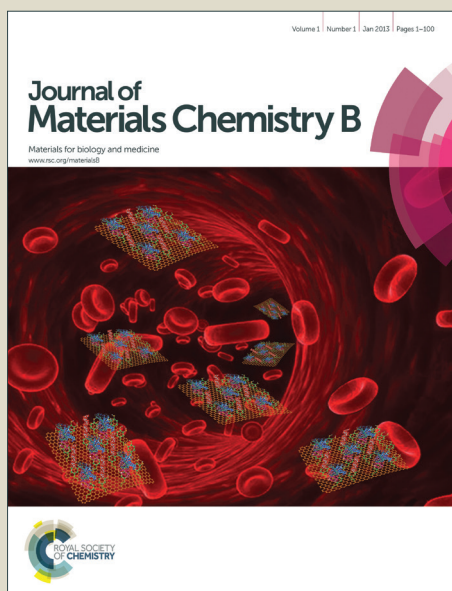


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Improved polyvinylpyrrolidone microneedle arrays with non-stoichiometric cyclodextrin

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Dissolving polymer microneedles have attracted much attention for their biocompatibility, fast dissolution,
and high drug loading. Among them, polyvinylpyrrolidone (PVP) is widely used, but its high water
absorption and poor mechanical properties constrain its broad applications. Herein we show that adding
cyclodextrin (CD) to form PVP-CD inclusion complexes can alleviate these problems. The water
absorption of PVP was reduced by 36%-40% at different RHs as the PVP-CD inclusion complexes
formed. Attractively, the water absorption at 10 and 20 days remained almost the same for the complexes
while it could dramatically increase for the pure PVP samples, particularly in high humidity environment,
indicating a possibly longer storage time for the complexes. It was also found that the Young's modulus
and hardness of the PVP-CD could be greatly improved, especially for low molecular weight PVP.
Furthermore, the glass transition temperature (T_g) of the PVP-CD increased by up to 39 °C. With the
improved properties, the fabricated PVP-CD microneedles possessed much sharper needle tips and the
patch had less cracks than those made from pure PVP. Pig skin application result suggested that the PVP-
CD microneedle arrays were able to reliably pierce the stratum corneum of the skin while it was not
achievable for the PVP microneedles with the same geometry. We anticipate that these PVP-CD
complexes microneedles are more suitable for vaccine and drug delivery because of their superior
properties.

Introduction

Microneedle patches are arrays of ultra-small needles with lengths well below one millimetre^{1,2} and have been broadly used for transdermal delivery of vaccines and drugs. Their major advantages include the ability to pierce skin in a non-invasive way and they can be integrated into "lab-on-a-chip" systems for monitoring glucose levels, etc.³ These microneedles are often made of metals^{4,5}, silicon^{6,7}, and polymers^{8,9,10}. Among them, dissolving polymer microneedles attract great attention for their biocompatibility, biodegradability, low price, and high drug or vaccine loading. Polymers such as chitosan¹¹, polyacrylic acid (PAA)⁹, carboxymethyl cellulose (CMC)¹², polyvinylpyrrolidone (PVP)¹³, silk¹⁴, and sugar glass¹⁵ have been reported for preparing dissolving microneedles. However, compared to metal and silicon microneedle arrays, dissolving ones usually have two disadvantages. One is their low mechanical strength hindering consistent and reliable penetration into skin³. The other is hygroscopicity, which is particularly serious for polymers like PVP. PVP shows excellent biocompatibility and water solubility

and therefore is often used as a main component for temporary skin covers and wound dressing¹⁶. PVP is also used in the pharmaceutical industry as coating agents, polymeric membranes, and materials for controlled drug release¹⁷. Although PVP has been reported to make microneedles, its poor mechanical properties and strong water absorption seriously limit the practical usage, especially for low molecular weight PVP.

Cyclodextrin (CD), manufactured from starch, has been widely used in pharmaceutical industry for drug coating and delivery¹⁸. β -CD is the most accessible and the lowest-priced type. During oral administration, it is minimally irritating and has many advantages including very small amounts (1–2%) being absorbed in the upper intestinal tract, no metabolism happening in the upper intestinal tract, and being able to be metabolized by bacteria in caecum and colon¹⁹. It is known that CD can form inclusion complexes (host-guest complexes) with a very wide range of solid, liquid and gaseous compounds by molecular complexation. The hydrophobic cavity of CD molecules provides a microenvironment for appropriately sized non-polar moieties to enter and form inclusion complexes, with no covalent bonding

between CD and moieties²⁰⁻²³. Replacement of water in the cavity by hydrophobic guest molecules leads to reduction of enthalpy, which is the main driving force of this host-guest complexes formation²⁴. The complexes can be formed in either solution or solid state. Being locked or caged within the CD cavity gives rise to beneficial modifications of the guest

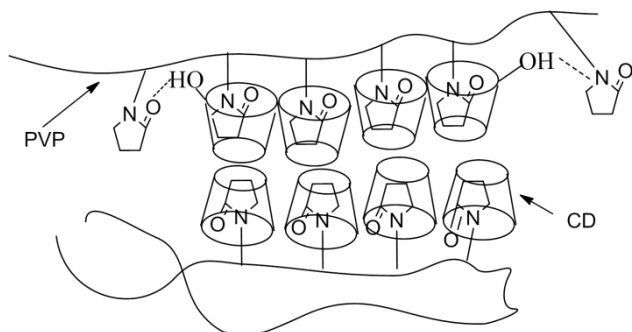


Fig.1 Schematic diagram of PVP-CD complexes

molecules including enhanced solubility^{25,26}, anti-oxidation under visible or UV light or heat, controllability of volatility and sublimation, physical isolation of incompatible compounds, masking off unpleasant odors²⁷ and controlled drug release²⁸.

Making use of the advantages of such host-guest complexes, we hypothesize that the formation of PVP-CD inclusion complexes can greatly decrease the water absorption of PVP (Figure 1). In the meantime, the hydroxyl group of the outer cavity of CD can form hydrogen bonding with PVP, which will restrict the movement of the PVP chain and correspondingly increase the mechanical strength.

To validate the hypothesis, in our work, we investigated the effect of adding two types of CD (Hydroxypropyl- β -Cyclodextrin (HP- β -CD) and Dimethyl- β -Cyclodextrin (DIME- β -CD)) into PVP of two different molecular weights ($M_n=58000$ (named as PVP58) and $M_n=10000$ (named as PVP10)).

Experimental Section

Materials

PVP58, PVP10, sodium chloride, potassium chloride, potassium acetate, HP- β -CD and DIME- β -CD were purchased from Sigma Aldrich. Poly (dimethylsiloxane) (PDMS, SYLGALD® 184) was ordered from Dow-Corning. All of the materials were used without further treatment.

Inclusion complexes preparation

The non-stoichiometric PVP58 and HP- β -CD inclusion complexes were prepared according to the following procedures. Briefly, 50 mg of PVP58 and 50 mg of HP- β -CD were dissolved in 1 ml of water followed by 30 minutes of sonication and 1 day of stirring. Secondly, the composite was placed at room temperature for two days till the water evaporated. After that, the sample was placed into containers containing various saturated salt solutions for relative humidity (RH) control. The product was named as PVP58-HP- β -CD-11 ("11" indicates that the weight ratio of PVP to HP- β -CD was 1:1). Other samples including

PVP58-HP- β -CD-51, PVP10-HP- β -CD-11, PVP10-HP- β -CD-51, PVP58-DIME- β -CD-11, PVP58-DIME- β -CD-51, PVP10-DIME- β -CD-11, and PVP10-DIME- β -CD-51 were prepared with the same process. PVP58 and PVP10 film were prepared similar process without adding CD.

Microneedle arrays preparation

The complexes microneedle arrays were prepared according to the previously reported methods^{8,29}. A mould was prepared by applying PDMS base and crosslinking agent with a volume ratio of 10:1 to a silicon master microneedle array followed by curing at room temperature for two days. To make polymer microneedles, PVP or PVP-CD aqueous solution was cast onto the PDMS mould. The solution was forced to the microneedle cavity in the mould by a vacuum environment. After drying at room temperature for two days, high concentration PVP58 or PVP10 solution (50 wt%) was cast to form the base of the microneedle patch.

Water absorption at various relative humidity conditions

PVP-CD complexes were firstly placed in a dry desiccator for two days to allow all samples to have equivalent conditions before water absorption measurement. Then the samples were stored at ambient temperature under various controlled RH conditions by using saturated salt solutions of potassium acetate (23% RH), sodium chloride (75% RH), and potassium chloride (85% RH)³⁰. Subsequently, water absorption was determined using a gravimetric method by drying samples in a vacuum oven at elevated temperature of 50 °C until a constant weight was achieved. The water content was calculated as the weight loss after drying in relative to the weight of the sample before temperature elevation.

Differential scanning calorimetry (DSC)

The glass transition temperatures (T_g) of samples were tested by DSC (TA Q1000) under nitrogen atmosphere. The first cycles were performed from 50 °C to 230 °C at a temperature increase rate of 10 °C/min and then maintained at 230 °C for 3 min to erase any previous thermal history. After that, the samples were cooled down to 50 °C at a rate of 30 °C/min. Finally, the samples were reheated to 230 °C at a rate of 10 °C/min. The registered changes on the calorimetric curves were evaluated.

Fourier transform infrared spectroscopy (FTIR)

Fourier transform infrared spectroscopy (Spectrum 100 PerkinElmer) spectra of samples were obtained using KBr disk for 40 scans with a resolution of 2 cm^{-1} in the range of 4000 to 400 cm^{-1} .

Hardness and Young's Modulus Test

PVP and PVP-CD films were prepared by drying the corresponding solutions on glass slides. A micro-indentation with a Vickers diamond indenter (Fischerscope HM2000, Fischer,

Germany) was used to measure the Young's modulus and hardness of the films under 70% RH. Under a load level of 10 mN, the mean values of hardness and Young's modulus were derived from load vs. indentation depth curves. At least 5 indentations were performed for each sample.

Scanning electron microscopy (SEM)

SEM images were taken with a Philips, XL30 Environmental scanning electron microscope (ESEM) with a voltage of 10 KV. To have high quality image of polymer microneedle patches, gold coating was applied to the patch.

Microneedle array application to pig skin

The experimental was set according to our previous work⁸. The experiment was performed according to our previously reported work⁸. Pig ears were obtained from the local abattoir and thoroughly cleaned. The ventral side of the ear was lightly shaved and rinsed. The skin was then stored at -20 °C before usage. Before microneedle array penetration test, the ventral skin (epidermis and dermis) was separated from the cartilage by tweezers and scalpel. The ventral skin was then stretched on a substrate and four of each type of microneedle arrays (PVP58, PVP58-HP-β-CD-11) were applied to the skin with a spring-based applicator. Immediately after the application, the microneedle arrays were removed from the skin. The treated area was excised with biopsy and fixed in 5 ml 4% formaldehyde in 0.1 M phosphate buffered saline overnight. Subsequently, the tissue was washed with 0.1 M phosphate buffered saline. The morphology of the microneedle penetrated pig skin and the used microneedle arrays were observed with ESEM (Philips, XL30).

Results and discussion

FTIR spectra of PVP, CD and PVP-CD complexes

The formation of PVP-CD inclusion complexes was first confirmed by FTIR. FTIR is a very useful tool to prove the existence of both guest and host molecules in complexes. Figure 2a shows the FTIR spectra of PVP58, HP-β-CD, and PVP58-HP-β-CD-11 inclusion complexes. The peak at 3466 cm⁻¹ is attributed to the hydroxyl group of water (although the sample was totally dried before FTIR test), which proves PVP quickly absorbs water. This peak overlaps with the hydroxyl group of HP-β-CD. The peaks at 3370 cm⁻¹, 2928 cm⁻¹, 1157 cm⁻¹, and 1029 cm⁻¹ correspond to the symmetric and antisymmetric stretching of -OH, -CH₂, C-C, and bending vibration of O-H, respectively. The peaks at 2962 cm⁻¹, 2933 cm⁻¹, and 2904 cm⁻¹ correspond to the stretching of C-H in the PVP chain³¹.

For HP-β-CD, the peak at 2929 cm⁻¹ is the stretching vibration of -CH₃ and -CH₂. The peaks at 1156 cm⁻¹ and 1079 cm⁻¹ are the stretching bending vibrations of C-O-C and C-O-H, respectively. The peaks at 946 cm⁻¹ and 856 cm⁻¹ correspond to α-1,4 skeletal vibrations and a pyranoside bond, respectively. At 757 cm⁻¹, there is a sugar ring breathing vibration peak. The peak at 707 cm⁻¹ is a ring vibration peak.

More importantly, the frequency movements of PVP-HP-β-

CD inclusion complexes can be seen from Figure 2b. The axial and angular bending C-C (=O) of PVP is located at 1172 cm⁻¹. After the formation of the complexes, this peak shifts 16 cm⁻¹ to 1156 cm⁻¹. In addition, the peak of the out of plane bending CH₂ of PVP shifts from 850 cm⁻¹ to 847 cm⁻¹ in the complexes. Overall, the shifts of the two peaks clearly confirm the formation of the PVP-HP-β-CD inclusion complexes. It is caused by the microenvironment change of the CD cavity due to the formation of the inclusion complexes. The increase³² and decrease³³ of the wavenumbers are dependent on the host-guest interactions. In this work, the non-stoichiometric PVP-CD inclusion complexes are heterogeneous. Parts of N-vinylpyrrolidone are included in the β-CD cavity and parts are dangling. The hydrogen bonding between the hydroxyl group of the outer cavity of CD and N-vinylpyrrolidone constrains the mobility of PVP chain, which corresponds to the decrease in the FTIR absorption wavenumbers of stretching and bending vibration of C-H, C=O and C-N.

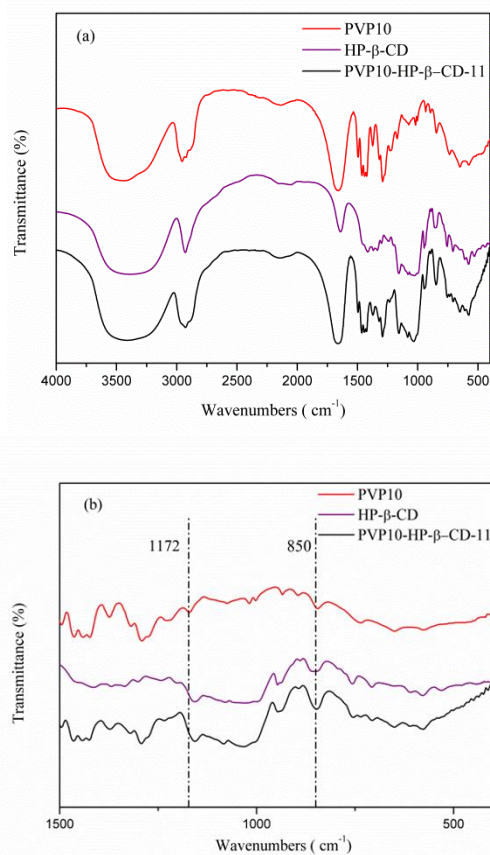


Fig. 2 FTIR spectra of the PVP10, HP-β-CD, and PVP10-HP-β-CD-11 complexes

Water Absorption of PVP and PVP-CD complexes

Water, a plasticizer of amorphous materials, often leads to degradation of their mechanical and thermal properties. Previous FTIR measurements suggested that water molecules can be bonded to C=O, and C-N groups in PVP³⁴. A Fourier transform Raman spectrum showed that the change of the properties of PVP via water absorption is not only due to hydrogen bonding, but also a result of the plasticizing effect of water³⁵. Water molecules

distribute uniformly throughout PVP at a concentration of 0.5%, but become remarkably heterogeneous at a higher content³⁶. Besides moderately strong hydrogen bonding, extra water molecules are in free state, which acts as a plasticizing agent³⁷. Therefore, reduction of water absorption by PVP will be beneficial to maintain mechanical and thermal properties. The water absorption of various PVP-CD complexes under different RH conditions is shown in Figure 3. It can be seen that under different RHs, the water absorption capacity varies. At low RH of 22%, the water absorption is low. Adding CD to PVP can reduce PVP58 and PVP10 water absorption by only around 1 and 3 wt%, respectively. If we calculate the relative decrease in water absorption, for PVP10, the water absorption decreases from 8% to 4.9% after 20 days exposure to RH 22% environment. This means that the relative decrease of water absorption is about 40%. When RH increases to 75% and 85%, the effect of CD incorporation is more obvious because higher RH leads to increased water absorption of PVP. If we compare the water absorption of PVP and PVP-CD inclusion complexes, the following can be observed. The water absorption was 50 wt% and 32 wt% for PVP10 and PVP10-CD complexes, respectively, after 20 days exposure to RH 85% environment. This indicates a relative 36% decrease in water absorption. For PVP58, the effect is about the same. At RH75%, for PVP58, the water absorption drops from 37 wt% to 23% after complexes formation, which suggests about 38% relative decrease. Overall, the data show that after formation of PVP-CD complexes, water absorption can decrease about 36-40% at different RHs.

Table 1 Glass transition temperature of PVP and PVP-CD complexes

Sample	T_g (°C)
PVP58	160
PVP58-HP- β -CD-11	199
PVP58-HP- β -CD-51	176
PVP58-DIME- β -CD-11	210
PVP58-DIME- β -CD-51	158
PVP10	128
PVP10-HP- β -CD-11	165
PVP10-HP- β -CD-51	136
PVP10-DIME- β -CD-11	155
PVP10-DIME- β -CD-51	135

Different PVP-CD ratios were investigated in our experiments and the results clearly indicate that the ratio of 1:1 worked the best in terms of decreasing water absorption of PVP.

In addition, it can also be found that, at a high RH of 85%, the water absorption of PVP dramatically increases if the time exposure to the environment extends from 10 to 20 days. In comparison, for the PVP-CD complexes, longer time exposure to the environment usually does not lead to increased water absorption. This result suggests that the formation of PVP-CD complexes is good for long term storage.

Glass transition temperatures of PVP and PVP-CD complexes

Figure 4 presents the DSC curves of PVP58 and PVP58-HP- β -CD-11 inclusion complexes. Compared with PVP, it can be observed that the T_g of PVP58-HP- β -CD-11 is greatly increased

from 160 °C to 199 °C, increasing by 39 °C. Table 1 also shows that, after formation of PVP-CD complexes, the glass temperatures increased for various compounds. This is expected because non-stoichiometric polymer-CD inclusion complexes often show different physical properties from the pure one. For example, nylon-6 CD inclusion complexes have higher T_m ³⁸ and non-stoichiometric PMMA-CD inclusion complexes show higher T_g than pure PMMA. In addition, N-s-PCL- α -CD inclusion complexes display shape memory effects depending on the coverage of inclusions and the storage modulus is significantly higher than that of the pure PCL³⁹.

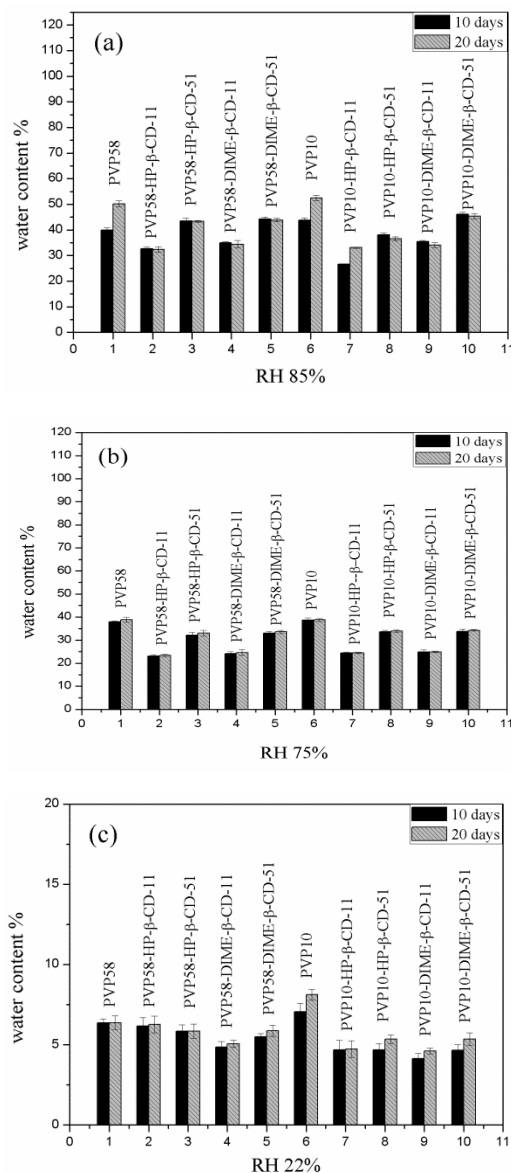


Fig. 3 Water absorption of PVP and PVP-CD complexes under different RH: (a) RH 85%, (b) RH 75%, and (c) RH 22%

During glass transition, an amorphous polymer undergoes secondary phase change, changing from a brittle solid state, to an elastic rubbery state, reflecting increased chain mobility. As N-vinylpyrrolidone is in the inner cavity of CD, the chain mobility

is limited and the dangling chain showed brush structure interacting with the hydroxyl group outside the cavity of CD, both of which contribute to tighter and more ordered structure⁴⁰.

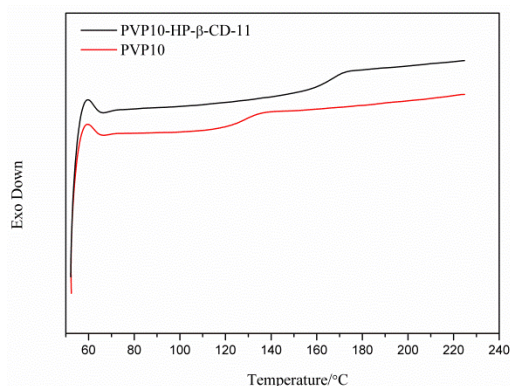


Fig. 4 DSC curves of the PVP and PVP10-HP-β-CD-11 complexes

Mechanical properties of PVP and PVP-CD complexes

The microindentation test results of PVP and PVP-CD complexes are shown in Figure 5. It can be seen that, after adding CD, the Vickers hardness (HV) and Young's modulus increase. For example, the hardness and Young's modulus of PVP58-HP-β-CD-11 are 127.7 MPa and 2.681 GPa, respectively, which increased 19.6% and 10.2% in comparison with those of PVP58 with hardness of 106.8 MPa and Young's modulus of 2.433 GPa, respectively. The hardness and Young's modulus of PVP58-DIME-β-CD-11 showed similar results.

For PVP10, the strengthening effect is more obvious. The hardness and Young's modulus of PVP10 could not be tested as the samples quickly absorb high amount of water and became viscous before measurement. In great contrast, after adding CD to PVP10, it can be clearly seen that the hardness and Young's modulus of PVP-CD were close to those of PVP58. For PVP10-HP-β-CD-11 and PVP10-DIME-β-CD-11, the hardness and Young's modulus were 128.7 MPa, 2.598 GPa and 194.8 MPa, 2.611 GPa, respectively, which is even close to PVP58. These results proved that the incorporation of CD enhances the mechanical properties, especially for low molecular weight PVP. It is known that low molecular weight PVP has faster water solubility than high molecular weight one. For microneedles, faster dissolving rates can be very important for vaccine delivery. As indicated by the data, low molecular weight PVP has poor mechanical properties, which restrains its use in this field. Now this problem can be alleviated by adding CD to PVP10 to form complexes. Overall, it can be concluded that the addition of CD significantly increases the mechanical strength of PVP.

If we compare the effect of the ratio of PVP to CD and the type of CD on the mechanical properties of the complexes, it is easy to find that the ratio plays an important role while the type of the tested CD does not have much influence. This is in accordance with previously reported findings^{38,39,41} and also in line with the water absorption results. The function of CD has been explained by the schematic diagram in Figure 1. The CD cavity is occupied by the N-vinylpyrrolidone molecules. This host-guest effect constrains the mobility of the polymer chain. Non-stoichiometric CD allows left PVP chains to be still dangling without being encompassed by CD molecules. In this case, the

hydrogen bonds formed between left N-vinylpyrrolidone and CD molecules will decrease the possibility of water interaction to N-vinylpyrrolidone. This is not related to outspace of CD. Therefore, the tested two different CDs had similar effects. However, due to the fact that there are many CD derivatives, this effect of the type of CD on the mechanical properties of the complexes will need further investigation.

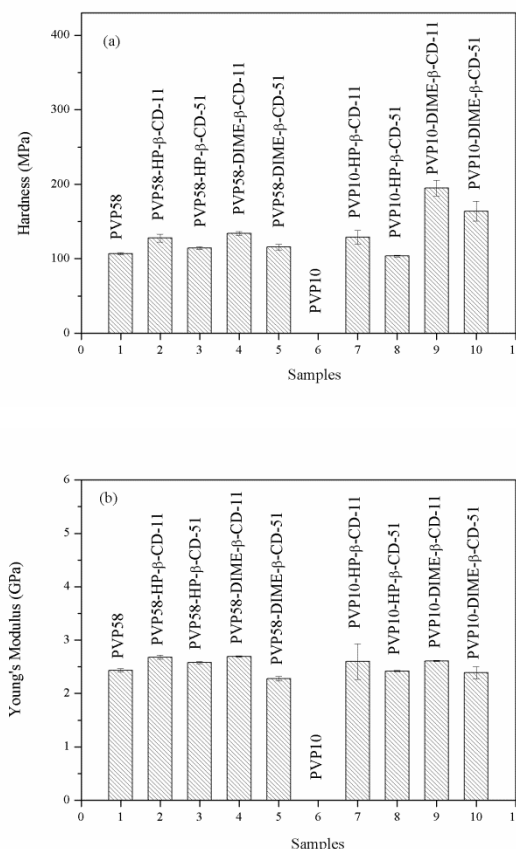


Fig. 5 (a) Hardness and (b) Young's modulus of PVP and PVP-CD complexes

Fabrication of PVP and PVP-CD microneedle arrays

Once the properties of PVP and PVP-CD complexes are studied, we next used them to make microneedle arrays and examined the morphology. All microneedle arrays were experienced same manufacturing and processing procedures before scanning electron microscopy observation.

The morphology of microneedles, particularly the radius of the tips, is one of the important factors which may affect the microneedles penetration to skin⁴². From Figure 6, it can be found that the morphology of the tips of the PVP and PVP-CD microneedles has great differences. The PVP-CD microneedles have much sharper tips, which allows them easily penetration to the skin. And this kind of microneedles has very low number of cracks on the base. In contrast, many PVP58 microneedles tips are even flat and bent, base has cracks. This phenomenon is more serious for PVP10 microneedles. The cracks and blunt tips were mainly caused by water absorption.

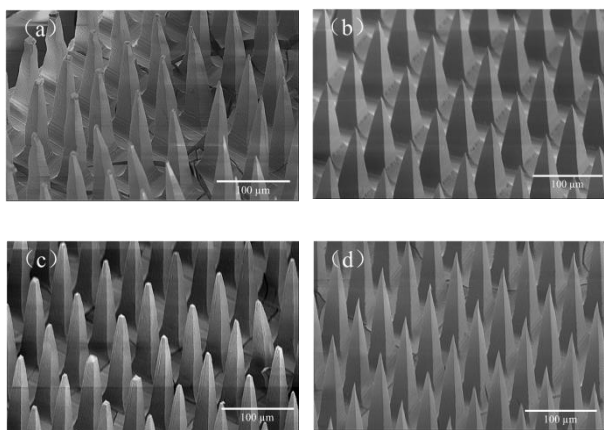


Fig. 6 SEM images of (a) PVP58, (b) PVP58-HP- β -CD-11, (c) PVP10, and (d) PVP10-HP- β -CD-11 microneedles arrays

5 PVP and PVP-CD microneedle arrays penetration to skin

Since the addition of CD to PVP dramatically improved the properties of the microneedle arrays, we further tested the application of the PVP and PVP-CD microneedles to pig skin to find out whether the incorporation of CD can improve the penetration. To perform the test, PVP and PVP-CD microneedle arrays were applied to pig skin separately and the morphology of the treated skin surface and the used microneedle arrays were characterized with ESEM. The SEM images are shown in Figure 7. From Figure 7a, it can be seen that the PVP microneedles were not able to pierce the stratum corneum of the pig skin. In great contrast, Figure 7b clearly shows that the PVP-CD microneedles successfully penetrate into the skin and ordered holes are created due to the penetration of the microneedles to the skin. Because the skin was not completely dehydrated before SEM characterization, the skin would shrink or distort due to water loss during the SEM observation⁴³. For PVP microneedle arrays, once applied to the skin, the patches were smashed to many small pieces. Most of the microneedle arrays disappeared after application. For the several remained microneedles, it was observed that some of them were bent possibly due to the fact that these microneedles were not mechanically strong enough to pierce the stratum corneum of the pig skin (Figure 7c). In comparison, all of the microneedles of the PVP-CD patches were remained after the application. However, the tips of the microneedles were dissolved after being penetrated into the pig skin within the very short period of penetration time (~ 1 s). Overall, the results clearly indicate that the PVP-CD microneedles can successfully penetrate into the pig skin and rapidly start to dissolve while the pure PVP microneedles with the same geometry are not capable of piercing the stratum corneum of the skin.

Conclusions

In conclusion, PVP-CD inclusion complexes were successfully prepared. The influence of PVP to CD ratios and CD species on the mechanical properties, thermal properties and water absorption of different molecular weight PVP were studied. With the addition of CD, the water absorption of the PVP-CD complexes reduced as much as 36%-40% in comparison with that of PVP. Meanwhile, the mechanical properties and T_g of the complexes were also increased. With the improved properties, the PVP-CD microneedles possess very sharp tips and the patches contain low number of cracks. Pig skin application result suggested that the PVP-CD microneedle arrays were able to

reliably pierce the stratum corneum of the skin while it was not achievable for the PVP microneedles with the same geometry. We expect that the PVP-CD microneedle arrays are more suitable for vaccine delivery.

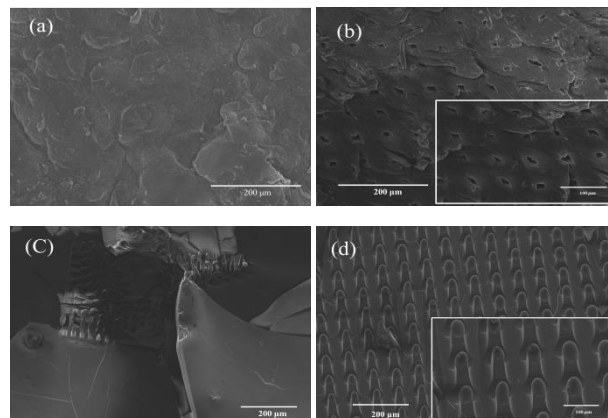


Fig. 7 SEM images of (a) pig skin after PVP58 microneedle array application; (b) pig skin after PVP58-HP- β -CD-11 microneedle array application; (c) PVP58 microneedle arrays after pig skin application test; (d) PVP58-HP- β -CD-11 microneedle arrays after pig skin application test.

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Notes and references

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^g Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.
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