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Review

Emerging integrated nanohybrid drug delivery systems to facilitate the intravenous-to-oral switch in cancer chemotherapy

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ABSTRACT

Nanohybrid drug delivery systems have presented lots of characteristic advantages as an efficient strategy to facilitate oral drug delivery. Nonetheless, oral administration of chemotherapy agents by nanoparticulate delivery technology still faces great challenges owing to the multiple biobarriers ranging from poorly physicochemical properties of drugs, to complex gastrointestinal disposition and to presystemic metabolism. This review briefly analyzes a series of biobarriers hindering oral absorption and describes the multiple aspects for facilitating the intravenous-to-oral switch in cancer therapy. Moreover, the developed nanoparticulate drug delivery strategies to overcome the above obstacles are provided, including metabolic enzyme inhibition, enteric-coated nanocarriers, bioadhesive and mucus-penetrating strategies, P-gp inhibition and active targeting. On these foundations, the emerging trends of integrated hybrid nanosystems in response to the present low-efficiency drug delivery of any single approach are summarized, such as mixed polymeric micelles and nanocomposite particulate systems. Finally, the recent advances of high-efficiency hybrid nanoparticles in oral chemotherapy are highlighted, with special attention on integrated approach to design drug delivery nanosystems.

Contents

1. Introduction

Malignant cancer still imposes great threat to human health, and strategies to cope with the challenges are limited [1,2]. Presently, the majority of effective chemotherapy agents are administrated by injection, resulting in reduced patient compliance. Oral delivery is

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considered to be a preferred route for drug administration because of its innate compliance [3,4]. Therefore, the superiority of the intravenous-to-oral switch in cancer therapy lies in simplified therapeutic process, improved patient compliance and reduced injection-associated adverse events [5]. However, orally administered drugs would encounter many difficulties during oral absorption process, including low solubility, poor chemical stability and low permeability of drugs, variable pH values, short residence time and abundant metabolic enzymes in gastrointestinal (GI) tract and the liver, etc. For instance, oral administration of the taxanes (paclitaxel and docetaxel) is strongly hampered by their poor solubility, metabolism by cytochrome P-450 (CYP-450) enzymes and good affinity with drug efflux pump P-glycoprotein (P-gp) [6]. Moreover, oral administration of chemotherapeutic agents could also cause certain damages to mucosal tissue in GI tract elicited by high drug concentration.

Before drugs or nanocarriers enter the systemic circulation, three consecutive stages during oral absorption process should be taken into consideration (Fig. 1): (i) disposition of drugs or nanocarriers inside GI tract, including dissolution or dispersion in GI fluid, stability and residence time in GI tract; (ii) passing through the GI epithelia or transmembrane transport; and (iii) presystemic drug metabolism in GI tract and the liver or avoiding first-pass effect by lymphatic transport. In response to the multiple biobarriers at the three consecutive stages, considerable efforts have been made for facilitating intravenous-to-oral switch in cancer therapy in the past few decades [7–9]. In addition to the improvement in aqueous solubility or dissolution characteristic, three main strategies are currently adopted to improve oral delivery efficiency: (i) enhance the stability of anticancer drugs and drug-loaded carriers; (ii) prolong the residence time in GI tract; and (iii) increase the membrane permeability.

Due to the multiple biobarriers in these consecutive stages, the oral delivery efficiency of any single approach is usually limited. As a result, there has been almost not a single product available switching from intravenous injection to oral administration in clinical therapy so far. Therefore, more rational and high-efficiency drug delivery systems (DDSs) should be designed to facilitate the progress of oral chemotherapy. Hybrid nanosystems, integrated multiple oral nanoparticulate drug delivery approaches, have become a notable trend over the recent years [10,11]. We have good reasons to believe that more rational and comprehensive hybrid nanocarriers will emerge to facilitate oral chemotherapy.

Several excellent reviews concerning oral delivery of antitumor drugs have been reported, and advances and challenges in oral chemotherapy are profoundly discussed based on the development of pharmaceutical science, nanotechnology and drug delivery systems (DDSs) [7,8,12–15]. However, most of them focused only on the progresses of several drug delivery strategies on the basis of the fragmental absorption limiting factors, and there is no attention paid to the rational design in the integrated hybrid DDSs considering the whole absorption process. The present overview briefly analyzes multiple biobarriers encountered for oral delivery of anticancer drugs and describes several oral drug delivery approaches to overcome the multiple barriers with special emphasis on improved stability, prolonged residence time in GI tract and enhanced transmembrane transport efficiency. Finally, the distinct advantages and promising applications of hybrid nanosystems are highlighted.

2. Biobarriers encountered in oral chemotherapy

According to statistics, more than 60% of all anticancer drugs are available for clinical therapy in oral dosage form, but very few of them are actually put into use in the clinic owing to the limited oral bioavailability [7]. The principal factors determining the oral absorption efficiency include aqueous solubility, stability in the GI tract, permeability through intestinal epithelia, and the presystemic metabolism, which depend on the physicochemical properties of antitumor drugs, the complex GI environment and the *in vivo* blood/lymph circulation after absorption [16].

As shown in Fig. 2, the principal biobarriers hindering intravenous-to-oral switch in cancer therapy can be simply divided into three categories [17–20]: (i) physicochemical properties of anticancer drugs; (ii) physiological barriers in GI tract; and (iii) biochemical barriers in GI tract. The poorly physicochemical properties of antitumor agents are the innate factors limiting their oral absorption potential and the physiological and biochemical conditions impose the external challenges to drugs or drug-loaded nanocarriers.

It is interesting to notice that some compounds can be readily absorbed but some can't when expose to the same environment of GI tract. Indeed, physicochemical properties of drug molecules have significant impact on oral absorption. Among them, solubility, pKa, log P, stability and P-gp affinity are essential properties determining oral absorption potential of drugs. As shown in Fig. 3, the main drug transport mechanisms across the intestinal cells can be broadly summarized as transcellular pathway and paracellular pathway. Transcellular pathway includes passive transport, carrier-mediated transport and P-gp-mediated efflux. Oral absorption of hydrophilic drug is generally believed to use the paracellular pathway or carrier-mediated transport. And some hydrophilic drugs (e.g. acyclovir and famotidin) transported mainly by paracellular pathway (Fig. 3B) generally have low bioavailability due to its low coverage of the total intestinal surface area (0.01–0.1%), but some other hydrophilic drugs (e.g. ofloxacin and pregabalin) transported mainly by carrier-mediated transport can achieve a good absorption [22]. As for lipid-soluble drugs, they transport through intestinal membranes mainly by passive diffusion (Fig. 3A)

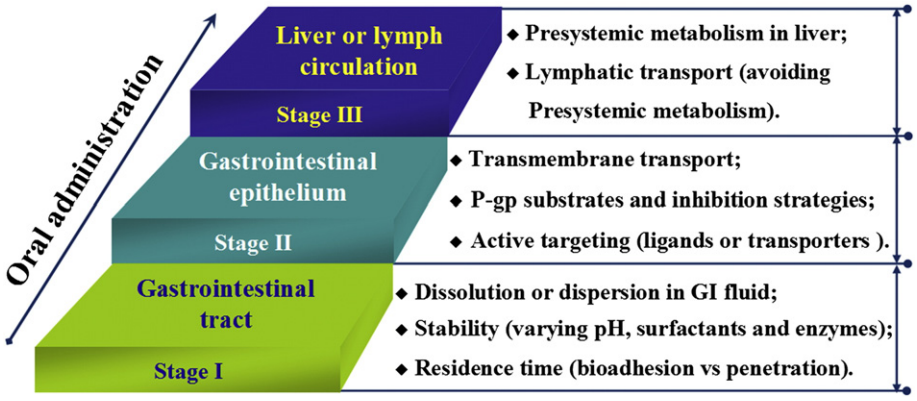

Fig. 1. Three consecutive stages before entering the whole body blood circulation in oral drug delivery process.