

## Drug Release Characteristics of Ternary Mica/Phosphatidylcholine/Drug Intercalation Compounds

Yasushi KANZAKI\*, Yuko SHIMOYAMA, Maki TSUKAMOTO, Motoko OKANO, Noriko SUZUKI, and, Yoshiteru WATANABE

Showa Pharmaceutical University, Machida, Tokyo 194-8543, Japan

The swelling layered inorganic layered compounds can intercalate various organic compounds with long alkyl chains, such as *n*-octadecylamine and natural phospholipids. In the case of phospholipids, the bilayers of phospholipids similar to the natural cell membrane are formed between the host inorganic layered lamellae. Such space of the lipid bilayer has a potentiality to accommodate the various functional compounds such as drugs. We have proposed to use the intercalation compounds of inorganic layered compounds with phospholipids as drug delivery systems (DDS). Synthetic mica (TSM) and reduced type phosphatidylcholine (H-PC) were used to prepare the lipid intercalation compounds. The second guest drugs were accommodated into the lipid layered compound, and the ternary TSM/H-PC/drug compound was prepared. There many inorganic layered compounds. In this study, tetrasilicic fluoro mica (TSM) was selected because it is very stable against acids and bases and is expected to be harmless to the human body. As for the phospholipids, reduced type phosphatidylcholine (H-PC) which was prepared by reducing the residual double bonds in the alkyl chains of natural soybean phosphatidylcholine using metal catalysis, was selected because it is relatively stable against oxygen. Two model drugs are examined in this study: one is the oil-soluble indomethacin (IM) and the other is the water-soluble imipramine chloride (IMC).

Two methods were used to prepare the ternary (TSM/H-PC/drug) intercalation compounds. One was the solvent method and in this, TSM powder was mixed with H-PC/chloroform solution at 37 °C for two days and the intermediate H-PC/TSM intercalation compound was prepared in advance. Well defined bilayers of H-PC were formed in each gallery between TSM monolayer sheets. The H-PC intercalation compound was then mixed with indomethacin or imipramine chloride. The mixture was heated at 180 °C for 10 min and the ternary drug intercalation compound was prepared. The other was the heating method and in this, the mixture of was heated at 180 °C for 10 min to prepare the ternary (TSM/H-PC/IM) intercalation compound

directly. Release of the model drugs accommodated in the layered compound was examined using either powdered or molded materials.

The intercalation of model drugs was first carried out by the solvent method. The gallery heights of the layered TSM, H-PC bilayer, TSM/H-PC, (TSM/H-PC/IM), and (TSM/H-PC/IMC) were 1.51, 6.13, 6.91, 6.25, and 5.4 nm, respectively, and suggested that bilayers of H-PC were successfully formed between host lamellae.

The release rate of IM and IMC into buffered aqueous solution (pH=7.0) was examined by the JP-13 puddle method. The release characteristics of the powdered intercalation compounds were compared with those of parent drug powders.

Very surprisingly, the initial rate of release was faster in the intercalation compounds than the simple drug powder in the case of IM contrary to our expectations because drug molecules must be accommodated deeply into the layered lattice. Generally speaking, IM molecules must located near the hydrophobic tail-to-tail region of the dual chain of H-PC because IM is hydrophobic and the release rate must be rather fast. However, the amount of IM released was about 1/3 that of intercalated IM. Accordingly, most IM molecules must be buried deeply near the hydrophilic head and release rate of such IM must be slow.

A similar results for IMC were obtained in the case of water soluble IMC. In this case, only TSM/H-PC/IMC prepared using solvent method was examined. The initial release rate of IMC from the TSM/H-PC/IMC intercalation compound was slow compared with the oil-soluble IMC. In the case of IMC, however, most of the intercalated IMC was released, unlike IM. Accordingly, IMC molecules must be dispersed randomly in the hydrophobic tails.

Further studies are required to elucidate the crystallographic property of ternary TSM/H-PC/drug intercalation compounds. According to such crystallographic studies, the potentiality of such compounds for DDS must be proved.

## References

- 1) Y. Watanabe, Y. Kanzaki, M. Fujii, Y. Matsumoto, I. Shiozaki, T. Tanaka, M. Matsumoto, *Chem. Pharm. Bull.*, 42, 163 - 166 (1994).
- 2) Y. Kanzaki, M. Hayashi, C. Minami, Y. Inoue, M. Kogure, Y. Watanabe, T. Tanaka, *Langmuir*, 13, 3674 - 3680 (1997).
- 3) Y. Kanzaki, Y. Shimoyama, M. Tsukamoto, M. Okano, N. Suzuki, Y. Inoue, T. Tanaka, K. Koizumi, Y. Watanabe, *Chem. Pharm. Bull.*, 42, 163 - 166 (1994).