetylated cashew gum nanoparticles (CGN) of varying size and combine them with diclofenac diethylamine (DDA), an NSAID. The researchers concluded that CGNs offer 'successful' transdermal penetration for NSAIDs [69].

Similarly, Raj et al. studied the use of hydrogel-based glyceryl monostearate SLNs in conjunction with aceclofenac, an analog of diclofenac. The anti-inflammatory action of SLN-loaded aceclofenac was increased when compared with the control group, which received only transdermal aceclofenac without nanoparticle loading [70].

The increased bioavailability and decreased toxicity of NSAIDs have also been demonstrated by transdermal administration with PAMAM dendrimers. Compared with the administration via pure drug suspensions in rat models, the bioavailability of indomethacin, diflunisal, and ketoprofen via transdermal PAMAM dendrimers was 1.6-, 2.73-, and 2.48-fold greater, respectively [34, 35]. These studies demonstrate the transdermal capability of dendrimers and spark further interest in the development of new transdermal drug formulations with dendrimers as the skin penetration mediators.

2.3.4 Other Therapeutic Agents

A 2014 publication by Zhang et al. studied the in vitro and in vivo effects of transdermal aconitine delivery with an SLN and a microemulsion (ME) delivery system. Aconitine is a known highly toxic topical analgesic anti-inflammatory drug. The SLN and ME delivery systems reduced aconitine toxicity, increased solubility and stability, and improved drug duration of action. The high viscosity of SLNs may also have limited permeability. However, SLNs provided a 'reservoir' of the drug within the epidermis which was more slowly released over a longer duration. The authors concluded that SLN provided more effective and reliable means for aconitine release [1].

Following these promising results, in 2015 Zhang et al. published a new study, this time using SLN-delivered aconitine versus aconitine tincture. They concluded that SLN-delivered aconitine produced a superior analgesic and anti-inflammatory effect [71].

A preclinical animal study published by Tronino et al. in 2016 utilized NLC instead of SLN carriers to enhance the transdermal permeability of N-palmitoylethanolamine (PEA), an agent with anti-inflammatory and analgesic properties but poor percutaneous absorption. The study compared the anti-inflammatory effects of intravenous PEA versus transdermal NLC-loaded PEA, and noted a delayed effect in the NLC transdermal group versus the intravenous group. However, the NLC group experienced a much longer therapeutic duration of the drug, up to 24 h following administration, versus the intravenous group, where the anti-inflammatory effects of PEA began to fail after the 3-h mark. The NLCs' prevention of hydrolytic metabolism of PEA and its slow drug-releasing capability through a rapid maintenance and constant absorption phase demonstrate the usefulness of this transport system when longer duration of analgesia or anti-inflammatory effects are desired [72].

Anirudhan et al. studied amine-functionalized hyaluronic acid (HA) microparticles for transdermal lidocaine encapsulation. Interestingly, the study found that the transdermal patch matrix pH significantly affected lidocaine release, with almost no drug being released at pH 1.2 versus almost 80% drug release at 24 h when the transdermal patch matrix pH was 7.4. This pH-dependent effect was attributed to reduced hydrogen bond dissociation energy between the matrix and lidocaine molecules with increased pH. The authors concluded that the pH of transdermal microparticles and nanoparticles may also strongly affect other highly saturated transdermal drugs [73].

3 Conclusions

The use of nanotechnology in transdermal delivery of analgesics has raised new questions regarding safety and ethical issues. The low molecular size of nanoparticles enables drug delivery to previously inaccessible body sites. Furthermore, nanoparticles allow targeted drug delivery to the desired destination, with consequent minimal systemic toxicity and side effects. Less than 8% of publications on nanotechnologies report their toxicity. To ensure safety, the interaction of nanoparticles with the human body requires further investigation on an individual drug basis, since different formulations have unique properties and side effects.

Compliance with Ethical Standards

Conflicts of interest Nicoleta Stoicea, Juan Fiorda-Diaz, Nicholas Joseph, Muhammad Shabsigh, Carlos Arias-Morales, Alicia A. Gonzalez-Zacarias, Ana Mavarez-Martinez, Stephen Marjoribanks, and Sergio D. Bergese declare that they have no conflicts of interest to disclose.

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