**Mechanism of the controlled release profiles of bisoprolol and its ion-pair from pressure sensitive adhesive in their transdermal drug delivery processes**

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**1. Introduction**

Transdermal drug delivery system (TDDS), a successful controlled release technology which provides stable systemic drug concentration, has attracted increasing attention over the last 40 years. Among the methods usually used in TDDS, ion-pair strategy, as a simple but effective approach plays an important role in bidirectional regulation of drug skin permeation profile. However, investigations into the underlying mechanisms involved in the controlled release process of ion-pairs are still limited.

**2. Purpose**

In this lecture, we shall present our recent studies on the molecular mechanism of ion-pair controlling the transdermal delivery processes of bisoprolol (BSP), especially focusing on the roles of doubly ionic hydrogen bond formed between ion-pair and acrylic pressure sensitive adhesive containing carboxyl group (carboxylic PSA) on the controlled release process of BSP ion-pair.

**3. Methods**

BSP and BSP-lauric acid ion-pair (BSP-C12) were used as model drugs due to their identical skin permeability coefficient (*k*p = 1.9 cm/h) based on our previous study [6]. Carboxylic PSA was designed and synthesized in order to improve drug loading and thus produce sustained release effect [4]. Effect of ion-pair on controlling BSP release from carboxylic PSA was investigated by *in vitro* drug release study and *in vitro* skin permeation study, then verified by pharmacokinetic study. Molecular mobility of PSA, along with the strength of drug-PSA interaction was evaluated by thermal analysis and dielectric spectroscopy (DES) [5, 13]. Molecular details of drug-PSA interaction were identified by Fourier transform infrared spectroscopy (FTIR), X-ray photoelectron spectroscopy (XPS) and Raman spectroscopy. Roles of drug-PSA interaction in the controlled release process were clarified by molecular modeling.

**4. Results**

**4.1 Effect of ion-pair on controlling BSP release from carboxylic PSA**

According to Fig. 1 – 3 and Table 1, both *in vitro* and *in vivo* skin permeation study testified that the skin absorption rate of BSP was successfully controlled, which was achieved by sustaining BSP release from carboxylic PSA by ion-pair.

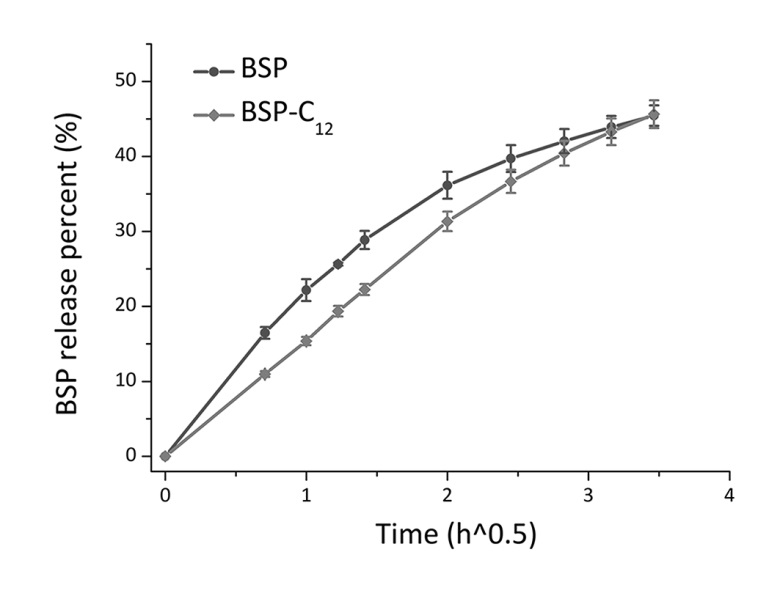


Fig. 1. Release profiles of BSP and BSP-C12 transdermal patches (*n* = 4).

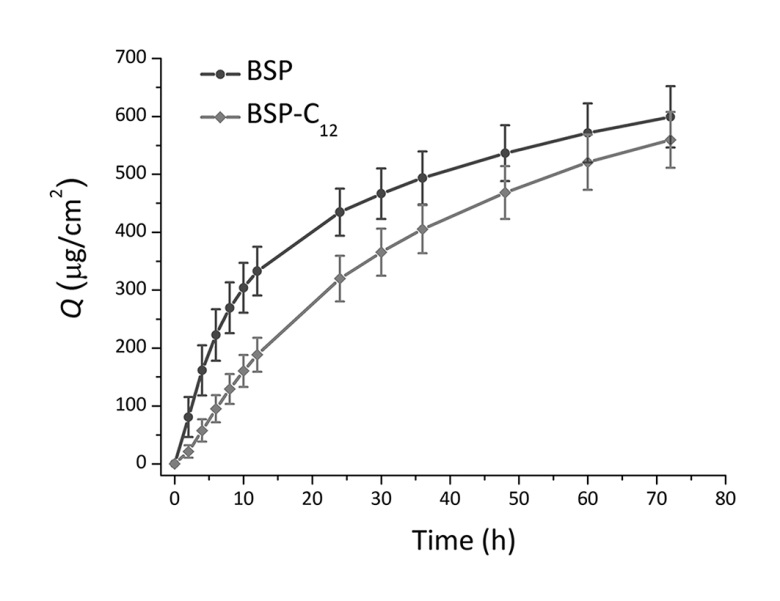


Fig. 2. *In vitro* skin permeation profiles of BSP and BSP-C12 transdermal patches (*n* = 4).

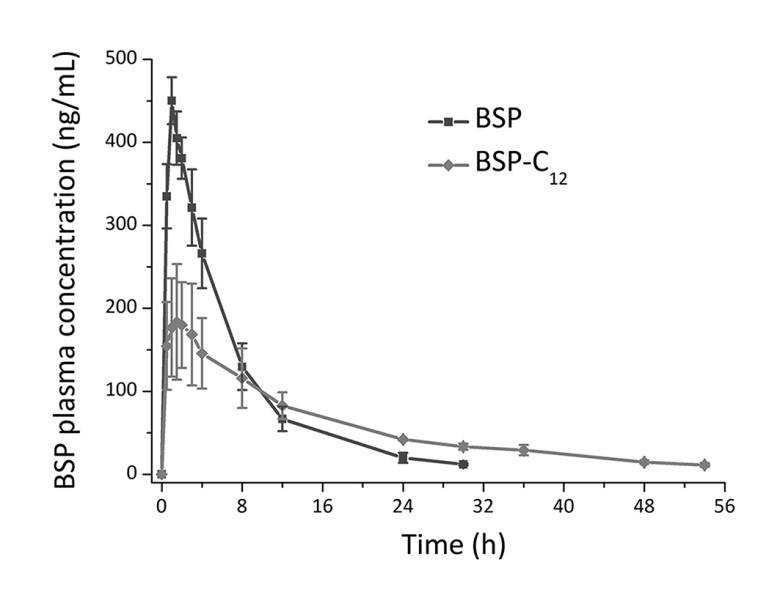


Fig. 3. Plasma BSP concentration-time curve after administration of BSP and BSP-C12 transdermal patches (*n* = 6).

Table 1Pharmacokinetic parameters of transdermal and *i.v.* administrations (*n* = 6).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Formulas | *t*max  (h) | *C*max  (ng/mL) | *AUC*  (h\*ng/mL) | *MRT*  (h) | *F*  (%) |
| BSP patch | 1.0 ± 0.0 | 450 ± 28 | 3265 ± 468 | 7.9 ± 0.9 | 57.2 |
| BSP-C12 patch | 2.0 ± 0.6 | 193 ± 63 | 3289 ± 454 | 19.9 ± 3.4 | 57.6 |
| BSP (*i.v.*) | - | - | 543 ± 51 | 0.9 ± 0.2 | - |

**4.2 Mechanism study on ion-pair controlling the transdermal delivery processes of BSP**

**4.2.1 PSA molecular mobility**

**4.2.1.1 Thermal analysis**

Glass transition temperature (*T*g) of PSA and polymer-drug interaction parameter (*A*) calculated by WLF equation [10] were listed in Table 2. *T*g value of BSP and BSP-C12 loaded PSA decreased about 3 °C and 7 °C separately compared with blank PSA. Besides, *A* value of BSP-C12 loaded PSA was lower than that of BSP loaded PSA. These results not only demonstrated that molecular mobility of BSP-C12 loaded PSA was higher than BSP loaded PSA, but it also indicated that stronger molecular interaction existed between BSP-C12 and PSA compared to that between BSP and PSA.

Table 2 *T*g and *A* value of blank PSA and drug loaded PSAs.

|  |  |  |
| --- | --- | --- |
| Sample | *T*g (°C) | *A* |
| blank PSA | -35.8 | - |
| PSA + BSP | -38.9 | 8.7 |
| PSA + BSP-C12 | -42.8 | 8.3 |

**4.2.1.2 DES**

Loss tangent spectra of PSAs were shown in Fig. 4. Relaxation times (**) of PSAs were obtained from Fig. 4, which further proved that molecular mobility of the BSP-C12 loaded PSA was higher than the BSP loaded PSA, and stronger molecular interaction existed between BSP-C12 and PSA compared to that between BSP and PSA, which were consistent with the results of thermal analysis [12].

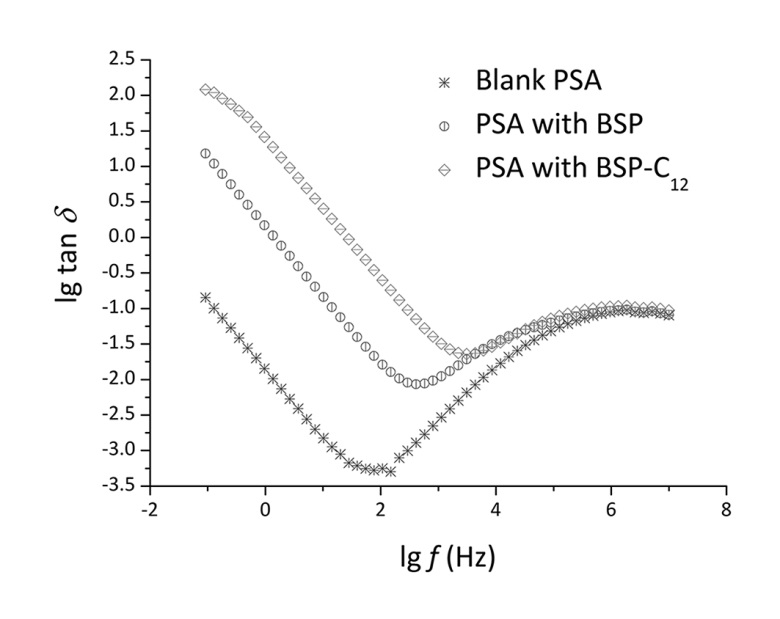


Fig. 4. Loss tangent as a function of frequency of blank PSA and drug loaded PSAs.

**4.2.2 Molecular details of drug-PSA interaction**

**4.2.2.1 FTIR spectra**

Wavenumber shifts in FTIR spectra shown in Fig. 5 – 6 indicated that apart from the ionic bond between BSP or BSP-C12 and PSA, there was also H-bond formed between BSP or BSP-C12 and PSA, with the deprotonated PSA-COO– being the H-bond interaction site of PSA [3, 8].

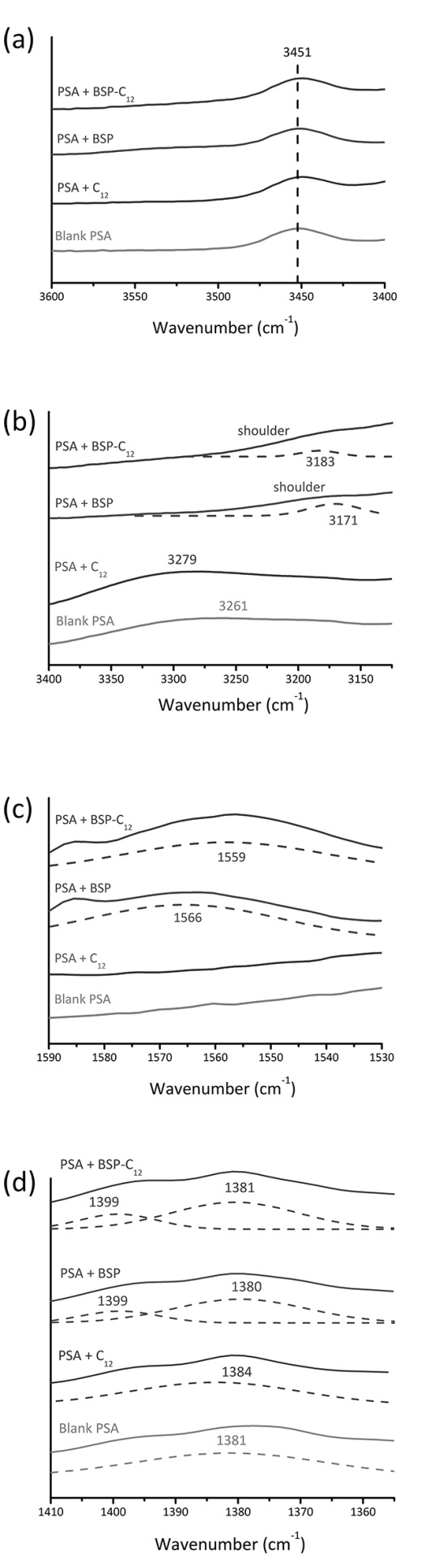


Fig. 5. FTIR spectra of blank PSA and PSA loading BSP, C12 and BSP-C12, with dashed lines referring to deconvoluted peaks.

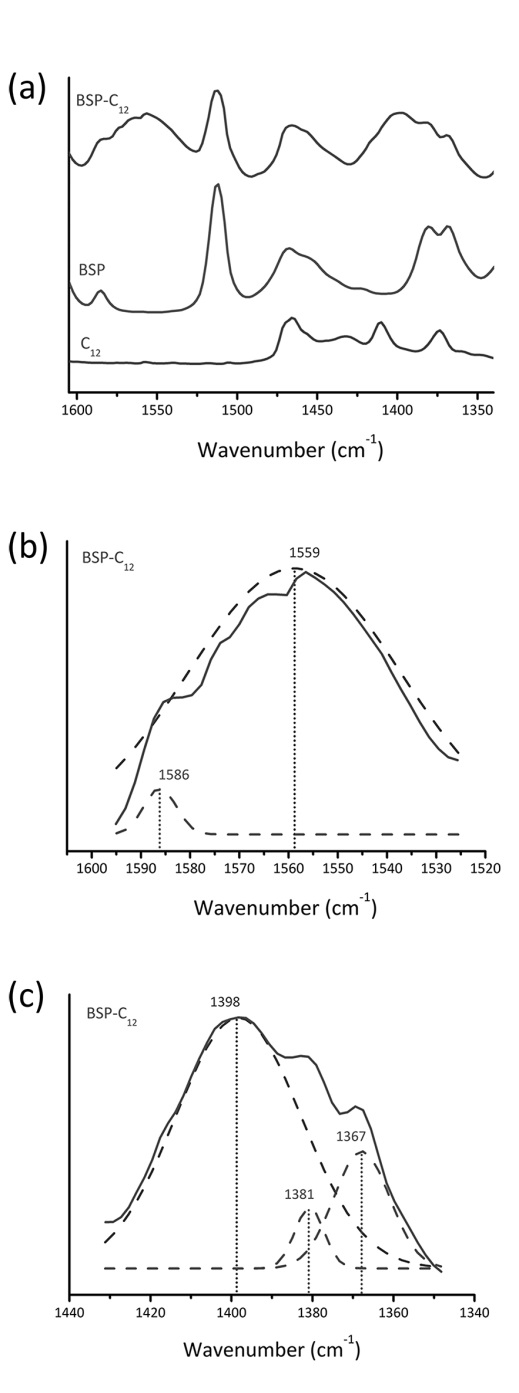


Fig. 6. FTIR spectra of BSP, C12 and BSP-C12, with dashed lines referring to deconvoluted peaks.

**4.2.2.2 XPS**

XPS spectra shown in Fig. 7 indicated that two states of BSP existed in the BSP loaded PSA: the protonated BSPH+ and the free BSP, while the BSP molecules were completely protonated to BSPH+ in the BSP-C12 loaded PSA [15].

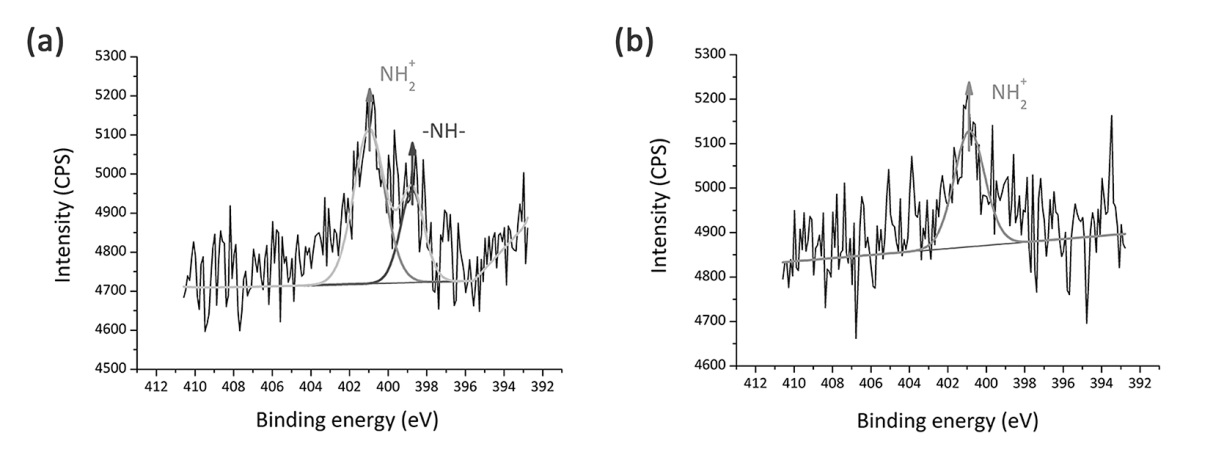


Fig. 7. XPS N 1 s peaks obtained from (a) BSP loaded PSA (b) BSP-C12 loaded PSA.

**4.2.2.3 Raman spectra**

Wavenumber shifts in Raman spectra shown in Fig. 8 indicated that in addition to ionic interaction, there was H-bond formed between BSP or BSP-C12 and PSA, with the secondary amine group (-NH-) being the H-bond donor of BSP, and the protonated secondary amine group (−NH+ 2−) being the H-bond donor of BSP-C12 [1, 14].

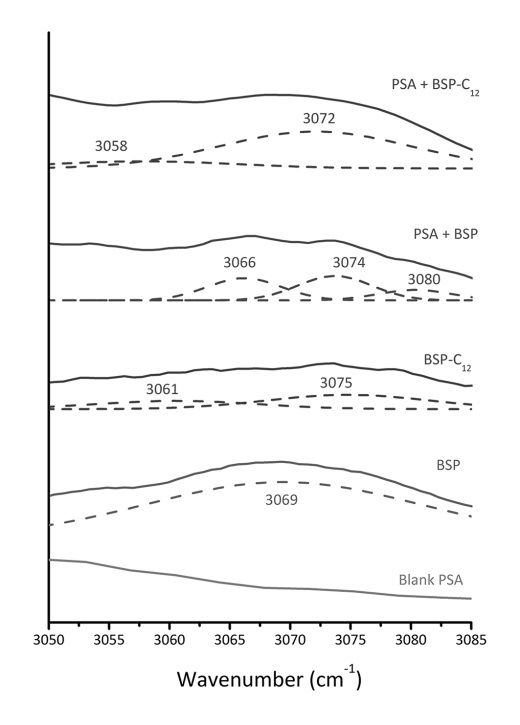


Fig. 8. Raman spectra of blank PSA, BSP, BSP-C12, PSA loading BSP and BSP-C12, with dashed lines referring to deconvoluted peaks.

**4.2.2.4 Molecular modeling**

Fig. 9 illustrated that BSP formed stable ionic interaction with PSA or C12, and the ionic interaction between BSP and PSA was more stable than that between BSP and C12. What’s more, according to Fig. 10, it was found that stronger H-bond interaction was formed between BSP-C12 ion-pair (−NH+ 2−) and PSA-COO– than that between BSP (-NH-) and PSA-COO– [2].

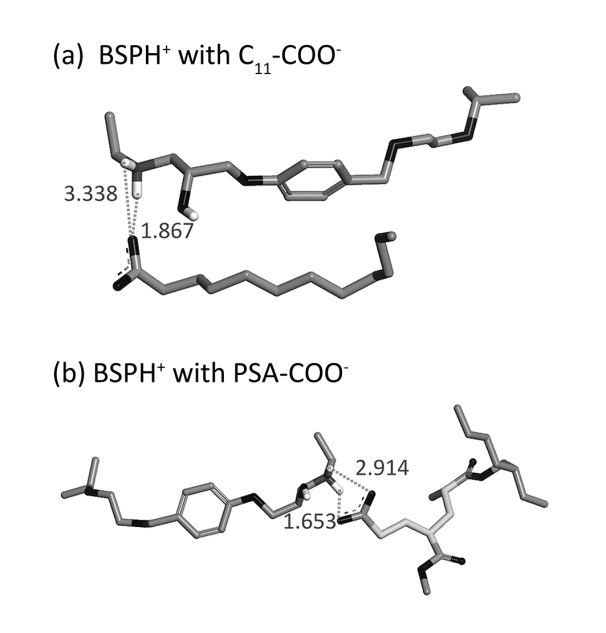


Fig. 9. Optimal conformations of (a) BSPH+ with C11-COO– (b) BSPH+ with PSA-COO−.

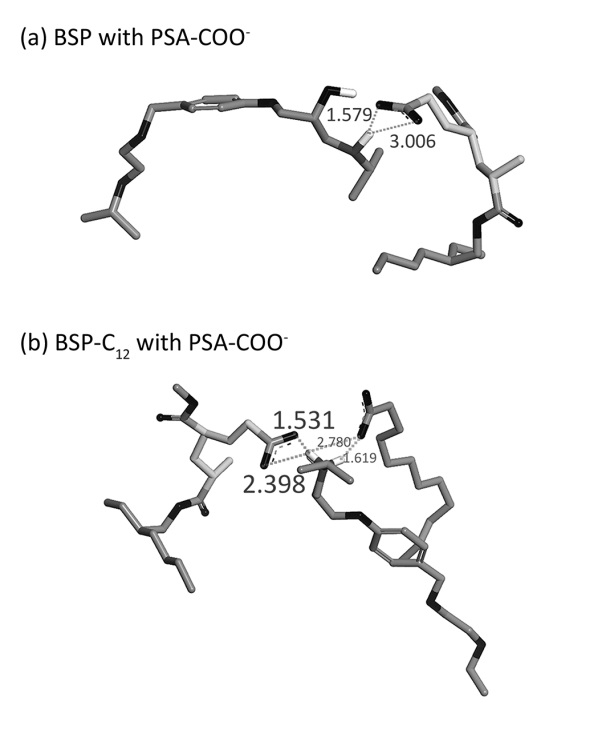


Fig. 10. Optimal conformations of (a) BSP with PSA-COO− (b) BSP-C12 with PSA-COO−.

**4.2.2.5 DES**

Apart from **, DES also provided dielectric constants of PSAs. Dielectric constant of BSP-C12 loaded PSA (**′ = 14.1 – 50.4 in 32 °C) was much larger than that of BSP loaded PSA (**′ = 6.8 – 10.4 in 32 °C) in all tested frequencies, indicating that the polarity of PSA loading BSP-C12 was higher that loading BSP [7].

**5. Conclusion**

In the present study, it was found that BSP-C12 ion-pair controlled the transdermal delivery rate of BSP without significantly influencing its delivery amount from transdermal patches. Molecular interaction between model drug and PSA played a dominant role in BSP’s release process instead of PSA mobility. As illustrated in Fig. 11, from thermodynamic aspect, whether BSP or BSP-C12 molecules were loaded to patches, the binding state of them both provided BSPH+ and formed identical ionic bonds with PSA-COO−, leading to their equivalent release amounts; from kinetic aspect, the doubly ionic H-bond formed between the undissociated BSP-C12 and PSA-COO− was stronger than the ionic H-bond formed between the free state of BSP and PSA-COO−, controlling the release rate of BSP [9, 11].

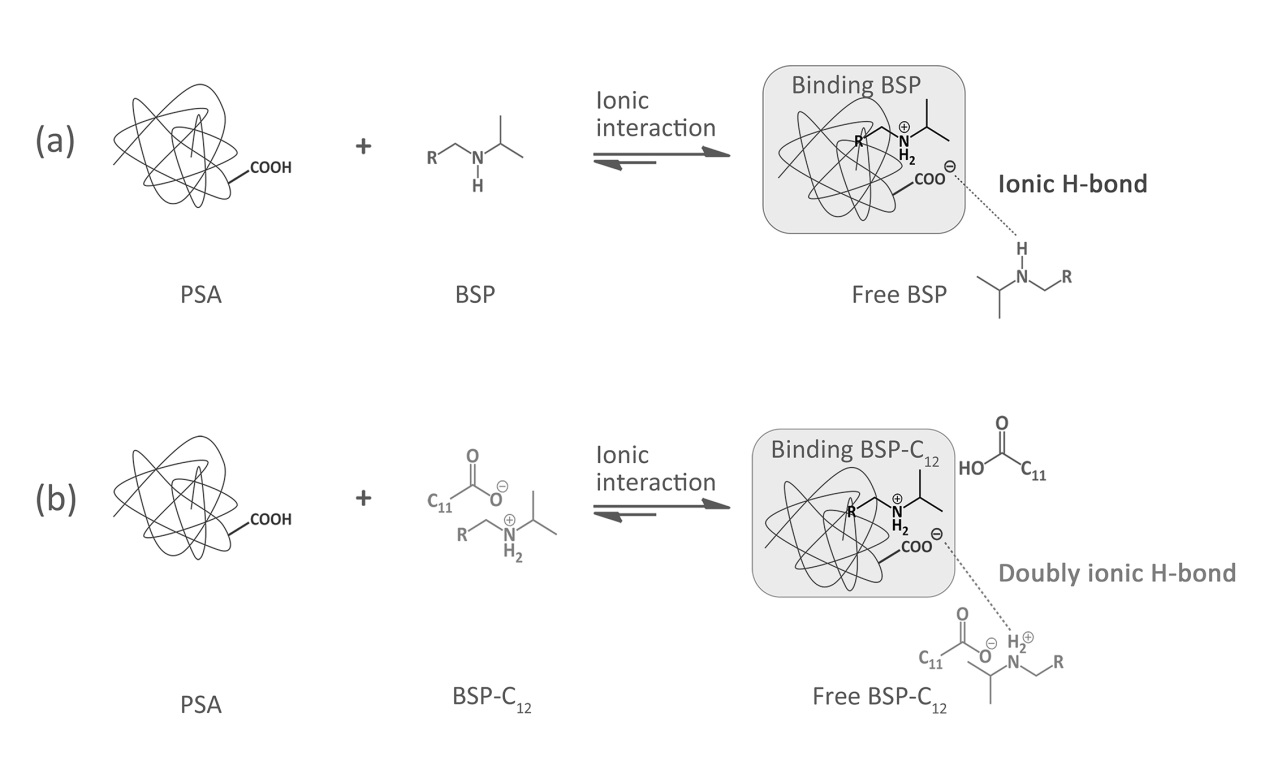


Fig. 11. Molecular interactions involved in the controlled release processes of (a) BSP and (b) BSP-C12.

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**Key words:** ion-pair, pressure sensitive adhesive, doubly ionic hydrogen bond, controlled release, transdermal