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3D printing applications for transdermal drug delivery

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ABSTRACT

The role of two and three-dimensional printing as a fabrication technology for sophisticated transdermal drug delivery systems is explored in literature. 3D printing encompasses a family of distinct technologies that employ a virtual model to produce a physical object through numerically controlled apparatuses. The applicability of several printing technologies has been researched for the direct or indirect printing of microneedle arrays or for the modification of their surface through drug-containing coatings. The findings of the respective studies are presented. The range of printable materials that are currently used or potentially can be employed for 3D printing of transdermal drug delivery (TDD) systems is also reviewed. Moreover, the expected impact and challenges of the adoption of 3D printing as a manufacturing technique for transdermal drug delivery systems, are assessed. Finally, this paper outlines the current regulatory framework associated with 3D printed transdermal drug delivery systems.

1. Introduction

The application of various therapeutic substances such as herbal ointments or various drugs (e.g. scopolamine, estradiol, fentanyl, rivastigmine) on the human skin is an ancient practice for medical as well as cosmetic purposes. Skin has always offered a large, “easily” accessible area for drug administration and scientific progress for the past decades (Prausnitz and Langer, 2008; Alkilani et al., 2015; Pastore et al., 2015), which illustrates that systematic therapy through percutaneous drug absorption is actually feasible. The transdermal route is an appealing alternative to the traditional administration routes; orally or through hypodermic injections. The first has been associated with efficiency issues in case of partial absorption of the drug, gastrointestinal metabolism-related complications and slow effect that renders it prohibitory for emergency cases. On the other hand, hypodermic injections are invasive and irritating, pose risks of infection (e.g. poor sanitation, immunosuppressed patients, needle re-usage in developing countries), requires administration by medically trained professional and generate medical waste (Awodele et al., 2016). On the contrary, in transdermal systems the drug does not pass through any metabolic systems, yielding higher degrees of bioavailability while it can be used as a tool to promote the sustained and controlled drug release. Moreover, due to the plethora of dendritic cells in the skin, vaccination through Transdermal Drug Delivery (TDD) is a promising alternative to typical vaccination routes. Furthermore, it is a patient-friendly approach since it is non-invasive, contributing thus to the psychological welfare of the patient,

while it does not require professional care and experience when the system needs repositioning, removal or replacement, providing the patient with independency.

However, TDD is not always naturally feasible. The major limitation of this route comes from the nature of the skin barrier itself. The outermost layer of the skin, the *Stratum Corneum* plays the dominant role in the impermeability of the barrier, being very dense and significantly low in hydration (15–20%). Circumventing, neutralizing or bypassing this impermeable barrier has been the actual research subject behind the TDD science and simultaneously the key to its future progress. Nowadays, the shift towards a more personalised patient care is a global trend in medicine and pharmaceutics. In this context, traditional fabrication methods of drug delivery systems that are mass-produced and mass-oriented are questioned in terms of permitting the tailoring of dosages according to individual patients' needs in a cost-effective and direct manner. To serve this purpose, the potential of new, cutting-edge technologies is investigated, using Additive Manufacturing (AM; e.g. 3D printing) being a very promising candidate. Since its introduction in the 1980s (Hull, 1984; Maulvi et al., 2017), this pioneering technology has attracted augmenting attention by several industries (e.g. automotive, aerospace, orthopaedics), proactively contributing to the minimisation of fabrication times and enabling the production of complicated structures beyond the complexity that any conventional technique can achieve. The introduction of 3D printing in pharmaceutical technology is a relatively recent attempt (Goole and Amighi, 2016), aiming to the production of targeted-release and customized drug delivery systems

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(Alomari et al., 2015). In the field of TDD systems the relative studies published are still limited, but demonstrate the untapped potential of 3D printing to completely alter stereotypical TDD systems. A review of the latter in combination with the up-to-date research on the use of 2D and 3D printing as a direct or indirect fabrication method of TDD systems, is presented. In this framework, materials and drugs that have been researched in association to 3D printing TDD systems are also reviewed.

2. Transdermal drug delivery systems: past and current trends

The ability to effectively convey drug molecules to lower skin layers where the drug will pass to the circulation through the rich capillary vasculature of the dermis, has been explored for a variety of materials (e.g. polymeric systems, metallic microneedles) and methods (e.g. transdermal patches, iontophoretic systems, chemical permeation enhancers). The first TDD systems acted as precursors of the modern methods and they feature the application of the medicine-containing formulation directly onto the skin, allowing for the absorption of drug molecules and their entrapment within the stratum corneum. The latter then operates as a tank, slowly channelling the drug into the epidermis. In the early systems, the whole drug amount was administered in one single dosage, through the topical application of ointments, gels and sprays, a method applied mainly for treating vascular diseases and hormone replacement (Prausnitz and Langer, 2008).

2.1. Patches

The transdermal drug therapy drew worldwide attention when the transition from the patchless systems to the TDD patch occurred in the 1970s with the introduction of the scopolamine patch (Graybriel et al., 1976), aiming to a more sustained, controlled and safe mode of drug delivery. The drug-storing patch is a multi-layered structure that generates a steady drug flux to the skin, permitting thus the continuous delivery within a prolonged period of time. Patches are designed following two distinct strategies; the first design, the ‘reservoir patch’, includes a compartment where the drug is stored in an appropriate formulation, while a membrane governs the delivery to the skin surface. This design yields generally stable release rates (Shaw and Theeuwes, 1985), yet overdose incidents have been reported due to defective membranes (Mansfield and Jatoi, 2013).

On the other hand, the ‘matrix patch’ was designed in an attempt to avoid the drawbacks of the reservoir-type patch and features the incorporation of the drug uniformly into a matrix, from which it is released to the skin (Margetts and Sawyer, 2007; Pastore et al., 2015). There are two main subcategories of this design, the first consists of a drug-containing polymer, while an adhesive substance is added to the system to reassure a stable fitting onto the skin. Alternatively, the design includes only the adhesive, where the drug is contained.

TDD patches initially gained a significant popularity with a number of patch-based systems actually being commercialised. Nowadays there is a range of commercial patches for the administration of various drugs, such as antidepressants under the name Emsam (Jessen et al., 2008), contraceptives under the name EvraTM/Ortho EvraTM (Abrams et al., 2002) and for the treatment of Alzheimer’s symptoms under the name Exelon (Dhillon, 2011). However, the broader adoption and application of the transdermal patch was hampered by a number of restrictive factors. Initially, due to the fact that after the absorption the drug is initially stored into the stratum corneum and then is gradually diffused to the lower tissues, there is a time interval between the system application and the effective drug concentration reaches a minimum therapeutic value. In this framework, efficiency issues may arise in case of drug crystallisation on the skin until diffusion or within the formulation during storage (Hadgraft and Lane, 2016). Moreover, the microporous membranes employed in the reservoir-type patch, reassure that the delivery rate is much lower than the rate of natural skin

absorption, which resolves the problem of varying diffusion rates from one skin to another, but hinders the potential of delivery in higher rates. Therefore, it is evident that for both patch designs, the maximum delivery rate reachable is equal to the one that is naturally permitted by the physiology of the stratum corneum. The forenamed limitations illustrate that those systems are unsuitable for fast, bolus-type drug administration.

Another major disadvantage stems from the fact that these systems suffer from their dependency on the drug type. This limitation has restricted the drug palette notably in the past, while it poses serious challenges for the transdermal delivery of a broader range of drugs with larger molecular masses or hydrophilic features as well as of peptides and macromolecules.

To circumvent the limitations, several permeability enhancing methods (Prausnitz and Langer, 2008) have been introduced over the years, aiming in modulating the permeability of the skin and in boosting drug transportation using both passive and active approaches. It is nonetheless notable, that the majority for these approaches has been associated with excessive costs, skin irritation or even pain (Andrews et al., 2011; Roustit et al., 2014; Alkilani et al., 2015).

2.2. Microneedles

After the limited success that permeation enhancers presented on the progression of the TDD route to incorporate a larger variety of drugs in cost-effective and patient-compliant solutions, the idea that changed the way those systems are perceived and developed is summed up in the question: *Why not simply bypass the stratum corneum?* In this rather entrepreneurial logic, the concept of small, minimally invasive, micro-sized puncturing devices was developed, that efficiently disrupt the outermost, most impermeable layers of the skin to directly reach the skin microcirculation. The microneedle arrays and their applications have been the subject of thorough investigation in the previous few decades and they are considered significantly promising since their potential is not circumscribed by the permeability restrictions of the stratum corneum (Prausnitz, 2004). Therefore, hopes that microneedles will actualise the efficient delivery of hydrophilic drugs, vaccines and macromolecules, are brought (Vrdoljak et al., 2016; Wang et al., 2017; Zhao et al., 2017).

Microneedles are fabricated in varying dimensions; their height (25–2000 µm) reassures that the needles will reach the depth of the skin’s capillary system, while their diameter (50–250 µm in base and 1–25 µm in tip) ascertains that nerves contained in the dermis layer will remain intact upon application (Alkilani et al., 2015). This absence of pain in combination to the ability of self-application, makes microneedle systems highly patient-compliant (Kaushik et al., 2001).

Microneedle systems enable the realisation of multiple drug delivery approaches. Initial studies employed microneedles as a permeability enhancer prior to the application of a drug loaded patch (Wermeling et al., 2008). Silicon, polymeric or metallic microneedle arrays were utilised to create pores on the skin surface that facilitate the drug diffusion towards lower tissues (Larraneta et al., 2016). Subsequent approaches had a more direct character; the drug was actively driven through the skin to reach the systemic circulation. The role of such systems is twofold, as they effectively puncture the skin while they operate as vessels carrying the Active Pharmaceutical Ingredient (API). One of these approaches features the pre-coating of the microneedles with the desired substance. Various methods such as dip coating, gas jet drying, spray coating and electrohydrodynamic atomisation have been tested and employed for the coating of titanium, steel, silicon and polymeric microneedles (Haj-Ahmad et al., 2015). Coated microneedle systems have succeeded in the percutaneous rapid bolus delivery of macromolecules, drugs and vaccines, however there is a serious restriction regarding the amount of API that they can carry (e.g. less than 1 mg for a typical microneedle array) (Kim et al., 2012). Larger amounts of drugs have been successfully delivered by another type of

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