Investigation of neighbour group effects in releasing of 5-aminosalicylic acid from acrylic polymeric prodrugs

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Acrylic-type polymeric systems having degradable ester bonds linked to 5-ASA were synthesized and evaluated as materials for drug delivery. prodrugs.

5-aminosalicylic acid (5-ASA) was linked to 2-hydroxypropyl methacrylate by carbonyldimidazole (CDI) to obtain metachryloyloxy propyl 5-amino salicylate. The resulting acrylic derivative of 5-ASA was copolymerized with 2-hydroxethyl methacryl , methyl methacrylate and 2-ethyl hexyl acrylate (in 1:3 mol ratio) by free radical polymerization method in N,N-dimethyl formamid solution, utilizing benzoyl peroxide as an initiator at 70 °C. The obtained polymer was characterized by FT-IR. Gel permeation chromatography was used for determination of average molecular weights of polymers bearing drug units as side substituents of the acrylic backbone. Release studies of 5-ASA were performed into dialysis bags by hydrolysis buffered solutions (pH 1, 7.4, 10) at 37 °C. Detection of hydrolysis by UV spectroscopy at selected interval showed that the drug can be released by selective hydrolysis of the ester bond at the side of drug moiety. The release profiles indicated that the hydrolytic behavior of polymeric prodrugs is strongly based on the hydrophobicity of polymer and the pH of the hydrolysis solution.

Keywords – 5-aminosalicylic acid, polymeric prodrug, acrylic polymeric, 2-hydroxypropyl methacrylate

I. Introduction

Polymeric prodrugs is a conjuction of a drug with a polymer, which has several advantages. The main advantages include: (a) an increase in water solubility; (b) protection of drug from deactivation and preservation of its activity during circulation, transport to targeted organ or tissue and intracellular trafficking; (c) an improvement in pharmacokinetics; (d) a reduction in antigenic activity of the drug leading to a less pronounced body response. The therapeutic use of non-steroidal anti-inflammatory drugs (NSAIDs) is often restricted by the necessity to deliver the drug to specific sites of target organ or tissue [1]. 5-aminosalicylic acid (5-ASA) is an active ingredient of agents used for long term maintenance therapy to prevent relapses of inflammatory bowel disease (IBD), and it is slightly soluble in water. these polymeric prodrugs have been 2-Hydroxypropyl methacrylate-5ASA (HPMA-5-ASA) with an increased solubility would be suitable for colon-specific delivery systems[2]. HPMA(2-hydroxypropyl methacrylate), 2-hydroxyethyl methacrylate (HEMA), methyl methacrylate (MMA) and 2-ethyl hexyl acrylate (EHA) were selected as model monomers in the present study.
II. Experimental

1.2. preparation of [methacryloy oxy propyl 5-aminosalicylate] (MOPS)

5-ASA (1gr, 6.5mmol) in 98% formic acid (10ml) was refluxed for 30 min and 20 ml of cold distilled water was added. The precipitates were filtered, washed several times with cold water, and dried. 5-Formylamino salicylic acid (5-FASA) was obtained with 82% yield. Mp: 251°C

To the solution of 5-FASA (1mmol) in dimethylformamide (DMF 5ml), CDI (1.5mmol) was added slowly and reacted for 1h at room temperature and HPMA in DMF was added dropwise. to the reactoin mixture, triethylamine (TEA 0.8ml) was added and stirred for 24h at room temperature and added excess 1mol/l HCL to produce precipitates. In 0.5mol/l HCL for 1h at 80°C, then HMPA-5ASA was obtained.

FT-IR (KBr, cm⁻¹) 3000 (C-H vinylic), 2500 (C-H aliphatic), 1714 (C=O ester), 1580-1663 (C=C aromatic), 2779-2986 (C-H aromatic).

¹H NMR (CDCL₃, ppm) 1.8 (a, 3H, =CCH₃), 4 (b, 2H, CH₂), 5.5-6.0 (c, 2H, CH₂=CH), 4.5 (d, 6H, CH), 1-1.5 (e, 3H, CH₃), 6.9-7.2 (f, 2H, Ar-CH₂), 4.9 (2H, NH₂). Shown in fig1.

Fig. 1

2.2. Copolymerization of MOPS with acrylic monomers

2-hydroxyethy methacrylate (1.2gr HEMA) and B.P (0.05gr) was added (in the polymerization tube) to HPMA-5-ASA (0.26gr) then this mixture was solved in 10ml DMF. after 12 hr polymerization process in 70°C. The brown mixture was obtained. Then this mixture was washed in ethyl acetate (as an non-solvent) to produce the relative polymer (MOPS-CO-HEMA). To produce the other polymer (MOPS-CO-MMA) and (MOPS-co-EHA) we worked like previous step.

Conclusion

In this work, the release profiles indicated that the hydrolytic behavior of polymeric prodrugs is strongly based on the polymer hydrophilicity and the pH value of the hydrolysis solution. the results suggested that these polymeric prodrugs could be useful for releasing 5-ASA in controlled release systems. In the low pH range the polymers have a low degree of swelling. In the high pH range, the polymers have reached a degree of swelling that makes them accessible to hydrolysis.

References