

The effect of intestinal bile on the stability of lipid-based vesicular system used as oral drug carriers

Mosab Arafat*

Mosab Arafat, Assistant Professor, College of Pharmacy, Al Ain University of Science and Technology, Al Ain, PO Box 64141, Al Ain, Abu Dhabi, UAE

Abstract

Many lipid-based vesicles such as liposomes have been investigated as a colloidal carrier for oral drug delivery systems. However, their low stability in the gastrointestinal tract is still a major issue. A solubilisation of the phospholipids membrane triggered by intestinal bile salts in the small intestine causes premature release of the bioactive compound prior to intestinal absorption. In contrast, inclusion of bile salt in the preparation of lipid-based vesicular systems seems to play an important role in stability by enhancing the vesicles integrity upon exposure to intestinal bile salt in the gut. Thus, the present review gives a suggestion on further understanding of colloidal and interfacial mechanisms underlying the role of bile salt in the partitioning, transport and uptake processes as this might be a key toward optimum strategies improving the stability of lipid-based vesicles.

Intestinal bile salts are bio-surfactants existing in the gastrointestinal tract (GIT) which have essential role either on fat and lipid digestion or absorption [1]. Acidic lipases, which are secreted by the gastric chief cells in the fundic mucosa of the stomach, regulate 10-30% of the lipid hydrolysis. In the other hand, pancreatic lipases make up to 90% of lipid hydrolysis in the small intestine. The process is supported by bile salts distributed through a network of bile ducts, first secreted from hepatocytes, transported via bile canaliculi, exit the liver via hepatic duct, joined with cystic and pancreatic duct to finally enter the small intestine. This hepatic bile contains large quantities of bile acids, cholesterol and other organic molecules. The main function of bile salt is to enhance emulsification and absorption of oils and lipoids upon aggregations. Thus, intestinal bile salts have an immediate effect on the lipolysis process of lipid-based components [2]. Similarly, lipid-based colloidal systems used for oral drug delivery system such as liposomes are expected to be subjected to these digestion processes. Being highly susceptible to the detergent effect of intestinal bile salt they tend to undergo destruction of the phospholipids bilayer and ultimately the solubilisation of the vesicular membrane [3]. As a result of the solubilising effect, a premature leakage of entrapped bioactive compounds might occur in the gut prior to intestinal absorption.

The lipolysis can take place on the surface as well as the interface of the lipid vesicles. Herein, the demolishing effect on the bilayer is dependent on the high bile salt concentration of the environment. A decreased integrity can convert the vesicles into mixed micelles based on the interaction of bile salt with lipids, causing further leakage to the entrapped bioactive compounds [4-8]. Exposed to the intestinal environment would be an issue for many drug, being either hydrolytically degradation by acidity or enzymes, or they might crush out due to low solubility.

The lipid composition of vesicles has been shown to influence the stability against intestinal bile salts and enzymes [9]. Furthermore, the incorporation of a particular amount of exogenous bile salt into lipid-based vesicles can resist the disruption and degradation through intestinal bile salts [10]. Thereby, inclusion of bile salts as an integral part

in the vesicle formulation can stabilize lipid-bilayer membranes against the further detergent effects of intestinal bile salts through repulsion [11]. The amount and type of exogenous bile salt to be incorporated in the lipid-based vesicles is critical and it mainly depends on their critical micelles concentration (CMC) [11]. Table 1 shows different types of bile salts, their CMC and their aggregation constant related to their hydrophobicity [12].

The amphipathic nature of exogenous bile salts is essential on enhancing the absorption of bioactive compounds by increasing their solubility and altering the membrane permeability by interacting with the local phospholipids [13]. Thus, bile salt can be used as penetration enhancers in drug formulations to support mucosal absorption especially due to the membrane destabilizing properties [14,15]. It was shown that bile salts can significantly enhance the intestinal permeability and oral bioavailability of class III drug [16,17]. Consequently, the incorporation of bile salt has a double positive effect protecting the vesicular integrity and supporting the transport through the intestinal mucosa.

Even being successful, only a few examples have been shown in literature. Almost 50 years ago, bile salts were described to enhance transport of poorly absorbable drugs through the intestinal mucosa [18]. Mixed micelles of lipids and bile salts were shown to increase oral bioavailability of poorly water-soluble silybin [19], Cucurbitacin B [20] or benzodiazepines [21], as well as acid-labile cefotaxime [16]. However, the bilosomes research has been mainly focused on oral vaccine delivery [10,22,23] or the protection of other peptidomimetic compounds such as insulin [24]. Lately, the application has been extended to hydrophobic drugs, for example fenofibrate [25], or the

Correspondence to: Mosab Arafat, Assistant Professor, College of Pharmacy, Al Ain University of Science and Technology, Al Ain, PO Box 64141, Al Ain, Abu Dhabi, UAE, E-mail: Mosab.arafat@aau.ac.ae

Received: December 02, 2016; **Accepted:** December 21, 2016; **Published:** December 23, 2016

Table 1. Overview of critical micelle concentration (CMC), aggregation number and aggregation constant for different bile salts.

Bile salt types	Minimum CMC	Maximum CMC	Aggregation constant
Deoxycholate	2 mM	5 mM	17
Chenodeoxycholate	6 mM	9 mM	15
Ursodeoxycholate	2 mM	19 mM	5
Cholate	4 mM	20 mM	7

acid-labile cefotaxime [17].

Today, lipids-based vesicular drug delivery systems are progressively being utilized for delivering various bioactive compounds. Hence, the integration of exogenous bile salt in the lipid bilayer membrane can support the development and preparation of stable vesicular systems to protect a wide range of sensitive active compounds. The use of bile salts combines two of their major advantageous properties which are as follow: 1) acting as permeation enhancer agent and 2) physically stabilizing the lipid-based vesicles to prevent premature release of the bioactive compounds, and finally degradation the gut before mucosal uptake. In this regards, considering the bile salt incorporation in the formulation of lipid-based vesicular systems is beneficial. However, a further understanding of the colloidal and interfacial mechanisms underlying the role of bile in the partitioning, transport and uptake processes is a key to lead to optimum strategies on improving the stability of lipid-based vesicles in oral administration.

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