Research in Pharmaceutical Sciences, 2012;7(5)
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Synthesis and evaluation of polymers containing 3-hydroxypyridin-4-one bidentate iron (III) chelating ligands for treatment of iron overload

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Background and Aims: Iron overload is a clinical problem which can be prevented by using iron chelating agents. An alternative method of relieving iron overload is to reduce iron absorption from the intestine by administering specific iron chelating agents, which can bind iron to form nonabsorbable complexes. Base on this strategy, a series of polymeric ligands containing the chelating moiety 3-Hydroxypyridin-4-ones (HPOs) with various iron binding capacities were synthesised.
Methods: The synthetic route involves the benzylation of hydroxyl group of (2-methyl-3-hydroxypyran-4-one (maltol) and conversion of benzylated maltol to 3-benzyloxypyridin-4-one derivatives by using three suitable primary amines (2,6-diaminohexanoic acid (lysine), 1,6-diaminohexane and 5-aminopentanol). The resulted compounds incorporated into polymer by copolymerization with acryloyl chloride using 2, 2'-azobisisobutyronitrile (AIBN) as the initiator. Finally, the benzyl groups of polymers were removed by catalytic hydrogenation. The iron binding capacity of the polymers and their ability to remove iron from the iron (III)-(EDTA) complex were also determined spectrophotometrically at physiological pH.
Results: In this work, three final polymers of HPO derivatives namely poly-2-propylamido-6-(3- hydroxy -1,4-dihydro-2-methy-4-oxopyrid-1-yl) hexanoic acid , 6-(3-hydroxy-1, 4-dihydro-2-methyl-4-oxopyrid-1-yl) hexyl-1-polypropylamide and 5-(3-hydroxy-1-,4-dihydro-2-methyl-4-oxopyrid-1-yl)-1-polyacrylate pentane were synthesized. Identification and structural elucidation of compounds were achieved by 1HNMR, 13CHNMR and IR. Percentage of iron (III) binding capacity and percentage of iron (III) removal from EDTA-iron(III) complex were in the range of 40-50 and 30-40, respectively.
Conclusions: The ability of the polymers to remove iron(III) from EDTA-iron(III) complex (EDTA is present in foodstuffs in appreciable quantities as preservatives, and hence is present in the gut as absorbable complexes) is indicated that polymers can likely take iron(III) from many none-haem complexes. This observation indicated that the polymeric pyridinones may have potential to be evaluated for treatment of both acute iron poisoning and thalassaemia intermedia.

Keywords: 3-Hydroxypyridin-4-ones; Iron overload; Iron chelating agents; *Thalassaemia intermedia*