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学位授与の要件	自然科学研究科生体機能科学専攻 (学位規則第4条第1項該当)
学位論文の題目	Development of Novel Polymeric Film Preparations That Can Improve Skin Permeation of Propranolol Hydrochloride by Use of Enhancers (塩酸プロプラノロールの経皮吸収改善を目指した促進剤類含有新規ポリマーフィルム製剤の開発)
論文審査委員	教授 木村聰城郎 教授 黒崎 勇二 教授 齋藤 寛

#### 学位論文内容の要旨

Transdermal route is one of the potent alternative routes that can improve undesirable characteristics of oral administration such as the intestinal and/or hepatic first-pass elimination, high variance in bioavailability due to variable condition of gastrointestinal tract. However, a much smaller number of drug are marketed using this route of delivery, compared to oral dosage forms, because drug absorption across the skin is very low due to the stratum corneum, a main barrier for drug absorption across the skin. Particularly, as propranolol, a  $\beta$ -blocker, has a short biological half-life and is subjected to extensive hepatic first-pass metabolism, propranolol must be a potential candidate for the transdermal use. In this study, therefore, the author intends to formulate novel polymeric film preparations of propranolol hydrochloride (PPL) by utilizing several chemical enhancers such as terpene enhancers and a mixture of sodium lauryl ether sulphate (SLES) and phenyl piperazine (PP) for achieving the desirable rate of drug penetration into the systemic circulation.

First of all, basic studies on skin permeation of PPL from solutions including enhancers such as menthol, cineole and propylene glycol were performed. Next, film preparations of PPL were developed by employing ethyl cellulose (EC) and polyvinyl pyrrolidone (PVP) as a film former and dibutyl phthalate (DBP) as a plasticizer. The film preparations were characterized in physical properties such as uniformity of drug content, thickness and moisture uptake capacity. The uniformity of drug content was evidenced by the low SD values for each film preparation. The moisture uptake capacity and drug release rate increased with the increase of PVP in each preparation. Enhancers except for a mixture of SLES and PP examined in the present study also increased the moisture uptake capacity and release rate of PPL from the film preparations. Then, release and permeation profiles of PPL from film preparations were examined in the in-vitro studies using a Franz-type diffusion cell, showing that film preparations containing cineole or a mixture of SLES and PP gave the highest permeation rate of PPL. The best polymeric film preparations selected based on the permeation studies, were applied to in-vivo study using Wistar rats by placing film preparation patches on the abdominal skin. It was found that the polymeric film patch with the suitable ratio of film former containing 10% w/w cineole or 0.5% w/v SLES+PP as an enhancer successfully improved the transdermal absorption of PPL. As the enhancers used in the present study have been evidenced to be low toxic, the films developed in the present study would be promising preparations for the clinical use, considering the balance between efficacy and toxicity.

## 論文審査結果の要旨

本論文は、塩酸プロプラノロールの経皮吸収改善を目指した促進剤類含有新規ポリマーフィルム製剤の開発を目指して種々の検討を系統的に行い、満足すべき製剤の開発に成功した過程の詳細を論述したものである。

ポリマーフィルムはエチルセルロースとポリビニルピロリドン（PVP）を成分とし、フタル酸ジブチルを可塑剤とした。吸収促進剤としてはテルペン類とプロピレングリコールを用いた。フィルム製剤の物理的性質として、含量均一性、厚さ、吸水性などを検討した結果、含量及び厚さの均一性に関しては良好であり、吸水性に関しては、PVP含量とともに増大し、薬物放出性も増大することを明らかにした。吸収促進剤も吸水性及び薬物放出性を増大させることがわかった。薬物含量を増大させると放出速度は速くなるが、吸収促進剤の濃度は放出速度にあまり影響しないことを明らかにした。インビトロのラット皮膚透過試験で、検討した吸収促進剤のうちシネオールがもっとも有用であることを見出し、基礎検討の結果到達した有望なポリマーフィルム製剤についてラットへの適用試験を行ったところ、プロプラノロールの血漿中濃度が長時間維持されることを証明した。本研究で用いた吸収促進剤は、皮膚刺激性の極めて低いものであり、ここで得られたポリマーフィルム製剤は臨床での適用が期待できるものと思われる。

本論文は、これらの系統的な検討をまとめたものであり、博士（学術）の論文に値するものと判定する。