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Pharmaceutical and Medicinal Applications for a Derivative of Starch, Hydroxyethyl Starch: A Global View

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Abstract

Hydroxyethyl starch (HES), a semi-synthetic material with various physico-chemical and biological properties is compatible with human body and benefit humanity in several branches of health care. A part of information given in the literature is reviewed in this study. Key pharmaceutical and medicinal applications of HES are highlighted in this mini-review. The following conclusions are drawn: (1) it improves blood viscosity and microcirculation within different organisms. A suitable HES preparation is used as a blood plasma volume expander or as a cryo-protective agent for erythrocytes; (2) it prevents shock following severe blood loss cause by trauma, surgery or some other problems; (3) it reduces growth rates of various tumors and has been used for cancer treatments; (4) the clinical misuse may yield accumulation and induce osmotic problem in kidney; and (5) HESs as different products with various properties and effects have potential to be used in several medicinal treatments and different drug preparations in pharmaceutical industries.

Keywords: Hydroxyethyl starch; Compatible; Blood volume expander; Anti-shock; Anti-tumor

Abbreviations

HES: Hydroxyethyl Starch; CHES: HES Concentration; Mw: Molecular Weight; MS: Molar Substitution; DS: Degree of Substitution; Substitution at the Glucose Subunit at Position C2 to that at C6, C2/C6 Ratio; FDA: Food and Drug Administration; kDa: Kilo Dalton; MWD: Molecular Weight Distribution

Introduction

Starches and their major components (amylose and amylopectin) are edible and safe materials and approved by Food and Drug Administration (FDA). Abundance, easily accessible, safety, sustainable, biodegradable, biocompatible, environmentally friendly and renewable resources make starch as a promising and interesting biopolymers for pharmaceutical, medicinal, food, and health care applications [1-5]. These biopolymers are important components of human diet, and as a supply of glucose production for energy generation. Derivatives or modified of starches are also widely used in several industries (food, pharmaceutical, medical, cosmetics, textile, paper, plastics) [6]. Among its derivatives, hydroxyethyl starch, HES, has medical and pharmaceutical applications.

Hydroxyethyl starch, HES, is a semi-synthetic polysaccharide. It is usually prepared from either amylopectin or starches that are rich in amylopectin such as waxy maize starch or potato starch with ethylene oxide in an alkaline medium [7-8]. The rationale for this selection, is that amylopectin is structurally similar to glycogen with two types [α-D-(1-4) and α-D-(1-6)] of linkages [4]. Glycogen is a branched glucose storage polymer in humans [8]. HES is a non-ionic derivative of starch, and a glycogen-like polymer. The substitutions yield in hydroxyethyl starches, HESs, having different chemical structures with the same backbone, but different side chain distributions. The introduction of a few hydroxyethyl groups (degree of substitution, DS, up to 0.2) results in an extensive modification of its physical properties [7,9]. The conversion of native starch into HES increases its solubility especially in water and increase its stability and reduces its rate of hydrolysis *in vivo* [7-8,10-11], as well as inhibits its rate of destruction by alpha amylase [12]. Major pharmaceutical and medicinal applications of HESs are presented in this report.

Pharmaceutical and Medicinal Applications

HES obtained from amylopectin, which is soluble in water, the solubility in water opens up extensive applications in pharmacology [13]. Starches are enzymatically unstable and degradable by amylase enzymes [14], whereas HES is more stable compared to natural starches. Thus, HES is

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a suitable foreign substance for entry into a blood or lymph vessel and can be used for drug delivery. Because of increasing international competition and the availability of developed starches, it is important to take into consideration pharmacological properties of HES and its advantages and disadvantages of individual preparations [15].

HES preparations are usually described with the key characteristics: (i) molecular size or molecular weight, Mw; (ii) degree of substitution, DS, or molar substitution, the average number of hydroxyethyl groups per anhydrous glucose unit, MS; (iii) C2/C6 ratio, the substitution at the glucose subunit at position C2 to that at C6; and (iv) HES solution concentration, CHES. The preparation may be described with or without being followed by the C2/C6 ratio. A variety of different HES solutions exist worldwide, which differ greatly in their pharmacological properties [16,17]. HES with a concentration of 6%, Mw of 130 \kDa and MS of 0.4 (6%/130/0.4) in 0.9% sodium chloride, is one of common HES specification [18]. There are physicochemical and pharmacokinetic differences among HES preparations (CHES, Mw, MS, C2/C6 ratio), mainly resulting from modifications to the MS and the pattern of substitution. These result in differences in the *in vivo* as well as plasma and tissue persistence. Apparently small variations in MS have significant effects on the coagulation system and renal function. Variation in the source material for HES also produces measurable pharmacokinetic differences in the end products. The available clinical data demonstrated that HES should not be regarded as one homogenous group, and data for one product should not be extrapolated to another one. In conclusion, HESs having different characteristics (different in CHES, MW, MS), yield in various products, and demonstrate different effects [12,16,17,19].

Hydroxyethylation of starch results in more enzyme-resistant product and prolongs half-life *in vivo*. A solution of natural starch is unstable *in vivo*. Half-life *in vivo* is of the order of only a few minutes (up to 2 hours) for native starches, due to rapid degradation by serum amylases [7,10,14]. The retention time for HES within the blood plasma (vascular compartments) and organisms (liver, lungs, splee, and reticuloendothelial system, RES) are significantly longer than that of the native starch [17]. The degradation time as well as the elimination time for HES in the body is prolonged with an increase in MS (or DS) [12,19-21].

The key characteristics of HES play a critical role on its half-life. The elimination of HES is a complex issue. The solutions contain molecules with a spectrum of sizes of which the smallest (<60-70 kDa) are quickly eliminated by renal excretion. Larger molecules first need to be cleared by endogenous alpha-amylase into smaller fragments before being excreted, a process that increases the osmotic strength per gram of the polysaccharide. The risk of adverse effects in the form of anaphylactoid reactions, coagulopathy and postoperative itching increases with the molecular size. High molecular weight of HES may cause acute kidney failure in patients with severe sepsis or may improve survival by up to 20% when compared to crystalloids. Low molecular weight is a preferred colloid intensive care unit and is a suitable choice for patients with severe sepsis [12,19,22]. Solutions with a low molecular weight (*in vivo*) contain more molecules at similar plasma concentrations. On the other hand, high plasma concentrations or high molecular weight *in vivo* can affect blood coagulation [16]. Although small-sized HES (for example, 130kDa), preparations have a shorter persistence in the blood, they have the same clinical efficacy as median-sized HES preparations, while being safer. A low-molecular weight of HES may serve as a desirable substitute for the erythrocyte sedimenting agents. It improves neutrophil yields in centrifugation and gravity. HES with a DS close to unity are resistant to enzymatic hydrolysis in the blood circulation system and it is possible to obtain from starches, a preparation corresponding to a group of the requirements set for blood substitutes with an anti-shock action.

The substance of HES is used in therapeutic as a blood plasma volume expander and as a cryo-protective agent for erythrocytes. It increases the blood volume, allowing red blood cells to continue to deliver oxygen to the body. Being an efficient plasma-volume expander, HES has been associated with a reduction of endothelial damage during inflammation and sepsis [23]. HES is one of the best carrier for nutrition and as the best colloidal plasma expander [7,20,24]. HES solution with a concentration of 6% in iso-osmotic saline or balanced electrolytes expands the plasma volume by almost as much as the infused volume [25].

HES is a synthetic fluid product that is commonly used in clinical practice. It becomes popular for clinical treatments, and no danger from hepatitis infection. When a person loses blood in an accident or during an operation, he/she may suffer shock and circulatory failure. Then the doctor must quickly give her/him a supplement of too low blood volume with an infusion. HESs solutions have proved to be especially suitable for this purpose. In contrast to banked bloods, HES solutions can be stored easily, thus, it can be carried in ambulances without any problem. In addition, the doctor saves time, because it is not necessary: to determine initially the blood group of the patient; and there is no potential risks of virus infections for the human blood transfusion. HES is used in medicine for the treatment of hypovolemic shock, artery occlusive disease, cerebral ischemia, or apoplectic insult [10,11]. The clinical misuse may yield macromolecule accumulation and induce osmotic-nephrosis-like lesions [23].

In medicine, HES may be used as a plasma substitute, due to a high degree of therapeutic safety. However, the administration of large volumes of highly substituted of high-molecular-weight starch, often leads to iatrogenic von Willebrand syndrome (vWS) with hemorrhagic complications [26,27]. HES has been used: (1) to prepare blood substitutes possessing anti-shock property [28]. The main application for HES in European countries, Canada and United states is the volume therapy. It helps to improve the rheological properties of the human blood [29]; (2) to stabilize the cardiovascular system or to perform shock and blood treatments in emergency medicine [29]; (3) to treat cancer by reduction of tumor growth rates [12,19,22,30]; and (4) as a carrier system for the simultaneous delivery of antigen along with compounds promoting cellular immune responses [31].

Analytical applications

HESs widely differ in physicochemical characteristics: average molecular weight (Mw), MS (or DS) [27], and molecular weight distribution (MWD). Fractionated HESs as well as HESs with a narrow dispersity, possess a significant commercial interest in pharmaceutics, medicine and food formulations. They have been used as standard materials for Mw and MWD determination of water-soluble polymers as well as for construction of a universal calibration curve for evaluation of size exclusion chromatography (SEC) results [32].

A Short Comparison of HES with Dextran and Gelatin

Colloid solutions such as gelatin, dextran and HES preparations

have medical applications as plasma volume expanders and can be used for blood loss replacement in emergency situations, while waiting to adequate blood substitutes, to avoid the risks associated with transfusion of allogeneic blood products and to limit the high costs of albumin solutions [33]. Gelatin solutions are derived from bovine collagen. Low Mw, and relatively fast degradation of gelatin molecules and loss via the kidneys explains its relatively poor and short-lasting plasma volume expanding effect. Gelatin has no or only moderate effects on coagulation, but anaphylactic reactions are more common with gelatin than with other synthetic colloids. Gelatin, and various preparation of dextran and HES inhibit neutrophil adhesion by a neutrophil-dependent mechanism rather than interfering with endothelial cell activation [34]. Similar to dextran, HES has medical applications as plasma volume expander [21,35]; leukapheresis [36]; and cryopreservative [37] agents. A desirable physiological effect can be achieved within a narrow range of molecular weights for both polysaccharides, HES and dextran: low molecular weight components contribute little to the effectiveness as they are quickly eliminated. High molecular weight components of HES and dextran result in anaphylactic responses.

Conclusions

HES preparations are usually described with three key characteristics: (i) molecular weight, Mw; (ii) degree of substitution, DS, or molar substitution, MS; and (iii) HES solution concentration. HESs with both low Mw and low MS have been reported to have a better safety profile in comparison with HESs with high Mw and MS. HES can be used as a blood volume expander, as an anti-shock component in surgeries, and as anti-tumor for different cancer treatments. Actually, different HESs (different in Mw, MS, CHES, C2/C6 ratio), are different HES products, and can be exhibited different effects. HESs as different products with various properties and effects has potential to be used in several medicinal treatments and different drug preparations in pharmaceutical industries.

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