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Polymeric bile acid sequestrants—Synthesis using conventional methods and new approaches based on "controlled"/living radical polymerization

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ABSTRACT

Polymeric bile acid sequestrants have received increasing attention as therapeutic agents for the treatment of hypercholesterolemia. These materials are usually cationic hydrogels that selectively bind and remove bile acid molecules from the gastrointestinal tract, decreasing plasma cholesterol levels. Due to their high molecular weight, the action of bile acid sequestrants can be limited to the gastrointestinal tract, avoiding systemic exposure, which constitutes an advantage over conventional small-molecule drugs.

Different polymers, such as vinyl polymers, acrylic polymers and allyl polymers have been used to prepare potential bile acid sequestrants based on conventional polymerization techniques. Also, much effort has been devoted to understanding the structure–property relationships between these polymers and their ability to bind bile acid molecules. The efficacy of these polymeric drugs can be ascribed to five major variables: (i) the density of cationic charges, (ii) the length and distribution of the hydrophobic chains, (iii) the polymer backbone flexibility, (iv) the degree of cross-linking and (v) the polymer shape.

This review summarizes the major synthesis pathways that are employed in the preparation of this type of polymer therapeutics and the polymer structural key factors that are of relevance to enhanced therapeutic efficacy. Herein, new synthesis approaches, based on "controlled"/living radical polymerization techniques, are highlighted.

Contents

Abbreviations: ATRP, atom transfer radical polymerization; BAS, bile acid sequestrants; CLRP, "controlled"/living radical polymerization; CVD, cardiovascular disease; FDA, Food and Drug Administration; FRP, free radical polymerization; GI, gastrointestinal; LDL, low density lipoprotein; LDL-C, low density lipoprotein cholesterol; RAFT, reversible addition-fragmentation chain transfer; SEM, scanning electron microscopy; TEM, transmission electron microscopy; UV, ultraviolet.

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1. Introduction

The use of polymeric materials in the pharmaceutical and medical fields have received great attention during recent years due to their distinctive physico-chemical characteristics, such as their biocompatibility and their appropriate mechanical properties. Polymers have been used for a wide range of applications in the biomedical area, namely in drug delivery systems, as components of artificial organs, in the delivery of antibodies and in medical devices, among others [1].

Recent progresses in this field has led to the development of a new class of drugs, namely polymer therapeutics [2], which can be divided in two major types according to the polymer function. These include polymers used as vehicles for targeted drug delivery and polymers with intrinsic therapeutic activity [3]. Examples of polymer therapeutics are polymer–drug combinations (pro-drugs), polymer–protein conjugates (bioconjugates) and polymers with sequestration properties [4]. Polymeric drug delivery systems have been extensively studied and there are many interesting reviews on this. However, reviews dealing with polymeric therapeutics are very few and recent [3,5].

The use of polymers as therapeutic agents is of great interest and offers considerable potential since they present some advantages in comparison to small molecule drugs. These advantages include long-term safety profiles, lower toxicity, the capacity to recognize and to bind molecular components and their polyvalence (raising the possibility of multiple interactions with the disease species) [3]. Furthermore, the structure of the polymers can be designed and the polymers functionalized with many different pendant molecules, leading to materials with different biological activities than those of conventional drugs. In addition, the action of these polymers can be limited to the gastrointestinal (GI) tract, since their high molecular weight prevents their absorption into the systemic circulation [1]. Therefore, polymers can be used to bind selectively and to remove detrimental molecules from the GI tract and also to eliminate viruses, toxins and bacteria. These polymers properties constitute an advantage in treatments in which systemic exposure of the drug is undesirable [6]. Through the manipulation of polymer structure and the incorporation of appropriate functional groups, it is possible to develop polymer therapeutics with high selectivity and potency towards specific molecules – polymer sequestrants [5]. In recent years, different polymer sequestrants have been developed to bind and to remove species that cause diseases, such as phosphate ions (renal diseases), potassium ions (hyperkalemia), iron salts/complexes (iron overload disorders) and toxins [7], among others [1,3]. Some of these polymer therapeutics are currently available, exhibiting and providing healing benefits at acceptable therapeutic doses [4]. Particular interest is devoted to the use of this approach to create materials that have the ability to sequester bile acid molecules, the so-called bile acids sequestrants (BAS).

BAS have an important application in the control of the blood cholesterol level, a major cardiovascular disease (CVD) risk factor, which is a leading cause of death, an increasing source of morbidity and a major factor in disability and ill-health, especially in the industrialized countries [8]. Commonly, cholesterol lowering drugs are based on statins, cholesterol absorption inhibitors, which rely on a different treatment strategy than BAS [6,9]. Statins act directly on the cholesterol conversion process into bile acids by inhibiting the HMG-CoA reductase (rate-controlling enzyme in the cholesterol production process), while cholesterol absorption inhibitors have the ability to reduce the intestinal absorption of dietary and biliary cholesterol at the level of the brush border of the intestine. On the other hand, BAS operate in an indirect way by capturing bile acids in the small intestine, which causes an organism response that leads to cholesterol consumption and, ultimately, to the reduction of the blood-cholesterol level. Due to their mechanism of action, BAS present some advantages in comparison to other therapies. For instance, statins therapy (the first line of treatment) is not advised in pregnant women, nursing mothers and patients with significant hepatic dysfunction [1,10]. Moreover, in about 10% of patients, long-term complications can arise such as liver dysfunction and musculoskeletal symptoms [10]. These are the more common reasons for statins discontinuation [1]. Thus, it is of utmost importance that new and more efficient BAS are developed for patients that cannot use statins or must take high statin doses. However, the presence of such polymeric therapeutics in the market is very limited at present.

The aim of this review is to present and to critically discuss the synthesis routes that are available for the preparation of BAS with a particular emphasis on future perspectives in this field, based on advanced