THE INFLUENCE OF FORMULATION ON THE IN-VITRO DIGESTION OF TRIGLYCERIDE EMULSIONS BY PANCREATIC LIPASE

D. Challis, C.W. Pouton, B.J. Meakin and S.P. Jones[1], School of Pharmacy and Pharmacology, University of Bath, BA2 7AY and [1]Sterling Winthrop Research Group, Alnwick, Northumberland.

Emulsions have potential advantages over solid dosage forms for the oral administration of drugs whose absorption is dissolution-rate limited. As the major route of drug absorption will be by passive uptake from the aqueous phase, the partitioning of the drug from the emulsion droplets is likely to be a determinant of absorption rate. Digestion of the oil phase by pancreatic lipase therefore will greatly affect the absorption of the drug. Our particular interest is in self-emulsifying drug delivery systems (SEDDSs) such as that formed by mixtures of 30% Tagat TO and 70% Miglyol 812 (Wakerly et al, 1986). In this study we have compared lipolysis of SEDDS with homogenised emulsions of Miglyol 812 formed in the absence of surfactant (M812) or with 1.2% crude egg lecithin (M812-EL).

5ml of each emulsion (5%w/w oil) was supplemented with 60mM sodium chloride and 30mM calcium chloride in the presence or absence of 6mM bile salt mixture (O'Connor et al, 1986). 0.25ml of 5%w/w crude pancreatic lipase was added to start the reaction. Lipolysis at 310K was monitored continuously at pH 7 or pH 8.5 by titrating the liberated free fatty acids with NaOH using a pH stat (Radiometer).

Lipolysis progressed until two fatty acids were liberated per molecule of triglyceride. Table 1 compares the rates of lipolysis for selected experiments expressed as the time taken to reach 50% completion of reaction (t50%). At both pHs in the presence and absence of bile salts the rate of lipolysis was slowest for the self-emulsified system despite the fact that its particle size was substantially finer than either of the other emulsions. This indicated substantial inhibition of lipolysis when Tagat TO was present at the oil-water interface. Inhibition of lipolysis by surface active agents has been reported previously by Gargouri et al (1983). M812-EL emulsion was digested more rapidly than the crude M812 emulsion in all experiments perhaps due to the low surface area available for reaction with the pure triglyceride. The inflence of particle size distribution on reaction rate was difficult to establish since solubilization and stabilization of the emulsions occurred in the presence of bile salts and colloidal lipase. Furthermore changes in particle size distribution took place throughout the reaction as evidenced by changes in the turbidity of the reaction mixture. Tagat TO is an ethoxylated triglyceride and was susceptible to enzymatic lipolysis though the reaction rate for finely dispersed Tagat TO was 29 times slower than that of the SEDDS emulsion.

Table 1. Mean (sd) t50% (min) of lipolysis reaction (n=3)

	pH 7 with bile salts	pH 8.5 without bile salts
SEDDS emulsion	90.3 (4.4)	> 4h#
M812 crude emulsion	18.7 (1.9)	104.5 (29.3)
M812-EL emulsion	12.7 (1.5)	50.9 (12.7)

#35.3 ± 1.3 % lipolysis had occurred after 4h

Our results suggest that the M812 present in a realistic dose of SEDDS would be digested during passage of the small intestine but that the rate of digestion would be slower than that for dietary triglycerides. Digestion of the Tagat TO present in a SEDDS emulsion is very much slower and may not be completed during normal gastrointestinal transit.

Wakerly, M.G. et al (1986) J. Pharm. Pharmac. 38 : 2P

Gargouri, Y. et al (1983) J. Lipid Res. 24: 1336-1342

O'Connor, J. et al (1986) in 'Surfactants in Solution Vol. 2' pp 875-889 (eds. Mittal, K.L. and Lindman, B., Plenum Press)