

DEVELOPMENT OF BIOCOMPATIBLE IONIC LIQUID-BASED ADHESIVE PATCH FOR ENHANCED TRANSDERMAL DRUG DELIVERY

ラシェドゥール, イスラム

<https://hdl.handle.net/2324/7329454>

出版情報：九州大学, 2024, 博士（工学）, 課程博士
バージョン：
権利関係：



氏 名 : ラシェドウル イスラム
(Rashedul Islam)

論 文 名 : DEVELOPMENT OF BIOCOMPATIBLE IONIC LIQUID-BASED ADHESIVE
PATCH FOR ENHANCED TRANSDERMAL DRUG DELIVERY
(経皮薬物送達を強化する生体適合性イオン液体ベースの接着パッチの
開発)

区 分 : 甲

論 文 内 容 の 要 旨

Though innovations in drug delivery systems are evolving continuously, still researchers in the pharmaceutical industry are confronting unprecedented obstacles in their quest to create efficient drug delivery systems that would enable numerous medications to exhibit the desired pharmacological response. These obstacles include polymorphism, limited solubility, permeability, and bioavailability. Despite having many advantages for example, non-invasive, painless, ease of use, patient compliance, and avoiding first-pass metabolism; transdermal drug delivery systems (TDDS) face additional challenges because of the barrier function of the stratum corneum (SC). Moreover, any drugs over 500 Da and hydrophilic drugs also cannot penetrate the skin due to the compact lipid layer of SC. Though transdermal patches are easy to use, they need to be attached to the skin for a long time which may also cause serious skin irritation.

Ionic Liquids (ILs) have been emerged as an excellent material in the pharmaceutical field due to their adjustable unique physicochemical properties. ILs can solubilize water-insoluble drugs which paves the way for making effective formulations. Another important advantage of ILs is that they can facilitate the skin penetration of large hydrophilic drugs by fluidization of the tight lipid layer of SC, the forbidding barrier of drug substances. Moreover, the fine-tuning nature of ILs allows researchers to design new ILs with targeted solubilizing abilities for particular drugs by optimizing molecular interactions. More importantly, biocompatibility, a paramount important parameter in TDDS can be achieved by engineering ILs that will lead to no or less skin irritation. To date, many biocompatible IL-based transdermal preparations have been developed. IL-in-oil (IL/O) microemulsion and IL-based solid-in-oil (IL-S/O) have been reported for the transdermal delivery of sparingly soluble drug acyclovir and macromolecular antigenic protein ovalbumin (OVA). However, these formulations are dispersed in an oil phase and exhibit low viscosity that is not enough to retain on the skin without additional assistance. Therefore, the development of IL-based adhesive transdermal patch that can be applied to the skin directly is highly necessary. In this thesis, we focused on developing IL-based adhesive transdermal patches and evaluating their potential application in the transdermal delivery of both sparingly soluble and water-soluble drugs.

In Chapter 2, we employed the choline propionate [Cho][Pro] IL to solubilize the sparingly soluble drug acyclovir and formulated IL/O microemulsion using oleic acid-based biocompatible IL [Cho][Ole] as the surfactant. Acyclovir-loaded IL/O microemulsion was then incorporated in a pressure-sensitive adhesive (PSA), DURO-TAK 87-4098, and IL/O microemulsion was mixed at an equal ratio (w/w), coated on a release liner, and covered by a backing membrane. The patch was characterized by scanning electronic microscope (SEM), rheometer, and confocal laser scanning microscope (CLSM). We prepared patches with different thicknesses (100 μm , 200 μm , 300 μm , and 500 μm). *In vitro* skin permeation study on Yucatan micropig (YMP) skin using Franz diffusion cells (FDCs) revealed that the drug delivery rate depends on the thickness of the patch. The thinner patch delivered the highest percentage of drugs, and the order of delivery efficiency is as follows $500\ \mu\text{m} < 300\ \mu\text{m} < 200\ \mu\text{m} < 100\ \mu\text{m}$. The patches were also found to remain unchanged at room temperature in terms of physicochemical properties after 30 days. Finally, an *in vitro* skin irritation study on reconstructed human epidermal tissue indicated that the patches do not cause skin irritation. It was concluded that the IL/O patch can be a good platform for the transdermal delivery of poorly water-soluble drugs.

In Chapter 3, we employed another class of biocompatible ionic liquid containing 1,2-dimyristoyl-sn-glycero-3 ethyl-phosphocholine (EDMPC) and linoleic acid (Lin) [EDMPC][Lin] to encapsulate a well-known technique called S/O. High molecular weight (42.7 kDa) model antigenic protein OVA was chosen for its known immunogenicity. The resulting IL-S/O nanodispersion was then mixed with three different PSAs; DURO-TAK 87-4098, DURO-TAK 87-4287, and DURO-TAK 87-235A with an equal ratio and named SP-4098, SP-4287, SP-235A, respectively. PSAs were selected based on their variability in modifying monomer and functional group monomers. Patches were characterized and found that SP-235A is not capable of fully detaching from the release liner. *In vitro* skin penetration was carried out using YMP skin. Both SP-4098 and SP-4287 could enhance the penetration of FITC-OVA. But, after 30 days of stability study, it was revealed the SP-4287 is detached from the release liner leaving some patch residue, that indicates patch failure. Therefore, we carried out an *in vivo* immunization experiment on the C57BL/6NJc1 mice model with SP-4098 and compared with that of aqueous formulation of OVA. Anti-OVA IgG titer was measured on 28 and 56 days after immunization and it was found that SP-4098 can produce a 10 times higher antibody compared to aqueous formulation. This result indicates that the IL-S/O patch can successfully induce immune response to mice model and stand out as a potential candidate in vaccine delivery.

In conclusion, the findings of the thesis suggest that IL based adhesive transdermal patch stands out as a new platform for transdermal drug delivery. This platform can be utilized for effective delivery of both sparingly soluble and water-soluble drugs.