Evaluation of the Impact of Surfactant Digestion on the Bioavailability of Danazol after Oral Administration of Lipidic Self-Emulsifying Formulations to Dogs

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Received 9 April 2007; revised 18 September 2007; accepted 5 October 2007

Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/jps.21246

ABSTRACT: Lipid-based formulations of danazol with varying quantities of included surfactant have been examined *in vitro* and *in vivo*. Formulations comprising fatty acid ester surfactants were readily hydrolysed during *in vitro* digestion, although Cremophor RH40 (CrRH) was less effectively hydrolysed than Cremophor EL (CrEL). Formulations comprising high quantities of digestible surfactant also appeared to less effectively prevent danazol precipitation during *in vitro* evaluation. These trends were replicated *in vivo* where danazol bioavailability in beagle dogs was higher after oral administration of self-emulsifying formulations employing 55% (w/w) CrRH when compared with CrEL. The oral bioavailability of danazol after administration of drug formulated in surfactant alone, however, was poor. Studies using predispersed and encapsulated formulations of CrRH subsequently suggested that the low bioavailability of the single surfactant formulations reflected poor dispersion. Mixtures of surfactants, improved dispersion and good oral bioavailability of danazol was evident after administration of formulations comprising CrRH and either Pluronic L121 or Gelucire 44-14, in spite of evidence of danazol precipitation during *in vitro* digestion of the Gelucire formulation. These data suggest that effective dispersion and resistance to precipitation during both dispersion and digestion are key design parameters for lipid-based formulations comprising high proportions of surfactant.
J Pharm Sci 97:995–1012, 2008

Keywords: self-emulsifying lipid-based formulations; poorly water-soluble drugs; surfactants; in vitro lipid digestion; oral bioavailability; danazol; Cremophor

INTRODUCTION

In recent years, *in vitro* lipid digestion models have been increasingly utilised to assist in the design of self-emulsifying lipid-based formulations and to better predict the ability of these formulations to enhance the oral bioavailability of poorly water-soluble drugs.[1–6] Using these models, previous

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Journal of Pharmaceutical Sciences, Vol. 97, 995–1012 (2008)

studies have shown that digestion of the lipidic components contained in self-emulsifying lipid-based formulations may, in some cases, lead to reduced drug solubilisation and therefore reduced drug absorption. In particular, lipid-based formulations containing medium-chain lipid have been shown, at least in the case of halofantrine, danazol and LU 28–179, to promote less effective drug solubilisation and absorption when compared to their long-chain comparators.[7–10]

Although self-emulsifying lipid-based formulations comprising long-chain lipids appear to effectively promote drug absorption for poorly water soluble drugs, recent studies have also shown that the oral bioavailability of danazol may be reduced after administration of self-emulsifying lipid-based formulations containing lower quantities of long-chain lipid and relatively higher quantities of surfactant and/or cosolvent.[11] These studies suggested that the surfactant (Cremophor EL, CrEL) present in the formulations did not maintain danazol solubilisation in the gastrointestinal tract (GIT) as effectively as the digestion products of long-chain lipids, and further suggested that the poor solubilisation properties of CrEL may reflect its susceptibility to digestion by pancreatic enzymes.

Understanding the performance of formulations comprising larger quantities of surfactants is becoming increasingly important as poorly water-soluble drugs with intermediate partition coefficients ($2 < \log P < 4$) are typically less soluble in most natural glyceride lipids than they are in more amphiphilic surfactants, cosurfactants and cosolvents. Formulations comprising large quantities of surfactants also typically produce fine dispersions when introduced in aqueous media and small particle sizes have been suggested to increase drug absorption.[12,13] As such the development of self-emulsifying formulations comprising primarily nonionic surfactants and cosurfactants/cosolvents with relatively smaller quantities of natural mono-, di- and triglycerides (i.e. types IIIB and IV formulations as classified by Pouton[14]) has become increasingly common.[15–17]

In the current studies, therefore, formulations classified as type IIIB (i.e. those containing relatively high proportions of hydrophilic and water soluble surfactants and lower quantities of glyceride lipids) and type IV (i.e. those which do not contain glyceride lipids and comprise surfactants, cosurfactants or cosolvents alone) have been employed in order to examine the issues associated with surfactant digestion. Specifically, the susceptibility of a range of commonly used nonionic surfactants to *in vitro* digestion and the effect of surfactant digestion on *in vitro* solubilisation and *in vivo* bioavailability of a series of self-emulsifying lipid-based formulations has been examined. Danazol, a poorly water-soluble steroid [aqueous solubility <1 μg/mL, $\log P = 4.53$[18]] has been included in all formulations as a model poorly water-soluble drug.

MATERIALS AND METHODS

Materials

Danazol (pregna-2,4-dien-20-yno)2,3-d(isoxazol-17-ol) was kindly supplied by Sterling Pharmaceuticals (Sydney, Australia). Soybean oil (C_{18} triglycerides), polyoxyl 35 castor oil (CrEL; HLB 12–14), sorbitan monooleate (Span 80; HLB 4), polyoxyl 10 oleyl ether (Brij 97; HLB 12.4), polyoxyethylene 20 sorbitan monooleate (Tween 80; HLB 15), polyethylene glycol 400 (PEG 400), sodium taurodeoxycholate 99% (NaTDC) and porcine pancreatin (8× USP specifications activity) were from Sigma (St Louis, MO). Maïsine 35-1, a blend of long-chain mono- and diglyceride consisting primarily of linoleic acid (55%, $C_{18:2}$), oleic acid (29%, $C_{18:1}$) and palmitic acid (11%, $C_{16:0}$); lauryol PEG-32 glycerides (Gelucire 44/14; HLB 14) consisting primarily of lauric acid (43%, $C_{12:0}$), myristic acid (17%, $C_{14:0}$), stearic acid (12%, $C_{18:0}$) and palmitic acid (10%, $C_{16:0}$); and PEG-8 caprylic/capric glycerides (Labrasol; HLB 14) consisting primarily of caprylic acid (68%, $C_{8:0}$) and capric acid (30%, $C_{10:0}$), were a generous gift from Gattefossé (St. Priest, France). Polyoxyl 40 hydrogenated castor oil (Cremophor RH40; HLB 14–16) was donated by BASF (Ludwigshafen, Germany) and the triblock polymer of ethylene oxide and propylene oxide Pluronic L64 (HLB 12–18) and Pluronic L121 (HLB 1.2) were from BASF (Parsippany, NJ). Lecithin (approximately 60% pure phosphatidylcholine (PC) by HPTLC[19] from egg yolk) was a gift from Pharmacia LKB (Uppsala, Sweden). 4-bromophenylboronic acid (4-BPB) was obtained from Aldrich Chemicals Co. (St. Louis, MO) and 1 M sodium hydroxide (Titrisol), which was diluted to obtain either 0.2 or 0.6 M NaOH titration solutions, was purchased from Merck (Darmstadt, Germany). Water was obtained from a Milli-Q water purification system (Millipore, Bedford, MA). All other chemicals and solvents