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Review

Perspective and potential of oral lipid-based delivery to optimize pharmacological therapies against cardiovascular diseases

Shasha Rao, Angel Tan, Nicky Thomas, Clive A. Prestidge *

Ian Wark Research Institute, University of South Australia, Mawson Lakes Campus, Mawson Lakes, SA 5095, Australia,

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ABSTRACT

Cardiovascular diseases (CVDs) remain the major cause of morbidity and mortality globally. Despite the large number of cardiovascular drugs available for pharmacological therapies, factors limiting the efficient oral use are identified, including low water solubility, pre-systemic metabolism, food intake effects and short half-life. Numerous *in vivo* proof-of-concepts studies are presented to highlight the viability of lipid-based delivery to optimize the oral delivery of cardiovascular drugs. In particular, the key performance enhancement roles of oral lipid-based drug delivery systems (LBDDSs) are identified, which include i) improving the oral bioavailability, ii) sustaining/controlling drug release, iii) improving drug stability, iv) reducing food intake effect, v) targeting to injured sites, and vi) potential for combination therapy. Mechanisms involved in achieving these features, range of applicability, and limits of available systems are detailed. Future research and development efforts to address these issues are discussed, which is of significant value in directing future research work in fostering translation of lipid-based formulations into clinical applications to reduce the prevalence of CVDs.

Contents

* Corresponding author. Tel.: +61 8 8302 3569; fax: +61 8 8302 3683.
E-mail address: clive.prestidge@unisa.edu.au (C.A. Prestidge).

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1. Introduction

1.1. Cardiovascular diseases (CVDs): prevalence and risk factors

Cardiovascular diseases (CVDs) refer to a group of disorders or dysfunctions that involve the heart and blood vessels. Specifically, common cardiovascular conditions as listed by the World Heart Federation, include rheumatic heart disease (damage to the heart, particularly the heart valves, caused by rheumatic fever), hypertensive heart disease (primary or secondary hypertension), ischemic heart disease (heart ailments caused by narrowing of the coronary arteries), cerebrovascular disease (disorders of the blood vessels supplying the brain), inflammatory heart disease (inflammation of the heart muscle, the membrane sac, the inner lining of the heart or the myocardium), and other conditions (Fig. 1) [1]. According to the World Health Organization (WHO), CVDs have remained the leading cause of morbidity and mortality globally, accounting for approximately 30% of global death in 2008 [2]. Major risk factors leading to CVD-related mortality include high cholesterol levels and high blood pressure. To control these risk factors, non-pharmaceutical strategies are often recommended, such as limiting tobacco or alcohol use, eating a healthy diet, increasing physical activities and maintaining normal body weight [3]. Apart from lifestyle changes, therapeutic/pharmaceutical strategies also play a key role in achieving optimum CVD treatment by providing cardioprotection such as removing the causes of ischemic heart disease, attenuating ongoing ischemic and reperfusion injury, and preventing progression of chronic heart failure.

1.2. Pharmaceutical approaches for CVDs: challenges and opportunities

Cardiovascular drugs (CVD drugs) have remained one of the largest categories of therapeutic treatment in the drug universe. More than 100 drugs have been approved by the US Food and Drug Administration (FDA) for CVDs [4]. Among them, global sales of antihypertensives and antihyperlipidemics alone in 2011 were well above $40 billion and $30 billion, respectively, which were just behind that of the oncology drugs which totaled $64.4 billion [5]. In the US, twelve CVD drugs are among the 100 best-selling drugs in the first quarter 2013 (Table 1) [5]. In addition, all CVD drugs that are commonly prescribed are summarized in Table S1 based on the mechanisms of action (supplementary data, Table S1). Except for the anti-platelets, most of these CVD drugs are given *via* the oral route. This is probably because the treatment of CVDs generally requires a long-term treatment/control, and that oral delivery is the most convenient drug administration route with the highest patient compliance [6]. However, it is realized that more than 80% of the CVD drugs have challenged oral bioavailability. The two major factors limiting the oral delivery efficacy of each CVD drug were identified to include poor water solubility and considerable first-pass metabolism in the gastrointestinal (GI) tract or liver. For several drugs, short elimination half-life, low permeability through intestinal mucosa, and instability under exposure to light also impede efficient oral delivery. The oral bioavailabilities of seven of the best-selling compounds (*i.e.*, rosuvastatin, fenofibrate, simvastatin, valsartan, dabigatran, olmesartan medoxomil and atorvastatin) are extremely low and sometimes erratic. Therefore, more advanced delivery systems are needed to optimize the oral delivery of CVD drugs.

Lipid-based drug delivery systems (LBDDSs) have captured much attention for compounds showing poor *in vivo* results when delivered using conventional oral tablet or capsule formulation strategies. Successful examples include Sandimmune Neoral® oil solution capsule and Norvir® oil solution, which are commercially available on the market for the oral delivery of cyclosporine A and ritonavir, respectively [7]. Mechanisms by which LBDDSs improve the oral bioavailability have been well reviewed, and primarily include i) improving drug dissolution in the intestine; ii) enhancing intestinal permeation; and iii) avoiding hepatic first-pass metabolism through enhanced lymphatic transport [8–13].

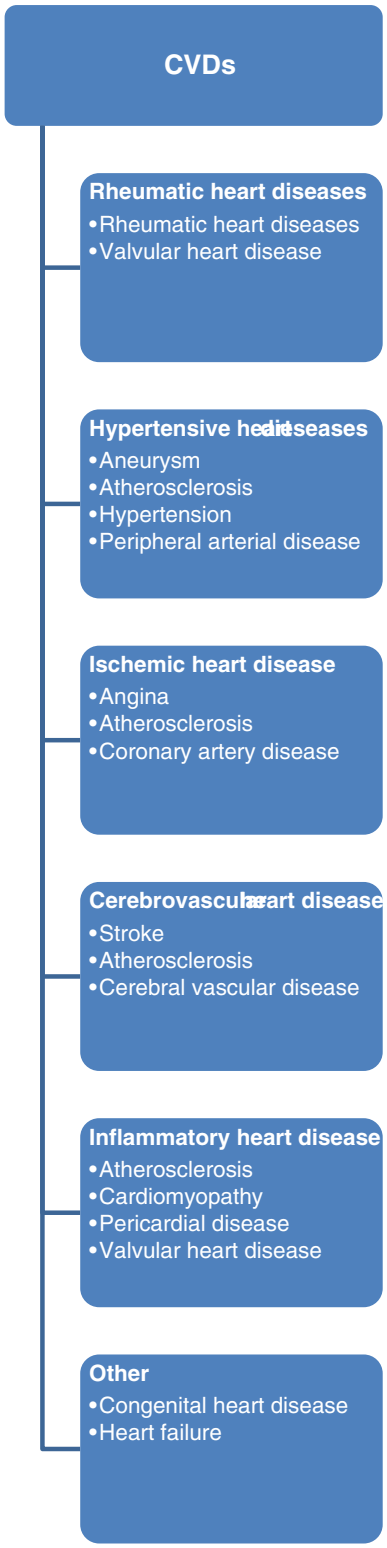

Fig. 1. Summary of common cardiovascular conditions [1].

This review primarily focuses on the recent efforts in the application of LBDDSs to optimize the pharmacological therapies for CVDs. An in-depth overview of the role of each type of LBDDS in improving the oral bioavailability of CVD drugs is provided. This is exemplified through preclinical and clinical case studies showing *in vivo* bioavailability