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Short communication

Dissolvable layered microneedles with core-shell structures for transdermal drug delivery

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ABSTRACT

Microneedle (MN) systems for painless transdermal drug delivery have been developed in the past few years to overcome the issues of hypodermic injections. This study introduces a novel dissolvable layered microneedle (LMN) with core-shell structure for efficient transdermal drug delivery. Fabricated by three-step-casting method, the LMNs encapsulated the drug into the HA layer as a "shell", which is supported by PVA layer as core and base. When the LMNs are inserted into the skin, the drug would be released immediately once the HA layer were separated or dissolved. What's more, little drug would be wasted on the residual base after insertion. It is demonstrated that the mechanical property of LMNs is kept well with 100% insertion percentage at 60% relative humidity. Moreover, in the transdermal delivery *in vivo* test, almost 90% of drug in LMNs could be successful delivered into the skin with 10 s, while the homogeneous HA MNs with wide drug distribution need more than 120 s to reach the same efficiency. Owing to the advantages of stable mechanical property and rapid efficient drug delivery, the LMNs are more reliable and satisfied for the self-administration in the future.

1. Introduction

Hypodermic injection is now the norm for the delivery of various biopharmaceutics and vaccines [1–3]. Compared with the oral administration, injection provides a more direct and effective way to deliver the drug molecule into the subcutaneous issue or the blood stream, avoiding the first-past elimination in the intestine and liver [4–7]. However, the pain, bleeding and the risk of broken-needle injures associated with injections cause the dissatisfaction and low compliance from patients [8–10]. Other drawbacks of injections include the risks of inflection because of needle re-use [11], the issues of medical waste, as well the difficulty and inconvenience for self-administration at home by patients. Facing to the issues above, microneedle (MN) with shrinking dimension (100–1000 μm in length) has been developed and widely investigated as a potential route for drug delivery by combining the direct drug delivery and the minimal pain or injures [12–15].

Generally, the drug-loaded MNs involve two categories, coated microneedle [16–19] and dissolving MN (DMN) [20–23]. The former is fabricated by coating the drug formulation on the surface of rigid MN base, which could be made out of metal [18,19], silicon [24], and biocompatible polymers [17,25]. The drug loading method of coated MNs involve dipping [17] or layered spray coating [24] methods as is reported. As for the DMNs, the drug can be encapsulated into the solvable matrix and released into the skins after insertion with the dissolving of needles [20]. Considering this characteristic, the matrix of DMNs is usually water-solvable carbohydrate or polymers, such as maltose [21], trehalose [23], sugar [26], CMC [22], PVA [27], PVP [20], HA [28], silk [29], gelatin [30] and so on. Micro-molding method combined with the solvent-casting is the most used method in the fabrication of DMNs [29,31]. In some previous reports, the drug and the matrix formulation were firstly dissolved into a solvent. And then the mixture was cast into the MN mold at centrifugation or vacuum conditions [32]. Alternatively, the drug could be loaded into the mold firstly and following with matrix casting process [31]. For certain thermosensitive drug or vaccine, the molding and drying process of DMNs could be carried out at mild temperature to protect the pharmaceutical activity. In consideration of the inexpensive materials and easy manufacture process, the mass production of DMNs is more likely to be achieved in the future than that of coated MNs [31]. For these reasons, increasing number of researches tend to put much attention onto the DMNs for the cure of various of disease, such as diabetes [30], cancers [33–37], influenza [23,38,39], tetanus [40,41] and so on.

As is known, owing to the elasticity of the skin and the inferior strength of materials, DMNs are usually difficult to be fully inserted and dissolved in the skin [22]. To ensure effective insertions and rapid drug delivery during administration, a series of novel DMN has been

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introduced. For instance, tip-loaded DMNs could encapsulate the drug into the tips or the top part of needles [33,38,42,43]. In this case, the drug molecules could be delivered in to the skin immediately with the dissolving of DMNs tips. For another example, a kind of partially dissolvable arrowhead DMNs array is fabricated by assembling a dissolvable arrowhead structure onto a metal [44] or polymer [27,45] rigid shaft. The drug loaded into the arrowhead could be inserted into the skins fully with the support of the shafts with superior mechanical properties. However, for the tip-loaded DMNs, the mechanical strength of them could not be guaranteed especially under high-humidity conditions. For the arrowhead DMNs, the fabrication process is so complicate that the scalable productions could be it is difficult. This study introduced a novel dissolvable layered microneedle (LMN) with core-shell structure combining the mechanical strength and efficient drug delivery. In this design, the shell layer encapsulated drugs of LMN was made out of HA, and the drug-free core structure and backing of LMN were made out of PVA. After insertions in the skin, the drug loaded MN tips of HA layer would be released efficiently. More importantly, the shell structures provide nice mechanical strength for LMNs at high humidity conditions, which is meaningful for the stability of MNs at high moisture environment.

2. Results and discussion

To fabricate LMN with layered core-shell structures, based on MN mold, three separating casting process (*i.e.* the drug, HA and PVA layer casting) was used (Fig. 1a). Briefly, the drug solution was firstly cast into the cavities of mold and dried under vacuum. As a result, the drug was gathered into the tips after drying. And then, HA solution (20 wt%) was cast on to the mold to fill the cavities but the residual HA on the surface was removed. In this process, the drug was re-dissolved into the HA solution. Moreover, with the loss of moisture, a sunken structure was formed in the cavities of the mold. In the last casting process, a layer of PVA solution (20 wt%) was cast on to the mold to re-fill the sunken structure and also form the MN base in the meantime. Finally, a tip-drug-loaded laminated layered MN with HA as “shell” and PVA as “core” was produced. As a control, traditional dissolvable MNs with homogeneous instead of layered matrix were fabricated with similar mold casting method (as shown in the Fig. S1, Supplementary data). And the detailed description of materials and preparation processes of LMNs and traditional DMNs were described in the Supplementary data.

As shown in Fig. 1b, to distinguish the two layered in LMNs, the red sulforhodamine B was used as model drug loaded in HA layers, and FITC-BSA was mixed into PVA solution. Using microscope, it can be seen that the red model drug was gathered into the tips or the top layered of LMNs, and the border line of HA and PVA layers are clearly visible under fluorescent filed (Fig. 1b). To evaluate the insertion ability, the 5 × 5 LMN arrays were inserted into the porcine skin with a home-made applicator. After 30 s, the LMN array was removed, and the porcine skin and residual LMN base were observed under bright and fluorescent filed. As shown in Fig. 1c and d, the drug loaded part of LMNs (*i.e.* the HA layer) was dissolved followed by the releasing of the drug into the skin. The result indicated that the LMNs showed not only good insertion ability but also successful drug delivery within 30 s.

Owing to the hygroscopy of the materials, it is possible that the LMNs would absorb moisture from air and the mechanical property of them would be effect. To verify the expectation, we conditioned the 5 × 5 LMN arrays at 40%, 60% and 80% RH for 1 h. As a control, we also fabricated the MNs made of homogeneous HA or PVA (as shown in the Fig. S1, Supplementary data) and conditioned them at the same condition. After that, a micro-mechanical test machine (Fig. S2, Supplementary data) was used to obtain the force-displacement cures of MNs, which could be used to evaluate the mechanical property of MNs under varying humidity. Besides the LMNs, and investigated the mechanical property of HA MNs and PVA MNs under the same conditions. As the force-displacement cures shown in Fig. 2a, before the exposure at humidity, the mechanical behavior of dried LMN shows little difference from HA MN. Although the mechanical strength of dried PVA MN is slightly inferior to the other two, all of them show successful insertion property at porcine skins. After 1-hour-exposure at 40% RH and 60%, the strength of LMN and HA MN decrease gradually but still keep good insertion ability. As for the PVA MNs, the strength decreased significantly with the addition of relative humidity. Moreover, the PVA MNs also showed obvious reduction at insertion abilities, which was indicated by the 70% insertion percentages and none insertion after the exposure at 40% RH and 60% RH condition respectively (Fig. 2b and c). When the humidity increased to 80% RH, all of the MNs showed poor mechanical property and the complete failure at skin insertion (Fig. 2d). The results above indicated that the LMN have a similar mechanical property and moisture resistance with pure HA MNs. This phenomenon could be explained by the protection of “shell” structures of the HA layer on the LMNs. Moreover, it is suggested that the LMNs should be used at conditions no more than 60% RH to ensure successful insertion.

Technically, the gathering of drug at the tips or the top of DMNs is favorable for enhancing the efficiency of drug delivery. Here we evaluated the drug distribution in LMNs and HA MNs quantitatively by the relative drug concentration (characterized by color depth) at varying distance from the base (Fig. S3, Supplementary data). More detailed description of the measurement method could be found at Supplementary data. As shown in Fig. 3a, the drug encapsulated in LMN is mostly gathered into the upper part, while the drug in HA MN distributed in the whole body of the needle. Specifically, from the drug distribution profiles (Fig. 3b), for LMN, the relative drug concentration is 0 at the distance from the MN base lower than 160 μm but increased dramatically from 7% to 89% at the locations from 180 μm to 600 μm. And almost half of drug is gathered into the part from 450 μm to the tip. For HA MN, however, the drug concentration increased from 12.5% to 50% as the distance from 0 to 600 μm. These results indicated that the drug loaded in LMN could be mostly concentrated at the tips and the upper HA layer, while the drug in homogeneous HA DMN had a wide distribution in the whole body of needle. The main reason for the difference of drug distributions between LMN and HA MN is the stepwise polymer casting process in the fabrication of the LMN. After the HA layer casing, the drug was re-dissolved into the matrix, which was dried gently with the sinking of matrix. In this way, the drug could not be furtherly diffused but blocked into the upper HA layer. Even at the PVA casting process, because of the resistance of the high viscosity, little drug could diffuse into the sublayer of PVA.

As is mentioned previously, the efficiency of drug delivery is quite important for drug-loaded DMNs. To demonstrated the superior of LMNs in rapid and efficient drug delivery, we investigated the transdermal delivery efficiency of LMNs and HA MNs *in vivo*. Briefly, the 5 × 5 LMN and HA MN arrays were inserted into the back skin of BABL/C mice with the same manner (Fig. 4a), and the MN arrays were removed after a specific time (*i.e.* 10, 30, 60 and 120 s). Using a microplate reader, the amount of drug delivered into the skin was measured (detailed description of the measurement method could be found at Supplementary data). Here we define the efficiency of drug delivery as the ratio of drug delivered into the mice skin to the whole drug loading before insertion. From the visible view as shown in Fig. 4a, it is apparent that the micro-holes caused by LMNs are clearer than those caused by HA MNs. In addition, as shown in the images of LMNs and HA MNs before and after test at varying time (Fig. 4b), it is apparent that the residual drug on LMNs after insertions is much less than that of latter, as well as for the residual MN base. In the subsequent quantitative investigation (Fig. 4c), the efficiency of drug delivery of LMNs was close to 90% within 10 s and increased furtherly with time. However, for the HA MNs, only 36% drug was delivered into the skins in 10 s. Despite the gradual increase with the growing of time, the drug delivery efficiency of HA MNs in 120 s was stilled below 88%, which is much lower than that of LMN with 10 s insertion. Overall, the LMNs showed apparent advantage at the rapid and efficient drug delivery *in*