EVALUATION OF SKIN PERMEATION OF NANOPARTICLES WITH 2-METHACRYLOYLOXYETHYL PHOSPHORYLCHOLINE (MPC) ACYL METHACRYLATE COPOLYMER IN VITRO
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Nanoparticles have been noted because it can be added functions such as solubilization, permeation enhancement and controlled release of drugs, however the permeation mechanism across the skin is unclear. The aim of the present study was clarification of the permeation of nanoparticles through the skin by using hydrolysis in the skin. Butyl p-aminobenzoate (PABB) was used as model ester drug. PABB was added in polymer solution and free-PABB was removed by dialysis. The diameter of nanoparticle (NP) was 24 nm. Skin permeation of PABB from solution and NP was performed using modified Franz-type diffusion cells. An aliquot of 10 µL/cm² was applied as donor phase. PABB and p-aminobenzoate (PABA) concentrations in skin and receptor phase were determined by a HPLC.

The esterase activity in epidermis of Yucatan micropig (YMP) was higher than that in dermis. When PABB was applied as NP, PABB amount on skin surface was higher but PABB in skin was lower than that in case of solution. When PABB amount in skin after application of NP was equal to that of solution, PABB: PABA was 1:1 for NP and 1:6 for solution, respectively. Pretreatment of phenylmethylsulfonyl fluoride (PMSF), inhibitor of esterase, did not affect the permeation of PABB from NP. But the permeation of PABB from solution with PMSF pretreatment was lower than without PMSF pretreatment. These results indicated that encapsulation of PABB to MPC acylmethacrylate copolymer changed permeation of PABB and prevented hydrolysis of PABB in the skin.

OPTIMIZATION OF IN VITRO ADME EXPERIMENTAL METHODS FOR WATER-INSOLUBLE COMPOUNDS
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Purpose: Recently, the number of the drug candidates with water-insoluble property has been increased by changing of drug development strategy. Even the experiment to get basic ADME information about those compounds is difficult to be performed. Therefore, solubilizers such as organic solvents or surfactants are often used to dissolve them. In this study, we investigated the effect of organic solvents or surfactants on in vitro metabolism experiments and viability of Caco-2 membrane. Methods: Midazolam (MDZ) is used as a model water-insoluble compound. MeOH and DMSO as organic solvents, and HCO-60, PUREBRIGHT® MB-37 and d-α-tocopheryl PEG 1000 succinate (V.E. TPGS) as surfactants are used. Final concentrations of these solubilizers are set from 0.01 % to 5 %. [Metabolism experiments] MDZ (2 µM) solution including each solubilizer is added to rat liver microsomes and incubated. 1-OH MDZ production rate was measured as a indicator of CYP3A activity. [TEER of Caco-2] The effect of each solubilizer on Caco-2 membrane viability is evaluated by the change of TEER during 90 min of incubation. Results and Discussion: Organic solvents inhibited CYP3A activity in a concentration-dependent manner. On the other hand, surfactants showed potent inhibitory effect even at low concentration (< 1 %). This result indicates that the direct contact between drug and CYP protein is inhibited by uptaking drug into micelle. TEER was lowered by DMSO (> 4 %) and HCO-60 (> 5 %). However, PUREBRIGHT has no effect on the membrane integrity. In summary, the effect of surfactants on drug metabolism is more potent than that of organic solvents, although surfactants have a better property for solubilization. On the other hand, the effect of solubilizer on the membrane viability is dependent on the kind of solubilizer.