The Effect of Indomethacin and Derivatives on the Phase Transition Parameters of DMPC

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INTRODUCTION: Nonsteroidal anti-inflammatory drugs (NSAIDs) are used worldwide due to their anti-inflammatory, analgesic and antipyretic properties. The NSAIDs-induced gastrointestinal (GI) injury may be related with their deleterious effect on the phospholipid lining that coats its mucosa and/or on the cell membranes.
OBJECTIVES: Therefore, we aim to study the effect of indomethacin and derivatives in the phase transition parameters of 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC), using liposomes as membrane model.
MATERIAL AND METHODS: Indomethacin and acemetacin (Sigma-Aldrich), NO-indomethacin (Cayman Chemical) and DMPC (Avanti Polar Lipids). DMPC and drug were solubilized in chloroform/methanol (3:2, v/v). The solvents were evaporated under a nitrogen stream and the obtained film was left under vacuum for 30 min. The films were hydrated with buffer, vortexed and extruded through polycarbonate filters (100 nm) at 40 ºC. Differential scanning calorimetry measurements were performed using a microcalorimeter (VP-DSC, MicroCal). The samples were analyzed from 10 to 40 ºC at a scan rate of 20 ºC/h.
RESULTS AND DISCUSSION: The effect of drugs on the temperature (T_m), the full width at half height ($\Delta T_{1/2}$) and the enthalpy (ΔH) of the main phase transition of DMPC were analyzed at pH 5.0 and 7.4. All three NSAIDs decrease T_m with increasing drug/lipid ratios at both pHs. However, the effect of indomethacin and acemetacin is higher at pH 5.0, at which they also increase $\Delta T_{1/2}$. Since pK_a of indomethacin and acemetacin are around 5, there are a higher percentage of neutral molecules at pH 5.0, facilitating their interaction with the bilayer, thus increasing their effect. NO-indomethacin (pK_a = 11.7) exerts a similar effect on the phase transition parameters at both pHs, decreasing T_m, increasing $\Delta T_{1/2}$ and maintaining ΔH.
CONCLUSION: Indomethacin and derivatives have the ability to interact with phosphatidylcholine bilayers and disrupt its phase transition properties. Such effect may contribute to their efficiency in causing GI injury.

Keywords: Nonsteroidal anti-inflammatory drugs, liposomes, lipid phase transition.
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