PHARMACOKINETICS AND METABOLISM OF ANTIPYRINE ENTRAPPED IN SMALL (DIAMETER <7μM) VESICULAR SYSTEMS

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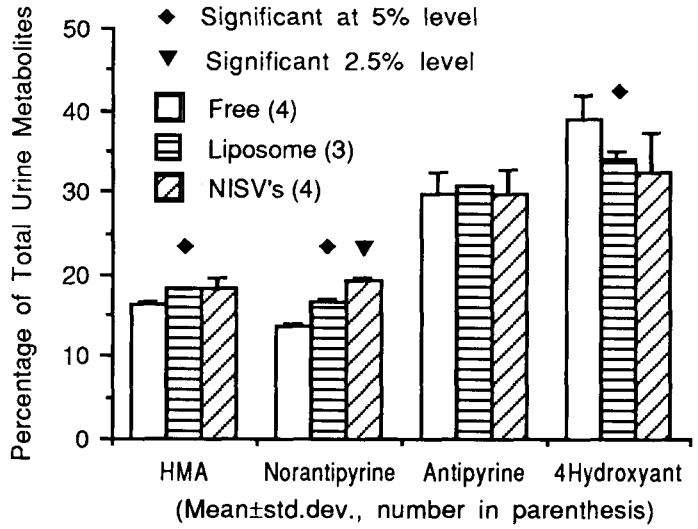
The microencapsulation of drugs in vesicular systems has been extensively investigated for drug targeting and drug delivery. Several authors have found that the pharmacokinetics, metabolism and distribution of the entrapped drug was markedly altered by these systems (Rogerson et al 1988). To assess these effects we have studied the pharmacokinetics and drug metabolism of antipyrine after entrappment in two small (diameter <7μm) vesicular delivery systems. The systems studied were liposomes and the recently introduced non-ionic surfactant vesicles (NISV).

The vesicular systems were prepared by the standard handshaking technique and then reduced in size by sonication. Vesicles composition was a 7:2:1 molar ratio of phosphatidyl choline: cholesterol: dicetyl phosphate for the liposomes and Surfactant IV: cholesterol: dicetyl phosphate for the NISV. The free and entrapped drug were adminsitered to male New Zealand White rabbits at a dose of 12.5mg/kg by IV injection via the marginal ear vein. Blood samples were withdrawn from the vein at various time intervals and a 24 hour urine sample collected by the use of a metabolic cage. The animal was allowed a 7 day recovery period between each experiment. Blood and urine samples were analysed for antipyrine and metabolites using the HPLC method of Teunissen et al (1983). Differences between the free and entrapped drug were assessed using a Mann Whitney U-Test

Figure 1. Urine Metabolites.



The results obtained for the free drug are in agreement with published figures (Chambers and Jefferson 1982) with a measured half life of 58 minutes. After entrappment the half life is markedly increased (Table 1) by a factor of three or four. The results are not system dependent and exhibit a marked variation in half life with the NISV providing the highest value. Both results are greater than those reported for antipyrine entrapped in large vesicular systems (Al-Angary et al 1989), probably reflecting different localisations of the smaller carriers. Urine metabolite values are presented in Figure 1, and there is a significant difference between free and entrapped drug. The vesicular systems reduce the quantity of 4-hydroxyantipyrine excreted but increase the levels of 3-hydroxymethylantipyrine and norantipyrine.

The results suggest that the encapsulation of drugs in small carrier systems is likely to alter both the pharmacokinetics and metabolism of the drug and the magnitude of the effect is dependent on the system used. The relevance of these results to the use of vesicular drug delivery systems remains to be elucidated.

Table 1. Pharmacokinetic Values (mean±std.dev., number in parenthesis)

Preparation	Half-life(min)
Free Drug	58 ± 16 (4)
NISV	214 ± 17 (4)
Liposome	151 ± 38 (3)

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Rogerson, A., et al (1988) J.Pharm.Pharmacol. 40: 337-342
Teunissen, M., et al (1983) J.Chromatography. 278: 367-342