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Review

Biomaterials for drug delivery patches

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ABSTRACT

The limited efficiency of conventional drugs has been instigated the development of new and more effective drug delivery systems (DDS). Transdermal DDS, are associated with numerous advantages such its painless application and less frequent replacement and greater flexibility of dosing, features that triggered the research and development of such devices. Such systems have been produced using either *biopolymer*; or *synthetic polymers*. Although the first ones are safer, biocompatible and present a controlled degradation by human enzymes or water, the second ones are the most currently available in the market due to their greater mechanical resistance and flexibility, and non-degradation over time. This review highlights the most recent advances (mainly in the last five years) of patches aimed for transdermal drug delivery, focusing on the different materials (natural, synthetic and blends) and latest designs for the development of such devices, emphasizing also their combination with drug carriers that enable enhanced drug solubility and a more controlled release of the drug over the time. The benefits and limitations of different patches formulations are considered with reference to their appliance to transdermal drug delivery. Furthermore, a record of the currently available patches on the market is given, featuring their most relevant characteristics. Finally, a list of most recent/ongoing clinical trials regarding the use of patches for skin disorders is detailed and critical insights on the current state of patches for transdermal drug delivery are also provided.

1. Introduction

Drug delivery systems (DDS) have been appointed as effective platforms to improve the pharmacological and therapeutic properties of drugs. These systems not only aid the handling and administration of drugs but also help the drug to overcome certain barriers such as the low solubility caused by drug's hydrophobicity reaching the targeted tissues without premature degradation (Allen and Cullis, 2004). Skin provides a large and readily accessible surface area for application and absorption of a patch-like device to its surface, constituting a non-invasive procedure that will promote a continuous intervention (Prausnitz et al., 2004). In the last years, transdermal DDS have been exploited as a successful controlled drug release platform that have received regulatory approval for a series of products (Wiedersberg and Guy, 2014). Transdermal DDS can be applied when a drug has a significant first-pass effect in the liver, being prematurely metabolized. Such type of drug delivery also allows for less frequent dosing or steady delivery profiles and may be easily applied with a painless application. Moreover, transdermal DDS promote a fast absorption of drug in superficial tissues, improving the wound healing process (Guy, 2010; Naik et al., 2000).

Distinct designs of transdermal DDS have been proposed ranging from the humblest system, based on passive drug delivery with little/no permeation enhancement, to more complex transdermal DDS that enable the delivery of small molecules and macromolecules (Prausnitz and Langer, 2008). The choice among these patches can mostly depend on the drug properties (e.g. molecular weight and physicochemical characteristics), as well as the required amount and release rate to accomplish an effective treatment (Naik et al., 2000). Drug carriers (either at nano- or micro-scale) can be incorporated in patches in order to improve drug pharmacological properties, prompting a more efficient treatment of such devices (Allen and Cullis, 2004).

This review highlights the efforts that have been performed in the last years regarding the production of patches with different designs and their potential application as drug delivery systems. Pros and cons of the currently available systems will be discussed, and future prospects will be discussed.

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2. Drug delivery systems

Conventional (“free”) drugs exhibit limitations that can be improved through their incorporation in DDS. The chemical nature of the drug molecule can be responsible for its poor solubility resulting in drug precipitation when in aqueous media. The use of drug carriers such as lipid micelles or liposomes, among others, can surpass this major limitation improving drug solubility (Lukyanov and Torchilin, 2004). Another common problematic is the expeditious breakdown of the drug in vivo due to physiological conditions, such as pH and enzymes. Such degradation that leads to a notable loss of drug activity can be prevented through the use of DDS that will protect the drug from premature enzymatic degradation (Qiu and Park, 2001). Moreover, drug carriers empower less non-specific distribution, reducing unwanted/toxic side effects in healthy tissues. DDS can be designed to improve selectivity towards the targeted tissues and cells (like for instance, targeting specific enzymes and membrane transporters), allows for an increased drug concentration in the specific site of action, enhancing drug effects in the diseased area (Han and Amidon, 2000; Jain and Chourasia, 2003). Through the association of particular carrier systems with conventional therapeutic molecules, properties such as pharmacokinetics and biodistribution are strongly improved allowing an improved therapeutic outcome at the target tissue (Takakura and Hashida, 1996).

3. Transdermal drug delivery systems

Although many efforts have been developed to promote topic/transdermal drug delivery, the systemic route is still the major strategy used for drug administration. A drug administered by this method reaches the systemic circulation (blood) inducing, therefore, a systemic action. On the other hand, drugs given by the topical route are mainly applied on skin or mucous membrane, being able to promote both of systemic and localized action (Berlin et al., 1997; Das Kurmi et al., 2017; Tanner and Marks, 2008; Wiedersberg and Guy, 2014). Transdermal DDS are not capable of performing a rapid drug input but are usually designed to retard and sustain the delivery of the drug (Naik et al., 2000), promoting a continuous intervention with system repositioning, removal or replacement.

In the last years, transdermal drug delivery has been exploited as a successful controlled drug release platform that has received regulatory approval for several products, with a large majority already available in the market (Wiedersberg and Guy, 2014). The worldwide transdermal patch market approaches £2 billion in USA, being the patches the most marketed transdermal DDS (Rizwan et al., 2009). There are several parameters that affect the delivery of the drug from the patch to the skin. Absorption, for instance, depends on the site of application, thickness and integrity of epidermidis, size of drug molecule, permeability of the drug delivery membrane, degree of skin hydration, pH of the drug, drug degradation by skin flora and body conditions, such as body temperature, that are responsible for blood flow alteration (Biradar and Sanghavi, 2014; Wokovich et al., 2006). Skin thickness and blood flow are two parameters that vary with age and are responsible for different responses to the same transdermal device, a notable effect on pharmacokinetics of the drug (Wokovich et al., 2006).

Transdermal devices can be divided based on their design in reservoir-type and matrix-type patches as briefly represented in Fig. 1A and B (Tanner and Marks, 2008). The reservoir-type patches allow the sustaining of the drug in a solution or gel, and its delivery is governed by a rate-controlling membrane that is positioned between the drug reservoir and the skin (Suedee et al., 2008). On the other hand, matrix-type patches, that were introduced in the 80s (Yutaka Konno et al., 1985), are characterized by a simple design based on the incorporation of drug in an adhesive. A mechanical backbone is used as an outer layer to prevent loss of drug from the adhesive. This design does not involve rate-controlling membranes and the rate of drug delivery is achieved through skin permeability. (Wokovich et al., 2006) The reservoir-type patches have been showing more advantages in terms of tighter control over delivery rate, not being influenced by the skin condition and intra- and inter-individual variations such as temperature and skin type. The rate limiting membrane will control the rate of drug delivery (Prodduturi et al., 2010).

4. Barriers to transdermal delivers

Skin is a highly efficient barrier that limits molecular transport both from and into the body, preventing molecular permeation. This natural barrier avoids the penetration of foreign molecules such as the flux of toxins, while minimizing the water loss (Brown et al., 2006). Skin is composed by multi-layers. On skin's outer surface there is a non-living layer of keratin-filled cells surrounded by a lipid-rich extracellular matrix named stratum corneum (SC), an extremely thin biomembrane (approximately 100 μm) that is considered the least permeable of the skin layers. SC has been proposed to play an important role in the barrier function and is the ultimate stage in the epidemical differentiation process, forming a laminate of compressed keratin filled with corneocytes attached in a lipophilic matrix (Christophers, 1971). The matrix lipids allow a continuous phase from the skin surface to SC base. The intercellular lipid lamellae form a conduit in which the drugs diffuse to access vascular infrastructure and, ultimately, to the systemic system (Elias, 1981; Naik et al., 2000). Nevertheless, due to SC high diffusional resistance, the transdermal permeation of a large pool of drugs is highly limited in a mechanism of passive permeation (Brown et al., 2006).

Pharmacologically potent drugs requiring small therapeutic blood concentrations (ng ml^{-1} or less), are usually subjected to passive transdermal delivery. The SC is a very selective barrier and only molecules with the adequate physicochemical properties can be transported across this outer layer. (Golden et al., 1987; Naik et al., 2000) The lipophilic nature of SC's barrier promotes a better acceptation of lipophilic molecules. Still, for an accurate passive permeation, the ideal drug should be amphiphilic and sufficiently “mobile” to diffuse across the SC. If the drug is only hydrophilic, the molecule will be unable to cross the SC. On the other hand, a lipophilic drug will tend to remain on the SC layer (Lipinski, 2000; Naik et al., 2000). Solute diffusivity decreases exponentially as molecular volume (related to molecular weight) increases. A favorable transport across the skin is normally achieved with restriction of drug particles molecular weight (< 500 g/mol). Also, an increased drug flux is favored when saturated drugs' solution are used. Conclusively, in order to improve transcutaneous fluxes, it is necessary to increase solute concentration and use an amphiphilic drug (Naik et al., 2000).

4.1. Enhancing skin permeation

Relatively poorly permeable molecules (e.g. high molecular weight and hydrophobicity) can be modified in order to improve their permeation through skin layers. Table 1 summarizes the advanced techniques to enhance drug delivery. Drugs per se can be modified, for example, by a derivatization strategy to alter the lipophilic nature of the drug. Other chemical modifications as well as physical alterations can also be performed in order to improve drugs permeation (Naik et al., 2000; Prausnitz et al., 1993).

However, current approaches are focused on the enhancement of skin permeation, being devoted to the development of new active and passive methods that improve membrane's permeability (Naik et al., 2000). Passive methods include the actual vehicles - creams, gels and “passive” patches. Some modifications have been proposed such as the use of penetration enhancers, supersaturated systems or drug-carriers liposomes. Chemical penetration enhancers have the ability of compromising skin's barrier allowing the entry of poorly penetrating molecules through the membrane (Naik et al., 2000). Chemicals like