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Review Article

Recent advances in oral delivery of drugs and bioactive natural products using solid lipid nanoparticles as the carriers

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ABSTRACT

Chemical and enzymatic barriers in the gastrointestinal (GI) tract hamper the oral delivery of many labile drugs. The GI epithelium also contributes to poor permeability for numerous drugs. Drugs with poor aqueous solubility have difficulty dissolving in the GI tract, resulting in low bioavailability. Nanomedicine provides an opportunity to improve the delivery efficiency of orally administered drugs. Solid lipid nanoparticles (SLNs) are categorized as a new generation of lipid nanoparticles consisting of a complete solid lipid matrix. SLNs used for oral administration offer several benefits over conventional formulations, including increased solubility, enhanced stability, improved epithelium permeability and bioavailability, prolonged half-life, tissue targeting, and minimal side effects. The nontoxic excipients and sophisticated material engineering of SLNs tailor the controllable physicochemical properties of the nanoparticles for GI penetration via mucosal or lymphatic transport. In this review, we highlight the recent progress in the development of SLNs for disease treatment. Recent application of oral SLNs includes therapies for cancers, central nervous system-related disorders, cardiovascular-related diseases, infection, diabetes, and osteoporosis. In addition to drugs that may be active cargos in SLNs, some natural compounds with pharmacological activity are also suitable for SLN encapsulation to enhance oral bioavailability. In this article, we systematically

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introduce the concepts and amelioration mechanisms of the nanomedical techniques for drug- and natural compound-loaded SLNs.

1. Introduction

Oral delivery is the most accepted drug administration route among the various delivery pathways because of its advantages: painlessness, easy self-administration, high patient compliance, and feasibility for outpatients [1]. Nevertheless, chemical and enzymatic barriers in the gastrointestinal (GI) tract hinder the effectiveness of oral drug delivery. The epithelial cell monolayer in the GI membrane also contributes to poor permeability for numerous drugs [2]. Some poorly soluble drug molecules are difficult to dissolve in the GI tract, resulting in low bioavailability. Novel and sophisticated drug delivery systems are necessary to conquer these limitations. By optimizing the formulations, the delivery efficiency and bioavailability can be ameliorated to promote the therapeutic potency with reduced side effects. The oral delivery improvement using nanocarrier systems has gained more attention recently [3]. Nanoparticles are defined as particles ranging in size from 1 nm to several hundred nanometers that can load drugs for efficient delivery. The drugs or actives can either be integrated in the core or matrix or attached to the surface of nanoparticles that have a high surface/volume ratio [4]. With respect to pharmacokinetics, the drugs in nanocarriers generally revealed prolonged circulation time, increased half-life, reduced clearance, and increased mean residence time (MRT) [5].

Among the different types of nanocarriers, solid lipid nanoparticles (SLNs) are at the forefront of the potential application in oral drug delivery systems [6]. SLNs are nanocolloids developed at the beginning of the 1990s by Schwarz et al [7]. They are used as alternative carriers to conventional colloids such as emulsions, liposomes, and polymeric micelles. Basically, SLNs are made of a solid lipid core with a monolayer phospholipid shell. The lipophilic moiety of phospholipids is embedded in the lipid matrix (Figure 1). Many drugs or diagnostics can be entrapped by SLNs, especially lipophilic ingredients [8]. The use of SLNs for oral administration is a promising approach for enhancing and controlling drug delivery. The solid state of the nanoparticulate matrix provides protection to chemically labile drugs and prolongation of drug release. SLNs show low cytotoxicity to mammalian cells, demonstrating an acceptable tolerance to the body. SLNs can be orally administered as aqueous dispersions or in the dosage forms of capsules, tablets, and pellets [9]. With the evolution of nanomedicine, the application of SLNs is expected to change the landscape of oral delivery. In this review, we highlight recent advances in the application of SLNs for oral delivery of drugs and bioactive natural compounds. We focus on the reports of SLN development during the past 5 years of orally administered drugs for therapy against cancers, central nervous system (CNS) diseases, cardiovascular (CV) diseases, bacterial/viral infection, and inflammation. The promising perspective in this emerging application is also discussed.

2. Nanocarriers for the oral route

The drugs should go through the stomach, intestinal lumen, the mucus membrane coating the intestinal epithelium, and finally the epithelium itself after oral administration. The inside of the stomach is composed of four layers; from the innermost layer to the outermost layer, these are the mucosa, submucosa, muscularis externa, and the serosa. The stomach is lined by a mucous membrane that contains glands (with chief cells) that secrete gastric fluid. The intestinal epithelium is made up of villi that vastly increase the surface region available for drug absorption [10]. Absorptive enterocyte cells and mucus-secreting goblet cells cover the villi, which are interspersed with the follicle-associated epithelium. The physiology of the GI tract can lead to poor absorption and availability of the drugs or actives because of the low mucosa permeability and drug degradation prior to absorption [11]. The multidrug efflux proteins such as P-glycoprotein rich in the epithelial cell membrane are another barrier for orally administered drugs. Some drugs or active ingredients show low aqueous solubility, and a high hepatic first-pass effect also limits GI absorption. The additional oral permeation challenges are chemical instability, a short half-life, and the effect of food [12]. Figure 2 summarizes the barriers and challenges for efficient oral delivery for administering drugs.

Nanomedicine offers improvement of oral delivery by bioavailability enhancement, adverse-effect minimization, and food-effect mitigation [13]. The nanocarriers can increase the dissolution rate of poorly soluble molecules in the GI tract. The poor stability in the GI tract can be overcome by

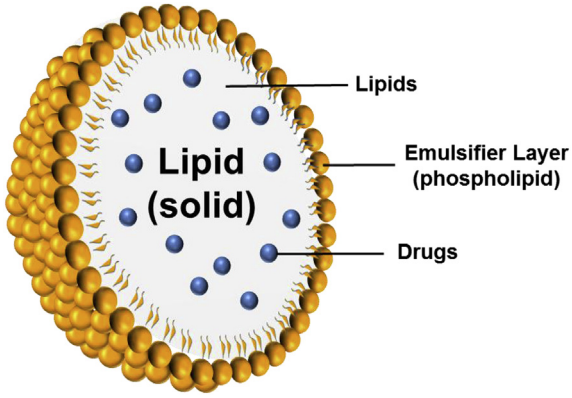

Figure 1 – Structures of solid lipid nanoparticles (SLNs).