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Review Article

Potential of combined ultrasound and microneedles for enhanced transdermal drug permeation: A review

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ABSTRACT

Transdermal drug delivery (TDD) is limited by the outer layer of the skin, i.e., the *stratum corneum*. Research on TDD has become very active in the recent years and various technologies have been developed to overcome the resistance of the *stratum corneum* to molecular diffusion. In particular, researchers have started to consider the possibility of combining the TDD technologies in order to have further increase in drug permeability. Both microneedles (MNs) and ultrasound are promising technologies. They achieve enhancement in drug permeation via different mechanisms and therefore give a good potential for combining with each other. This review will focus on discussing the potential of this combinational technique along with other important issues, e.g., the mechanisms of ultrasound and MNs as it is and these mechanisms which are coupled via the two systems (i.e. MNs and ultrasound). We discuss the possible ways to achieve this combination as well as how this combination would increase the permeability. Some of the undeveloped (weaker) research areas of MNs and sonophoresis are also discussed in order to understand the true potential of combining the two technologies when they are developed further in the future. We propose several hypothetical combinations based on the possible mechanisms involved in MNs and ultrasound. Furthermore, we carry out a cluster analysis by which we determine the significance of this combinational method in comparison with some other selected combinational methods for TDD (e.g., MNs and iontophoresis). Using a time series analysis tool (ARIMA model), the current trend and the future development of combined MNs and ultrasound are also analysed. Overall, the review in this paper indicates that combining MNs and ultrasound is a promising TDD method for the future.

1. Introduction

Transdermal drug delivery (TDD) methods intend to deliver drug molecules to the blood circulation at a controlled rate for which the molecules need to pass through different sub-layers of the skin. TDD is developing fast and there are now many approved drugs for TDD, e.g., nineteen (19) drugs have been approved by the Food and Drug Administration, USA [1]. The potential of TDD for treating human diseases is also huge. For example, TDD can provide prolonged treatment time in the cure of chronic diseases whilst maintaining the permeation of the active drug molecules at a controlled level [2]. The diseases may be either psychological or physiological, and may need TDD ranging from nicotine patch for smoking cessation to the treatment of eczema [3,4]. However, the full potential of TDD is not fully exploited yet, which is evidenced by the fact that new questions continue to be asked on how to develop the TDD methods further, for example, to resolve specific issues and/or incorporate the latest technological advances. For instance, it has been asked if it is possible to make functionalised delivery system for vaccines that can be applied in a simple way such as topical administration [5]. To develop a TDD method for clinical purposes, one may require a significant amount of finances and many technical impediments would need to be resolved [6]. For example, it is evident that the market of TDD products has developed very fast and they were worth a market value of US $21.5 billion in 2010 which accounts for more than 12% of global drug delivery market. The development of the TDD market is predicted to reach US $31.5 billion by 2015 in which US $3 billion belongs to transdermal patch market [7]. However, the diversity of the drugs that could be delivered and various applications of these TDD techniques for treating human diseases are still limited.

Despite the commercial successes of the TDD methods, further development and success of these methods cannot solely depend on the transdermal patches. Improvement on the drug delivery efficiency and increment on the numbers of applicable drug

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molecules need to be achieved in the future by extending the TDD technology in multiple ways. In this regard, one of the main technical obstacles that should be overcome is the low efficiency on delivering large molecules such as proteins, vaccines, and microparticles [8] using the TDD methods. Microneedles (MNs) [9] and ultrasound [10] are two TDD techniques which work using different principles/mechanisms but they have shown great potential to remove this obstacle either on their own or in combination with each other. There are a number of publications now which have reviewed these two technologies on their own [11–15]. There are also some recent studies where MN and ultrasound have been combined to increase skin permeability of large molecule [16,17]. However, there is a lack of systematic review which discusses thoroughly the potential of combining MNs with ultrasound for enhanced drug permeation. Therefore, this review will focus on discussing the possible ways by which these two technologies could be combined. The first section of this paper will focus on explaining why the combination of MNs and ultrasound is important for TDD. The second and third sections will review the mechanisms of ultrasound and MNs, respectively, as these are the keys in the success of a TDD method that combines MNs and ultrasound. The fourth section will discuss the possible ways of combination and try to suggest what combinations one may be interested in the future with the help of a cluster analysis. The last section of the paper is the conclusion section of the paper. The scope of this paper is discussed further in detail later in this section.

1.1. Roles of TDD

In order to provide further context to this review paper, we discuss the roles of TDD method briefly in this section. Not until the 1940s, has the TDD been specialised as one of the most essential drug delivery methods including the parenteral delivery (hypodermic injections) and oral formulations (solutions, suspensions, tablets and capsules) [18]. The main advantages of TDD over drug delivery through other routes are that: (a) TDD is user friendly, so that it can prevent needle phobia and avoid the pain perceived during the parenteral delivery [19], (b) TDD can dodge the gastrointestinal and liver metabolisms which are the most common issues in oral drug delivery [20], and (c) TDD can provide long-term treatment without causing significant inconvenience, e.g., patients do not need to carry bulky medical instruments during the intravenous therapy which usually takes many hours [21]. In the past, the TDD methods mostly involved the uses of skin ointments and creams until a great progress was made in the 1980s when a transdermal patch was first introduced for the treatment of space motion sickness aimed at delivering scopolamine by attaching the transdermal patch on the back of the ear [22]. In general, the transdermal patches can prevent evaporations during treatment as well as achieve control rates of drug delivery [23]. However, their mechanism for drug delivery is based on passive diffusion. For this reason, the outermost layer of the skin, i.e., the *stratum corneum* (SC), restricts the choice of the drug molecule that can be administrated. For example, the molecular weight (MW) cut off for these molecules is generally taken to be under 500 Da [24] whilst their partition coefficient K_{ow} should be between 1 and 5 [25,26].

1.2. Different TDD technologies

It is a matter of fact that the transdermal patch is a low efficient method in terms of drug permeability and area of skin covered by drug transport. However, there are a number of other technologies which particularly aim to increase drug transport rate and they may extend the diversity of the drug molecules that may be used in TDD (e.g., microneedles [27], sonophoresis [28] and iontophoresis [29]). All of these technologies are non-invasive or minimally invasive, and thus they provide painless drug administrations.

The technologies that aim to enhance the permeability of the drugs through the skin as compared to transdermal patches alone can be grouped broadly according to the following five classifications: (i) methods that adjust the physicochemical properties of the drug molecules or increase the chemical potential of the drug solution to acquire better delivery rate, e.g., prodrug [30]; (ii) methods that tentatively alter the skin structure or modify the drug/skin partition coefficient to reduce the resistance of *stratum corneum*, e.g., chemical enhancers [31,32]; (iii) methods that deliver drugs or microparticles directly into skin with the help of particle accelerator, e.g., gene guns [33–36]; (iv) methods that use a gradient field (e.g., pressure gradient, electrical charge, any others) to induce convective flow increasing drug delivery rate, e.g., iontophoresis [37] and sonophoresis [38]; and (v) methods that physically disrupt or damage the skin to create new pathways which allow the drug molecules to be delivered through the skin barrier, e.g., MNs [39]. These five approaches are shown in more detail in Fig. 1. From the figure we can see that some TDD techniques may increase the diffusion rate via multiple mechanisms (sonophoresis, electroporation, etc.) whilst others may work similarly under the same categories. The combination of more than two or more than two techniques under the same category may not be able to yield a promising permeability increment due to the possible redundancy/suppression of a particular mechanism in the presence of another, e.g., microneedles and SC removal methods are both under category (iv) that aiming to bypass SC layer physically, thereby combining these two methods will be unnecessary. On the contrary, some TDD approaches indicate more potential for combinational methods because there are improved possibilities for them working in a synergetic way with another approach. Because the categories in Fig. 1 are subjectively divided, they are not necessarily able to provide every possible patterns of combination.

As stated earlier, the existing work in the literature suggests that it is possible to combine more than one method for enhancing drug permeability and there is a significant amount of work on different combinational approaches [40,41]. However, it needs to be pointed out that the researches on the development of individual technology are very important for the development of the combinational methods because the researches on the individual method can provide a better understanding and stronger bases for the applications of these technologies. These improvements are crucial factors to ensure diversity and quality of the combinations.

The ultrasound and MNs combination has covered four branches (categories ii, iii, iv and v) in Fig. 1 which suggests that there could be much more possible forms of combination in the future. To have better understanding on the possible combinations between ultrasound and MNs, a detailed review based on the mechanisms of both technologies is necessary which has been carried out on following sections. In order to discover more opportunities in the ultrasound and microneedles combination, the main mechanisms of these two techniques will be reviewed individually. However, there are also many other minor factors amongst those mechanisms which could be important in some circumstances or will become significant factors when accuracy of the TDD is taken into account. Therefore, these factors and their main mechanisms will be discussed (fourth section).

2. Ultrasound applications in TDD

The ultrasound participated applications cover many cross-cutting research areas which include physics, chemistry, biology, engineering, and others. One of the main areas where ultrasound has