Mechanistic studies of self emulsifying drug delivery systems for the oral delivery of hydrophobic drugs: digestion kinetics and effect of formulation digestion on drug release

Fulden Buyukozturk[1], James Benneyan[2], David Budil[3], Rebecca L. Carrier[1]

[1]Department of Chemical Engineering, Northeastern University, Boston, MA, 02115
[2]Department of Mechanical and Industrial Engineering, Northeastern University, Boston, MA, 02115
[3]Department of Chemistry and Chemical Biology, Northeastern University, Boston, MA, 02115

Introduction

Oral drug delivery is a $35 billion dollar industry [1] and the most preferred way of drug administration. However, the oral route is not possible for 50% of currently marketed drug compounds due to their low solubility in water. Forty percent of prospective drugs coming out of discovery pipelines are lipophilic compounds, which leads to difficulty in achieving acceptable oral bioavailability. Lipid based drug delivery systems, and in particular self-emulsifying drug delivery systems (SEDDS), show great potential for enhancing oral bioavailability of lipophilic drugs, as well as offering the advantage of minimal processing and inherent stability, but have not been broadly applied, largely due to lack of general formulation guidance and lack of knowledge of how these systems function to enhance bioavailability [2, 3]. SEDDS are oil in water emulsions that typically have droplet sizes ranging from tens of nanometers to hundreds of nanometers and consist minimally of oil, surfactant, and the drug to be delivered dissolved in oil (Figure 1). SEDDS are spontaneously formed in the gently mixed aqueous gastrointestinal (GI) environment [4].

To gain a better understanding of the dependence of emulsion drug delivery function in the GI tract on formulation composition, a quantitative study of properties central to emulsion function was conducted utilizing representative self-emulsifying formulations based on a 3^3 factorial experimental design. Formulations have been studied as follows. Oils from three different structural classes (long chain triglyceride (Soybean oil), medium chain trigylcerides (Neobee M5), propylene glycol dicaprylate/dicaprate (Captex 200)) and surfactants with hydrophilic-lipophilic balance (HLB) values ranging from 10-15 (Cremophor EL, Tween 80, a mixture of Capmul MCM and Labrasol) were combined at three different oil-to-surfactant weight ratios (9:1, 5:1, 1:1)..

A major reason why SEDDS influence oral bioavailability of a hydrophobic drug is the increased overall solubility in intestinal fluid upon oral administration. Mechanism by which SEDDS are believed to increase drug solubility is by digestion of lipid component of SEDDS formulation in the intestine and consequently solubilization of formulation lipid component digestion products into endogenous bile salt micelles leading to formation of complex colloidal structures which alter the overall drug solubility in the intestine. In this study, kinetics of formulation digestion was studied using an in vitro lipolyis set up and digestion profiles were expressed using a mathematical expression that relates digestion rate to droplet surface area. Secondly, partitioning of model drug Tempol Benzoate from emulsion droplets into aqueous phase (including mixed micelles) during in vitro lipid digestion was monitored using Electron Paramagnetic Resonance (EPR). Multi-component analysis of EPR spectra will give quantitative information on drug relase and partitioning processes during in vitro digestion. This information will be used together with mathematical expressions on digestion and absorption kinetics which will allow building an overall kinetic model to predict oral drug absorption.

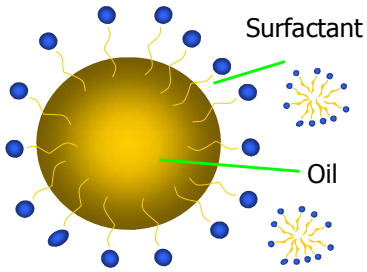

Figure 1. Schematic of an oil in water emulsion system

Experimental Methods

Spontaneous emulsification of 27 formulations was assessed by visual observation upon introducing formulations to DI water at 37°C under mild agitation conditions (300 rpm). Formulations that formed SEDDS were then characterized by measuring particle size and zeta potential utilizing a particle size analyzer. In vitro lipolysis experiments were conducted in biorelevant simulated intestinal fluid containing 100 mM tris-maleate, 65 mM NaCl, 5mM $CaCl\text{-}2H_2O$ at pH 6.5; with the addition of 5 mM NaTDC/1.25 mM PC solution (digestion buffer) in order to mimic fasted intestinal conditions. Formulations including Tempol Benzoate were added to 18

ml digestion buffer at 1:100 ratio and lipolysis was initiated with the addition of 2 ml pancreatin extract. Change in pH was monitored with a pH meter. Fatty acids produced due to digestion of long chain triglycerides were titrated with NaOH. Samples were collected at specific time intervals (0, 5, 20, 50 minutes), and the digestion process was terminated by the addition of enzyme inhibitior, 4-BPB (4-bromophenacyl bromide). Samples were analyzed with EPR.

Results and Discussion

Upon reaching the intestine, SEDDS begin to be hydrolyzed by lipase. Upon inception of digestion, digestion products are release from the surface of SEDDS into aqueous media forming complex colloidal structures. Meanwhile, drug compounds are released from SEDDS into intestinal fluid, and a portion of released drug further partitions into colloidal structures. In order to study digestion rates of statistically designed set of SEDDS formulations, digestion rates were expressed with a kinetic mathematical model and rate constants were calculated. Digestion rate was highest for formulations of medium chain triglyceride followed by medium chain diglyceride and long chain triglyceride and showed the same trend regardless of surfactant concentration or type. Overall, formulation consisting medium chain triglyceride oil with Tween 80 at 9:1 ratio had the highest and long chain triglyceride oil with Cremophor EL at 9:1 had the lowest rate of digestion.

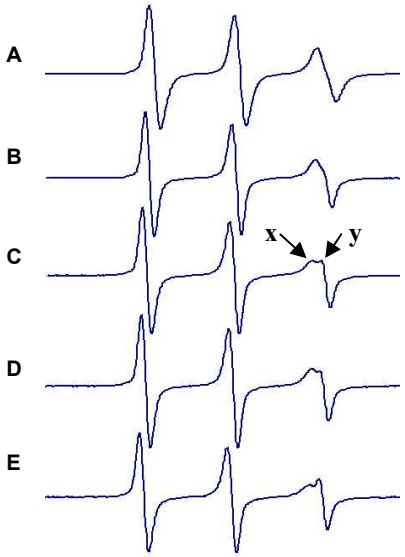

Figure 2. EPR spectra of 1:100 dilution formulation (Soybean oil-Tween 80 at 1:1 ratio) including probe Tempol Benzoate during in vitro lipolysis. A:0, B:5, C:25, D:50, E:90 minute into digestion. “x” indicates the peak location of oil, “y” indicates the aqueous phase.

In order to perform real time tracking of drug partitioning during the digestion process, EPR technique was utilized. Differences in peak to peak distances (a_N) and peak widths among EPR spectra (Figure 2), especially evident on the third peak, give information on the probe distribution among different phases (oil vs. vesicles and micelles vs. water). For the specific formulation studied (Figure 2), results indicate an increased partitioning of the probe from the oil phase into the micellar/water phase over a period of 90 minutes , which is seen by decrease in the “x” peak indicating oil phase and increase in the height of the “y” peak indicating water phase on the specta. This information, along with multi-component analysis performed by EPR software, will allow determination of the ratio of the spin probe in each phase.

Quantitative results on digestion kinetics and drug partitioning during digestion will be ultimately incorporated in an overall mechanistic mathematical model to predict and optimize oral absorption of a drug administered with SEDDS.

References

[1] Drug Deliver Markets. Edition 2 Volume I: Oral Delivery, Jan. 2007

[2] A.J. Humberstone, W.N. Charman, Lipid-based vehicles for the oral delivery of poorly water soluble drugs. Adv. Drug Deliv. Rev 25(1) (1997) 103-128.

[3] R. Neslihan Gursoy, S. Benita, Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs. Biomed. Pharmacother. 58(3) (2004) 173-182.

[4] J. Yamamoto, H. Tanaka, Transparent nematic phase in a liquid-crystal-based microemulsion. Nature 409(6818) (2001) 321-