

THE ROLE OF LIPIDS IN DRUG ABSORPTION THROUGH THE GIT

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RESUMO

Os vectores lipídicos apresentam inúmeras vantagens para a administração oral de substâncias farmacológicas, p.ex. são compostos por moléculas lipídicas semelhantes às aquelas que figuram nos tecidos humanos, tornando-se biocompatíveis, biotoleráveis e biodegradáveis. São exemplos as tradicionais emulsões O/A, as suspensões de nanopartículas lipídicas (SLNs e NLCs) e, recentemente, as SolEmuls®, que permitem localizar fármacos fracamente solúveis em ambas as fases das emulsões, na camada interfacial de lecitina. Este artigo aborda o papel dos lípidos no aumento da absorção e da biodisponibilidade de fármacos administrados oralmente.

PALAVRAS-CHAVE: administração oral de fármacos; lipossomas; nanopartículas de lípidos sólidos; vectores lipídicos nanoestruturados.

ABSTRACT

Lipid carriers show several advantages for oral delivery of pharmacologically active drugs, e.g. are composed of lipid molecules similar to those in human tissues, becoming therefore biocompatible, biotolerable and biodegradable. Examples include traditional o/w emulsions, suspensions of lipid nanoparticles (SLNs and NLCs) and, recently, the SolEmuls®, which allows localizing poorly soluble drug molecules both in oil and aqueous phases, in the interfacial layer of lecithin. This paper reports on the role of lipids in enhancing both drug absorption and bioavailability when administered orally.

KEY-WORDS: oral drug delivery; liposomes; solid lipid nanoparticles; nanostructured lipid carriers.

1. INTRODUCTION

Administration of drugs through the oral route is usually the most acceptable way of self-medication due to both enhanced patients convenience and compliance. Nevertheless, drug absorption through the gastrointestinal tract (GIT) is deeply hampered by different biological barriers (biochemical and/or physical), of which the first pass metabolism occurring both in enterocytes and in liver is but a good example (Lennernäs, 1998). Biochemical barriers include enzymes existing in the gastrointestinal (GI) lumen as well as efflux pumps present in the epithelial cells, whereas physical barriers consist of epithelial cell membranes, tight junctions and mucus layer. Overcoming these barriers is currently one of the most challenging goals in oral drug delivery (Majumdar and Mitra, 2006; Leonard *et al.*, 2006; Hamman *et al.*, 2005; Ghilzai, 2004). Many drug molecules cannot be effectively and efficiently delivered orally in their original form due to several factors, viz. instability, low membrane permeability, poor solubility and efflux transport mechanisms (Merisko-Liversidge, 2002). Thus, several strategies have been developed aiming at improving drug bioavailability following oral administration (Morishita and Peppas, 2006; Hamman *et al.*, 2007). Some of those strategies include maximizing the intestinal uptake of drug molecules while others focus on protecting the drug molecules from degradation, but combinations thereof have also been reported (Goyal *et al.*, 2005; Hamman *et al.*, 2007). With their ability to solubilize hydrophobic drug molecules, lipid-based drug delivery systems have proven to improve drug absorption and dissolution rates in the GIT. Parenteral oil-in-water (o/w) emulsions are used as intravenous (i.v.) carriers for poorly water-soluble drug molecules, which are carried in the inner oil phase. This strategy allows 'solubilisation' of such water-insoluble drugs without using organic solvents and avoids at the same time the use of solubilisers potentially having side effects (Crauste-Manciet *et al.*, 1998). Compared to other particulate carriers such as liposomes and polymeric nanoparticles, o/w emulsions possess several advantages: they integrate accepted excipients; are physically long-term stable; can be produced on large scale using existing production lines; and can be sterilised by autoclaving. However, despite these manifold advantages, there are only a small number of drugs on the market formulated as i.v. emulsions, and two major reasons account for this: (i) poor solubility of drug molecules in regulatory accepted (GRAS – Generally Recognized As Safe) oils, and (ii) poor solubility of drug molecules in water and simultaneously in oils in general.

2. DRUG ABSORPTION THROUGH THE GASTROINTESTINAL TRACT

Following oral administration, a drug passes sequentially the mouth, esophagus, stomach, duodenum, jejunum (small intestine), colon (large intestine) and finally leaves the body if not absorbed. The first requirement for absorption to occur is drug dissolution, i.e. only dissolved drugs have the ability to permeate the GI membrane. As a result, drug solubility is a parameter of paramount importance. In the upper part of the intestine, duodenum, the bile released by the gallbladder may enhance the *in vivo* solubility of drugs to a large extent (Wiedmann and Kamel, 2002; Bakatselou *et al.*, 1991; Horter and Dressman, 1997). Once dissolved, the drug is available in the intestine to be promptly absorbed. In order to facilitate the efficient absorption of nutrients from the intestinal lumen, the available surface area of the intestine is very large; the small intestine is invaginated and contains *villi*, with additional surface area being provided via the *microvilli* present on the apical side of the enterocytes (intestinal absorptive cells). The enterocytes are covered by mucus and an unstirred (quiescent) water layer. The biological membrane of enterocytes, consisting of a bilayer of phospholipids (PPL) integrating other structures and molecules such as proteins, cholesterol, carbohydrates, fatty acids, acylglycerols, etc. (Lee, 2003; McConnell and Radhakrishnan, 2003), presents the main barrier for absorption. As PPL (amphiphilic in nature) are the most abundant biomolecules in the lipid membrane and possess specific physicochemical properties, they will dictate the required characteristics of drugs in order to permeate through the double PPL bilayer. If PPL were much more hydrophilic, the membrane would be unstable and simply dissolve in water. On

the other hand, if PPL were too hydrophobic, not enough material would be present in the aqueous phase to form membranes. A drug molecule may pass through the layer of enterocytes in many different ways, but passive diffusion is the most important one. Besides passive diffusion, other mechanisms to reach systemic circulation include facilitated diffusion, paracellular transport, and endocytosis (Duizer, 1999). Prior to reaching systemic circulation, the drug molecule may be metabolized during absorption by enzymes existing in the enterocytes. Furthermore, when the drug reaches the portal vein it will directly be delivered to the liver where further metabolism may also take place. After passage through the liver, the drug finally reaches systemic circulation and is duly carried by the blood towards specific targets. Bioavailability is usually defined as the relative amount of an administered drug dose that reaches the systemic circulation (Jantratid *et al.*, 2008). Before a drug is able to pass through a physiological barrier it must be in a dissolved state (Ruckenstein and Shulgin, 2005). Important parameters that affect drug absorption and thus its bioavailability through the GIT include: (i) solubility and ionization state of drug in the lipids, (ii) aqueous solubility of drug required to provide an appropriate concentration gradient, (iii) oral dosage form, i.e. the drug release profile and dissolution rate, (iv) GIT motility, (v) blood flow and eventual pathological changes, (vi) gut microflora, which may metabolize some drugs, and (vii) presence of food and/or other medicines in the GIT. The following sections describe several state-of-the-art approaches to increase drug bioavailability following oral administration, by means of liposomes, lipid nanoparticles and, quite recently, by means of the so-called SolEmuls® Technology.

3. LIPID-BASED CARRIERS FOR ORAL DRUG DELIVERY

3.1. LIPOSOMES

Liposomes have been one of the most extensively investigated colloidal carriers in particular to improve the therapeutics of potent drugs (Samad *et al.*, 2007; Goyal *et al.*, 2005), and can be used to control retention of entrapped drugs in the presence of biological fluids and enhanced vesicle uptake by target cells (Goyal *et al.*, 2005). Liposomes are lyotropic liquid crystals (because they form liquid crystal phases due to the addition of a solvent) (Decher and Ringsdorf, 1993) composed of relatively biocompatible and biodegradable materials. They consist of an aqueous core entrapped by one or more bilayers of natural (PPL) and/or synthetic lipids, which may differ in dimensions, composition, surface charge and structure (Samad *et al.*, 2007; Goyal *et al.*, 2005). Drugs with widely varying lipophilicities can be encapsulated in liposomes either in the PPL bilayer, in the entrapped aqueous core or at the bilayer interface. Besides their ability to entrap hydrophilic and hydrophobic drug molecules, liposomes composed of natural lipids display highly interesting advantages by being biodegradable, biotolerable between their components and the human tissues, biologically inert, weakly immunogenic, produce no antigenic or pyrogenic reactions and reveal limited intrinsic toxicity (Decher and Ringsdorf, 1993; Goyal *et al.*, 2005). Liposomes are also easy to prepare, and their composition can be varied (e.g. including cholesterol molecules, cationic PPL) to obtain more efficient formulations (Goyal *et al.*, 2005; Zhang *et al.*, 1997), and to inhibit rapid clearance of liposomes by controlling particle size, charge and surface hydration (Mohammed *et al.*, 2006). With respect to oral administration, liposome formulations are targeted to reduce toxicity, enhance bioavailability and increase accumulation at the target site (Iwanaga *et al.*, 1997; McAlister *et al.*, 1999; Taira *et al.*, 2004; Lee *et al.*, 2005). The latest developments in this field include (i) specific binding properties of a drug-carrying liposome to a target cell such as a tumour cell and specific molecules in the body (antibodies, proteins, peptides); and (ii) stealth liposomes, which are being especially employed as carriers for hydrophilic anticancer drugs like doxorubicin and mitoxantrone (Samad *et al.*, 2007). Liposomes display a quite low physicochemical stability and in most cases require liophilization of the product to achieve proper stability during shelf-life. Moreover, chemically labile drugs (e.g. peptides and proteins) suffer a relatively fast release when entrapped into liposomes, and thus, no controlled release is achieved.

3.2. LIPID NANOPARTICLES

Lipid nanoparticles (LN) are colloidal-sized carrier systems that have been developed at the beginning of the nineties to overcome some of the drawbacks pointed out for liposomes (Muller *et al.*, 2000; Souto and Muller, 2007). LN can also be composed of PPL, which are used as surfactants surfacing the nanoparticles and stabilizing them in aqueous dispersions. LN are characterized by a solid matrix revealing high physicochemical stability, including the possibility to achieve controlled release and also protection of chemically labile drugs entrapped within their matrix. The literature reports two types of LN, the Solid Lipid Nanoparticles (SLN) and the Nanostructured Lipid Carriers (NLC). SLN consist of a matrix composed of a lipid being solid both at room and body temperatures, which is covered by a surfactant film that stabilizes them in aqueous dispersions. With regard to NLC, these are produced by mixing solid lipids with liquid lipids in NLC, instead of highly purified lipids with relatively similar molecules in SLN. This mixture has to be solid at least at 40°C. The major difference between SLN and NLC lies in the fact that production of the latter is performed by nanostructuring the lipid matrix, in order to increase drug loading and to prevent its leakage, giving more flexibility for modulation of drug release. The result is a less ordered lipid matrix with many imperfections, which can accommodate a higher amount of drug. Regarding oral protein delivery, an ideal formulation should allow an enhanced drug bioavailability with low blood profile variations, and simultaneously avoiding plasma peaks (Muller *et al.*, 2006, 2008). These systems can be alternative carriers for peptides, proteins and antigens (Almeida and Souto, 2007). Proteins and antigens intended for oral drug therapy can be entrapped within, or adsorbed onto the surface of LN. Several advantages may be pointed out, such as improved protein stability, avoidance of proteolytic degradation, and sustained release. Examples of peptides that have been successfully entrapped in LN are cyclosporine A (Muller *et al.*, 2006, 2008; Ugazio *et al.*, 2002; Varia *et al.*, 2008; Hu *et al.*, 2004), insulin (Iwanaga *et al.*, 1997; Zhang *et al.*, 2006a,b), and calcitonin (Garcia-Fuentes *et al.*, 2005a,b). Immunisation with protein antigens, infectious disease treatment, chronic diseases and cancer therapy might also be promising application areas for these carriers (Almeida and Souto, 2007). The therapeutic efficacy of anti-HIV agents (e.g. nucleoside and nucleotide analogues) is often hampered by poor bioavailability and lack of drug penetration in infected target tissues and cells (Li and Chan, 1999; Hillaireau *et al.*, 2006). However, the need of high doses due to the rapid elimination of these compounds, to their poor activation, and/or to their nonspecific distribution, often leads to side effects and resistances. LN have been demonstrated as potential carriers for antiviral nucleoside analogues, especially for anti-HIV agents, regarding both intravenous and oral routes (Li and Chan, 1999; Snedecor *et al.*, 2006). Paclitaxel is an essential drug for the treatment of human cancers. Due to both poor drug solubility and efflux systems in the GIT, peroral delivery of paclitaxel has been a significant challenge (Merisko-Liversidge, 2002). A mucoadhesive oral formulation (DHP107™, containing paclitaxel in a mixture of monoolein, triacprylin, and Tween 80) has been developed by several researchers (Hong *et al.*, 2007; Salles, 2007), that can directly and effectively deliver paclitaxel to intestinal endothelial cells without concomitant use of P-glycoprotein inhibitors: DHP107 is effectively absorbed through the intestinal lipid transport system, by changing spontaneously into droplets smaller than 100-µm and micelles in the intestine, which in turn adhere to mucoepithelial cells and is absorbed via lipid uptake mechanism, forming subsequently lipid bodies in the epithelium (Hong *et al.*, 2007; Salles, 2007).

3.3. SOLEMULS® TECHNOLOGY

Different methods can be approached to formulate poorly water soluble drugs, including use of solvent mixtures, surfactants for solubilisation, partial combination of surfactants and solvent mixtures, mixed micelles, and o/w emulsions (Muller, 2001; Muller *et al.*, 2004; Boyd *et al.*, 2007). However, for many poorly soluble drugs of interest no mixtures of water-organic solvent are available providing sufficiently high

solubility and oral acceptance. The main method to localize a drug in the interfacial lecithin layer of emulsions, is dissolution of both lecithin and the drug in an organic solvent, removal of the solvent by evaporation, and using the remaining lecithin-drug mixture for emulsion production (Lance *et al.*, 1995; Junghanns *et al.*, 2007). However, this process is not production-friendly, not suitable for sterile production, and is also costly. Thus, a novel approach has been described: solubilisation by emulsification (SolEmuls® technology) (Akkar and Muller, 2003a,b; Junghanns *et al.*, 2007). This process can in principle be applied to all poorly water-soluble and poorly oil-soluble drugs. Drugs that are poorly soluble in both water and oil phases of o/w emulsions can be successfully incorporated into the lecithin layer by accelerating the drug crystal dissolution process using high pressure homogenization. The drug dissolution process can also be performed during production of the emulsion. This approach shows several advantages, e.g. no additional excipients are needed in the formulation, the established production process of high pressure homogenization can be used without any changes leading to a product of high acceptance by the regulatory authorities.

4. CONCLUSIONS

The issue of poorly soluble drugs and their formulation has attracted increasing attention during the last few years. Special formulation approaches have been developed, being those of a lipidic nature highly suitable for oral drug delivery. Nevertheless, absorption of drugs through GIT is dependent on the nutritional state of the patient and on the presence of bile salts. In general, the presence of lipid molecules usually induces secretion of bile salts. The biosensors existing in the duodenum regulate the release of bile salts from the gallbladder, independently of the presence of fatty acids and triacylglycerols. Secretion of lipases from the pancreatic ducts is also regulated. The lipase in combination with co-lipase degrades triacylglycerols to surface active mono and diacylglycerols, which can in turn solubilize the drug, thus promoting its absorption. Furthermore, mono and diacylglycerols, which can solubilize a poorly soluble drug, can form mixed micelles with bile salts, and these mixed micelles promote drug absorption. The lipid molecules taken up simultaneously with the drug molecules are absorbed in a kind of a “mechanism of absorption promotion effect”. The use of liposomes, lipid nanoparticles and SolEmuls® technology appears to be suitable for oral drug delivery purposes, and to achieve such effect increasing thereafter drug bioavailability. The ability of lipid-based drug delivery systems to enhance bioavailability of drug molecules that are poorly soluble in water after oral administration, is quite well known, and reflects the ability of lipids and their hydrolysis products to interact with endogenous bile salt phospholipid micelles in the GIT, hence resulting in increased solubilization capacity of the GI fluids.

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