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Challenges in oral drug delivery of antiretrovirals and the innovative strategies to overcome them☆

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ABSTRACT

Development of novel drug delivery systems (DDS) represents a promising opportunity to overcome the various bottlenecks associated with the chronic antiretroviral (ARV) therapy of the human immunodeficiency virus (HIV) infection. Oral drug delivery is the most convenient and simplest route of drug administration that involves the swallowing of a pharmaceutical compound with the intention of releasing it into the gastrointestinal tract. In oral delivery, drugs can be formulated in such a way that they are protected from digestive enzymes, acids, etc. and released in different regions of the small intestine and/or the colon. Not surprisingly, with the exception of the subcutaneous enfuvirtide, all the marketed ARVs are administered orally. However, conventional (marketed) and innovative (under investigation) oral delivery systems must overcome numerous challenges, including the acidic gastric environment, and the poor aqueous solubility and physicochemical instability of many of the approved ARVs. In addition, the mucus barrier can prevent penetration and subsequent absorption of the released drug, a phenomenon that leads to lower oral bioavailability and therapeutic concentration in plasma. Moreover, the frequent administration of the cocktail (ARVs are administered at least once a day) favors treatment interruption. To improve the oral performance of ARVs, the design and development of more efficient oral drug delivery systems are called for. The present review highlights various innovative research strategies adopted to overcome the limitations of the present treatment regimens and to enhance the efficacy of the oral ARV therapy in HIV.
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Abbreviations: ABC, ATP-binding cassette superfamily pump; AIDS, Acquired Immunodeficiency syndrome; API, Active pharmaceutical ingredient; ARVs, Antiretrovirals; AUC, Area-under-the-curve; AZT, Zidovudine; BCS, Biopharmaceutic Classification System; BCRP, Breast cancer resistance protein; b.i.d., Twice-a-day; BMS, Burning mouth syndrome; CD, Cyclodextrin; CEHDA, Concentric electrohydrodynamic atomization; CMC, Critical micellar concentration; CNS, Central nervous system; ddI, Didanosine; DDS, Drug delivery systems; EU, European Union; FDCs, Fixed-dose combinations; GRAS, "Generally Recognized As Safe"; HAART, High activity antiretroviral therapy; HIV, Human Immunodeficiency Virus; Log*P*, octanol–water partition coefficient; NE, Nanoemulsion; NiMDS, Nanoparticle-in-Microparticle Delivery System; NNRTI, Non-nucleoside reverse transcriptase inhibitor; NRTI, Nucleoside/nucleotide reverse transcriptase inhibitor; O/W, Oil-in-water; PCL, Poly(epsilon-caprolactone); PD, Pharmacodynamic; PEO-PPO, Poly(ethylene oxide)-*b*-poly(propylene oxide) block copolymer; P-gp, P-glycoprotein; PI, protease inhibitor; PK, Pharmacokinetic; SEDDS, Self-emulsifying drug delivery system; SMEDDS, Self-micro-emulsifying drug delivery system; SNEDDS, Self-nano-emulsifying drug delivery system; t.i.d., Three-times-a-day; US, United States; US-FDA, US Food and Drug Administration; W/O, Water-in-oil.

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1. Introduction

1.1. Oral drug delivery

Due to remarkable advantages such as minimal invasiveness, painfulness, ease-of-use (no need of trained personnel), cost-effectiveness, reproducibility of the administration and feasibility in the whole range of patient ages, the oral route is the most patient compliant. In addition, since the gastrointestinal transit takes place along several hours, slow-release formulations may be tuned to prolong the duration of the action. Moreover, drugs can be formulated in such a way that they are released in the stomach or different portions of the small intestine and/or the colon to tune the absorption site or attain localized activity (e.g., inflammatory bowel disease). On the other hand, oral drug delivery must overcome numerous challenges, including the acidic gastric environment, the poor aqueous solubility and chemical stability of many drugs and the presence of digestive enzymes [1]. The mucus barrier is another hurdle because it can prevent timeous penetration and absorption of the released drug, making the oral bioavailability often unpredictable. Further, it is unsuitable in patients who are uncooperative, strictly "nil by mouth", vomiting profusely or have ileus. Finally, upon intestinal absorption, many of them undergo extensive first-pass metabolism in the liver, a pathway that decreases the oral bioavailability. Regardless of the difficulty to ensure high bioavailability and plasma concentrations within the therapeutic window, the advantages of oral drug delivery are more prominent than the disadvantages, and thus it remains the preferred option in patients affected by chronic diseases.

1.2. The HIV infection

Even though countless efforts have and are being made to eradicate the HIV from the host, to date, the cure is not possible and a chronic combined antiretroviral (ARV) therapy is required to ensure viral suppression and reduce the rate of progression from the infection to the active phase of the disease, the acquired immunodeficiency syndrome (AIDS). In addition, effective therapeutic strategies must be adopted to target HIV reservoirs such as those at the central nervous system (CNS) and lymphatic cells, to reduce the gradual deterioration of the host tissues and systems and to improve the quality of life of patients [2].

The current clinical therapy, known as 'high activity antiretroviral therapy' or HAART, is one of the most significant advances in the field. Since the middle of 1990s, HAART has made a remarkable contribution towards reducing the patient mortality and, as more recently demonstrated, the transmission rates among high-risk individuals [3]. ARVs are classified into different families based on the stage of the HIV life cycle where they act on. Presently, there are five different classes of approved ARVs: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) [4], non-nucleoside reverse transcriptase inhibitors (NNRTIs) [5], protease inhibitors (PIs) [6], entry/fusion inhibitors [7] and integrase inhibitors [8]. A gold-standard cocktail comprises a minimum of three ARVs from two classes, while in the case of PIs they are co-administered with the ARV ritonavir (used in sub-therapeutic dose) as boosting agent. All the ARVs, with the exception of the subcutaneous oligopeptide enfuvirtide, are administered at least once a day by the oral route [9]. Rilpivirine, a second-generation NNRTI, is currently being clinically trialed in a long-acting injectable formulation [10,11].

Patient compliance represents one of the greatest challenges to achieve therapeutic success [12]; due to pill burden and/or complicated administration schedules patients tend to cease the therapy, a phenomenon that results in viral rebound and favors the development of resistance. The use of fixed-dose combinations (FDCs), namely formulations that contain more than one ARV in one single administration unit (e.g., pill) and at a fixed dose and drug ratio, has made the administration regimens simpler and more patient compliant. However, FDCs are still conventional oral drug delivery systems (DDS) and they do not address the relevant biopharmaceutical and pharmacokinetic (PK) drawbacks of the approved ARVs [13]. In this scenario, to improve the oral bioavailability of ARVs, the design and development of advanced oral DDS are called for [14,15]. The present review describes the state-of-the-art pharmaceutical products for the therapy of HIV and highlights innovative microtechnology and nanotechnology research strategies adopted to overcome the most relevant limitations of the present treatment regimens and hence, to enhance the efficacy of the oral ARV therapy against HIV. It is worth remarking that a detailed description of the first-line treatment regimens is out of the scope and it could be found in the review by Sued et al. (**16**, current theme issue).

2. Challenges in oral delivery of ARVs

The design of conventional and advanced oral delivery systems in general and for ARVs in particular demands a deep understanding of the conditions to which the active pharmaceutical ingredient (API) will be exposed during its transit from the mouth to the absorption site, usually the small intestine and the obstacles that exist to reach the systemic circulation (Fig. 1). In this section, the main challenges in the oral delivery of ARVs will be overviewed in sequential manner, from the mouth until the intestinal absorption of the drug and its clearance from the body by the feces together with the most relevant attempts to address them by means of innovative DDS.

2.1. Undesirable taste

The interaction of the drug with the gastrointestinal tract begins in the oral mucosa. Most of the ARVs have undesirable taste that leads to lack of patient compliance especially in the case of liquid formulations developed for pediatric (or eventually geriatric) treatment, a phenomenon that in turn causes treatment failure [17]. Moreover, HIV medications are intended for chronic use and unpleasant drug taste influences the psychological wellbeing of the patient and favors treatment interruption [18]. In the case of pediatric medicinal products, the selection of an appropriate and palatable liquid dosage form can make a large difference between treatment success and failure. Since the recent adoption of Pediatric Regulations in the US and EU, there is a greater demand of age-appropriate medicines for children.

Extended research on the use of milk in drug administration in the pediatric population has shown multiple benefits. Milk exhibits great solubilizing, gastroprotective and taste masking properties, which are very important characteristics in the case of insoluble, irritating and bitter-tasting active compounds. Milk-based formulations rely on a novel, simple and user-friendly approach for the delivery of ionized and unionized lipophilic drugs. In parallel, they can provide critical nutritive elements and a wide range of biologically active peptides, very important elements especially for pediatric patients [19]. Other flavored soft drinks such as orange juice have been assessed as well. However, these approaches often neglect the effect of these vehicles on the physicochemical stability and the oral bioavailability of the ARV. In this

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