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Poly(aspartic acid) with adjustable pH-dependent solubility

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ABSTRACT

Poly(aspartic acid) (PASP) derivatives with adjustable pH-dependent solubility were synthesized and characterized to establish the relationship between their structure and solubility in order to predict their applicability as a basic material for enteric coatings. Polysuccinimide, the precursor of PASP, was modified with short chain alkylamines, and the residual succinimide rings were subsequently opened to prepare the corresponding PASP derivatives. Study of the effect of the type and concentration of the side groups on the pH-dependent solubility of PASP showed that solubility can be adjusted by proper selection of the chemical structure. The Henderson–Hasselbalch (HH) and the extended HH equations were used to describe the pH-dependent solubility of the polymers quantitatively. The estimate provided by the HH equation is poor, but an accurate description of the pH-dependent solubility can be found with the extended HH equation. The dissolution rate of a polymer film prepared from a selected PASP derivative was determined by fluorescence marking. The film dissolved rapidly when the pH was increased above its pK_a. Cellular viability tests show that PASP derivatives are non-toxic to a human cell line. These polymers are thus of great interest as starting materials for enteric coatings.

Statement of Significance

Poly(amino acid) type biocompatible polymers were synthesized for future use as pharmaceutical film coatings. To this end, we tailored the pH-dependent solubility of poly(aspartic acid) (PASP). It was found that both the solubility and the pK_a values of the modified PASP depended strongly on composition. Fluorescent marking was used to characterize the dissolution of a chosen PASP derivative. In acidic media only a negligible amount of the polymer dissolved, but dissolution was very fast and complete at the pH values that prevail in the small intestine. As a consequence, enteric coatings based on such PASP derivatives may be used for drug delivery in the gastrointestinal tract.

1. Introduction

Use of conventional solid formulations can not only cause various side effects but also limits the bioavailability of drugs owing to the inability of these carriers to ensure targeted release of the active molecule in the gastrointestinal (GI) system [1]. Liberation of orally administrated drugs at the desired levels of the GI tract can be achieved by employing enteric tablet coatings based on pH-responsive anionic polymers [2,3]. Enteric coatings must be protective at the acidic pH of the stomach while dissolving easily at the elevated pH of the intestines. These coatings are generally made from polycarboxylic acids. Aqueous solubility of these polymers depends strongly on the pH because of the deprotonation of the dissociable groups above a well-defined pH [4].

Although, several polymers of natural origin, e.g. zein, shellac [5], cellulose acetate succinate [6], hydroxypropyl methylcellulose phthalate [7], hypromellose acetate succinate [8] and cellulose acetate trimellitate [9], are commonly used in enteric coatings, synthetic polyacrylates play a leading role in the market [1,10]. The reason for their extensive use is that their pH-dependent solubility can be controlled by the copolymerization of (meth)acrylic acids and properly chosen (meth)acrylic esters [11]. In contrast to polyacrylates, the solubility of polymers of natural origin cannot be adjusted precisely, because the functionalization of these polymers is complicated [12]. The disadvantage of polyacrylates is their relatively complex synthesis, which often requires toxic and environmentally harmful reagents (azobisisobutyronitrile, transition-metal activators such as copper, iron, or manganese, BuLi/pyridine,

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