THE EFFECT OF PH AND BILE SALTS ON THE HYDROLYSIS OF A SELF-EMULSIFIED SYSTEM BY PANCREATIC LIPASE

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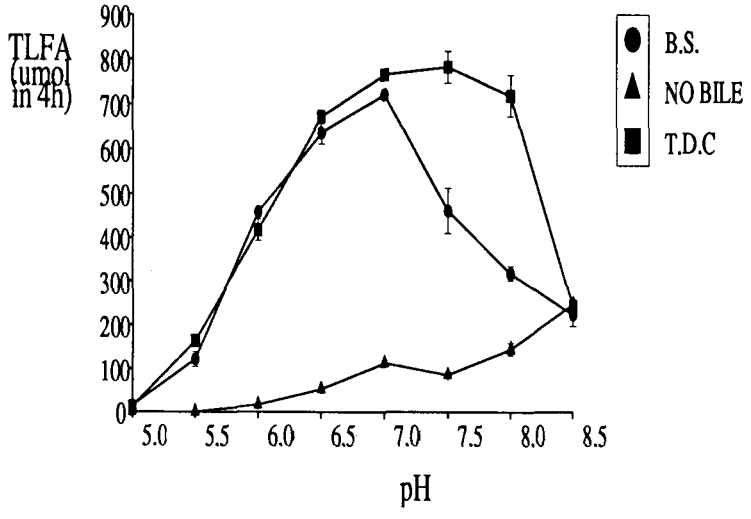
A SEDDS has been developed comprising 30% w/w Tagat TO (polyoxyethylene-25-glyceryl trioleate) and 70% Miglyol 812 (a mixture of medium chain triglycerides) (Wakerly et al, 1986). The absorption of drugs from SEDDSs after peroral administration is expected to be affected by the digestion of the triglycerides in the gut. Here we report the effects of pH and bile salts on in vitro digestion of a typical formulation by pancreatic lipase.

5 % w/w SEDDS emulsion was formed under gentle conditions of agitation, as previously described (Challis et al, 1989). Lipolysis of 5ml samples of such emulsions after addition of 250 ul of 5 % w/v lipase solution was followed for four hours by continuously titrating the liberated fatty acids with sodium hydroxide using a pH Stat (Radiometer). The lipase used was a crude preparation from porcine pancreas (Sigma), which contained the lipase-colipase complex. The reaction was conducted at 310K in the presence of 60mM sodium chloride and 30mM calcium chloride. Lipolysis was studied in the presence or absence of 6mM bile salts either as pure sodium taurodeoxycholate (TDC) or as a simulated human bile salt mixture (BS) (O'Connor et al, 1986).

Lipolysis proceeded in a reproducible manner at each pH studied but the precise shape of the reaction profile (versus time) and the ultimate end-point were dependent on pH. At pH 8.5 the reaction proceeded at a constant comparatively slow rate until the equivalent of two moles of fatty acid were cleaved from the triglycerides present. The rate of lipolysis in the presence of bile was greatest at pH 7 when the reaction profile was typified by a lag phase before a very rapid phase of lipolysis which continued towards the end point as above. The overall rate decreased when the pH was lowered further and was negligable below pH 5. Below pH 6.5 completion of the reaction occurred before all the triglyceride had been converted to monoglyceride. This was thought to be due to increased solubilization of diglycerides at low pH. A convenient practical measure of reaction rate was the total liberation of fatty acid (TLFA) over 4h. Figure 1 shows TLFA as a function of pH in the presence and absence of bile salts. The bile salt mixture had similar effects to pure TDC greatly enhancing lipolysis at neutral pH. In the absence of bile activity was greatest at pH 8.5 but this would seem to have little relevance to in vivo lipolysis

Figure 1



Challis, J. et al (1989) J. Pharm. Pharmac. 41: 115P

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

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