S.T.P. Pharma Sciences, 13(3), 215-218 (2003).

Effect of chondroitin sulfate on the diffusion coefficients of drugs in aqueous solutions

Toshinobu Seki,[a,b] Maiko Okamoto（岡本麻衣子）,[c] Osamu Hosoya,[b] Daiki Aiba（相場大樹）, [c] Kazuhiro Morimoto,[a] Kazuhiko Juni（従二和彦）[c]

[a] Hokkaido College of Pharmacy, 7-1 Katsuraoka-cho, Otaru, Hokkaido 047-0264, Japan. [b] Research Institute of TTS Technology, 1-1 Keyakidai, Sakado, Saitama 350-0295, Japan. [c] Faculty of Pharmaceutical Sciences, Josai University, 1-1 Keyakidai, Sakado, Saitama 350-0295, Japan.

In order to examine the effects of pH and the presence of chondroitin sulfate (ChS) on diffusion coefficients (D) of drugs in aqueous solutions, the chromatographic broadening method (CBM) was applied. ChS, a major component of the extracellular matrix, was used as an acid mucopolysaccharide model. D of methylparaben (MP) decreased by about 10% with ionization, and the smallest D value of cefalexin (CEX), an amphoteric electrolyte, were observed at pH 5.0 at which CEX is a zwitterion. These observations are consistent with the knowledge of the effects of hydration to ions on the movement of ionized drugs. The effects of ChS on D were examined at pH 5.0 for several drugs with different states of ionization. In the case of MP, which is non-ionized at pH 5.0, the D value decreased only by 6% with the addition of 1% of ChS, although the macro-viscosity of the solution increased by 83% with the addition of 1% ChS. These observations also are consistent with the fact that micro-viscosity mainly contributes to the diffusivity of drugs. In the cases of morphine (MOR) and isoproterenol (IP), which are cations at pH 5.0, the values of D decreased by 25 and 21%, respectively, with the addition of 1% ChS. The decrease extents in D of cationic MOR and IP (25 and 21%) were considerably larger than those of zwitterionic CEX (5%), and anionic flurbiprofen (8%) and salicylic acid (6%). Although the addition of sodium chloride (125 mM) did not affect D of MP, the effects of ChS on D, of MOR and IP, were significantly decreased by the addition of sodium chloride because of the reduction of ion-ion interactions with ionic strength. These results suggest that CBM is useful, as an *in*

vitro method, for examination of influence of ion-ion interactions on diffusion of drugs.