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Review

Design of clinically useful macromolecular iron chelators

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Abstract

Objectives In recent years, macromolecular iron chelators have received increasing attention as human therapeutic agents. The objectives of this article are: one, to discuss the factors which should be considered when designing iron binding macromolecules as human therapeutic agents, and two, to report recent achievements in the design and synthesis of appropriate macromolecular chelators that have resulted in the production of a number of agents with therapeutic potential.

Key findings Macromolecular drugs exhibit unique pharmaceutical properties that are fundamentally different from their traditional small-molecule counterparts. By virtue of their high-molecular-weight characteristics, many are confined to extracellular compartments, for instance, the serum and the gastrointestinal tract. In addition, they have potential for topical administration. Consequently, these macromolecular drugs are free from many of the toxic effects that are associated with their low-molecular-weight analogues.

Summary The design and synthesis of macromolecular iron chelators provides a novel aspect to chelation therapy. 3-Hydroxypyridin-4-one hexadentate-based macromolecular chelators have considerable potential for the development of new treatments for iron overload and for topical treatment of infection.

Keywords antimicrobial; dendrimers; hydroxypyridinones; iron; polymers

Introduction

Polymeric chelators have been used for water treatment,[1,2] pollution control,[3,4] recovery of metals[5,6] and in analytical chemistry.[7–9] Recently several iron binding polymer applications in the biomedical field have also been reported.[10–13] As iron is an important element for all living processes, in principle targeting iron is a useful approach for the treatment of microbial infectious diseases.[14,15] Targeting iron is also a promising strategy for the treatment of malaria,[16–18] tumors,[19,20] the HIV virus[21] and neurodegenerative disorders.[22,23] Macromolecular iron chelators also have a role in the treatment of both chronic and acute iron overload.[24] Although most of the present-day iron-chelating therapeutics are designed as small molecules, a re-evaluation of the attributes of polymers has revealed a number of advantages associated with polymeric therapeutics that cannot be readily achieved with traditional small-molecule drugs. For example, when taken orally, the high-molecular-weight characteristics of polymers render them largely non-absorbed by the gastrointestinal tract.[25] Dendrimers, a class of synthetic macromolecules with highly branched structures, have been investigated for potential uses in drug delivery,[26–30] but they also have potential for scavenging metal ions. This article focuses on the factors that should be considered when designing iron-binding macromolecules, both polymers and dendrimers, as therapeutic agents.

Factors Considered When Designing Iron-Binding Macromolecules

When designing an ideal iron-binding macromolecule for clinical application, a range of specifications must be considered, such as metal selectivity and affinity, kinetic stability of the complex, iron-binding capacity, bioavailability and toxicity.

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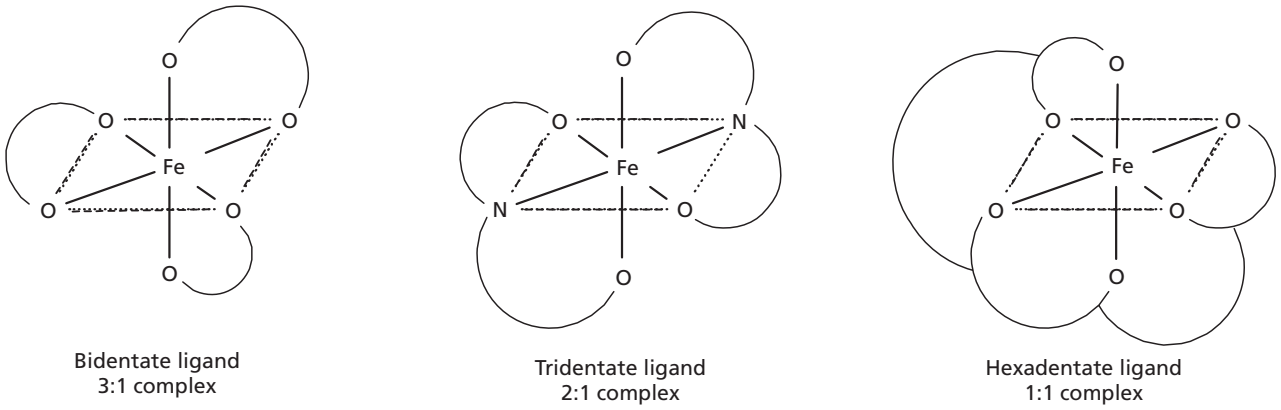


Figure 1 Schematic representation of chelate ring formation in iron-ligand complexes.

Thermodynamic stability of iron(III) complexes

The stability of iron(III) complexes of macromolecular chelators depends on the ligands that are incorporated into the macromolecules. Ligands can be structurally classified according to the number of donor atoms that each molecule possesses. When a ligand contains two or more donor atoms it is termed bidentate, tridentate, tetradentate, hexadentate or generally multidentate. The coordination requirements of iron(III) are best satisfied by six donor atoms ligating in an octahedral fashion to the metal centre. A factor of great importance relating to the stability of a metal complex is the number and size of chelate rings formed in the resultant ligand–metal complex. The most favourable chelate ring sizes consist of five or six atoms. The number of chelating rings can be enhanced by increasing the number of donor atoms attached to a single chelator; for example, a metal ion with a co-ordination number six may form three rings with a bidentate ligand or five rings with a hexadentate ligand (Figure 1). Thus, to maximize the thermodynamic stability of the iron(III) complex it is necessary to incorporate all six donors into a single local moiety thereby creating a hexadentate ligand. The stability of iron–ligand complexes follows the order hexadentate > tridentate > bidentate. It is probably for this reason that the majority of natural siderophores are hexadentate compounds and can therefore scavenge iron(III) efficiently at low metal and low ligand concentrations.[31]

Ligand selection

Catechols, hydroxamates, hydroxypyridinones (HPOs) and aminocarboxylates (Figure 2) are currently the most widely used iron chelators. Catechol moieties possess an extremely high affinity for iron(III). This strong interaction with tripositive metal cations results from the high electron density of both oxygen atoms. However, this high charge density is also associated with high affinity for protons (pKa values, 12.1 and 8.4). Thus the binding of cations by catechol has a marked pH sensitivity.[32] An additional problem with catechol-based ligands is their susceptibility to oxidation.[32]

The hydroxamate moiety possesses a lower affinity for iron than catechol. The selectivity of hydroxamates, like catechols, favours tribasic cations over dibasic cations. Due to

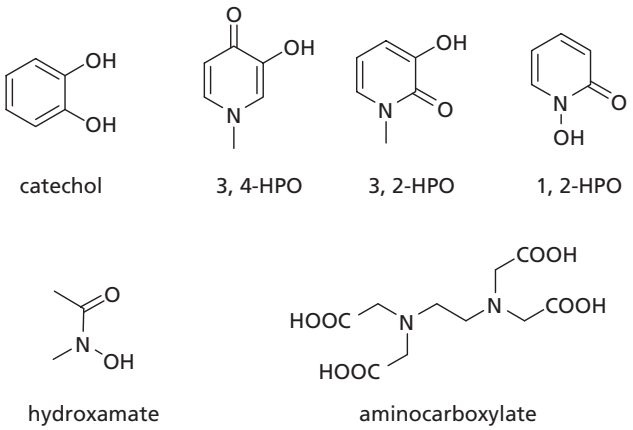
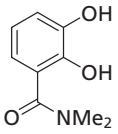
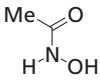
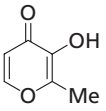
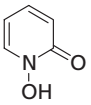
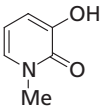
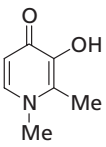


Figure 2 Generic structures of catechols, hydroxamates, hydroxypyridinones (HPOs) and aminocarboxylates.

the relatively low protonation constant (pKa ~ 9), hydrogen ion interference at physiological pH is less pronounced than for that of catechol ligands; consequently the 3:1 complex predominates at pH 7.0 when sufficient ligand is present. However, the affinity of a simple bidentate hydroxamate ligand for iron is insufficient to solubilise iron(III) at pH 7.4 at clinically achievable concentrations, thus only tetradentate and hexadentate hydroxamates are likely to be effective iron(III) scavengers under such conditions.

HPOs combine the characteristics of both hydroxamate and catechol groups, forming 5-membered chelate rings in which the metal is coordinated by two vicinal oxygen atoms. The HPOs are monoprotic acids at pH 7.0 and thus form neutral *tris*-iron(III) complexes. The affinity of such compounds for iron(III) reflects the pKa values of the chelating oxygen atoms–the higher the affinity for iron(III), the higher the pKa value (Table 1[33–38]). There are three classes of metal-chelating HPO ligands, namely 1-hydroxypyridin-2-one, 3-hydroxypyridin-2-one and 3-hydroxypyridin-4-one (Figure 2). Of these ligands, the pyridin-4-ones possess the highest affinity for iron(III) (Table 1) and are selective for tribasic metal cations over dibasic cations. The surprisingly high pKa value of the carbonyl function of 3-hydroxypyridin-4-one results from extensive delocalisation of the lone pair

Table 1 pKa values and affinity constants of dioxobidentate ligands for iron(III)

Ligand	Structure	pKa_1	pKa_2	$\log\beta_3$	pFe^{3+}
N,N-Dimethyl-2,3-dihydroxybenzamide (DMB)		8.4	12.1	40.2	15
Acetohydroxamic acid		–	9.4	28.3	13
2-Methyl-3-hydroxy-pyran-4-one (maltol)		–	8.7	28.5	15
1-Hydroxypyridin-2-one		–	5.8	27	16
1-Methyl-3-hydroxy-pyridin-2-one		0.2	8.6	32	16
1,2-Dimethyl-3-hydroxy-pyridin-4-one (deferiprone)		3.6	9.9	37.2	20

Data obtained from references.[33–38] The pFe^{3+} value is defined as the negative logarithm of concentration of free iron(III) in solution under defined conditions: total [ligand] = 10^{-5} M, total [iron] = 10^{-6} M, pH 7.45

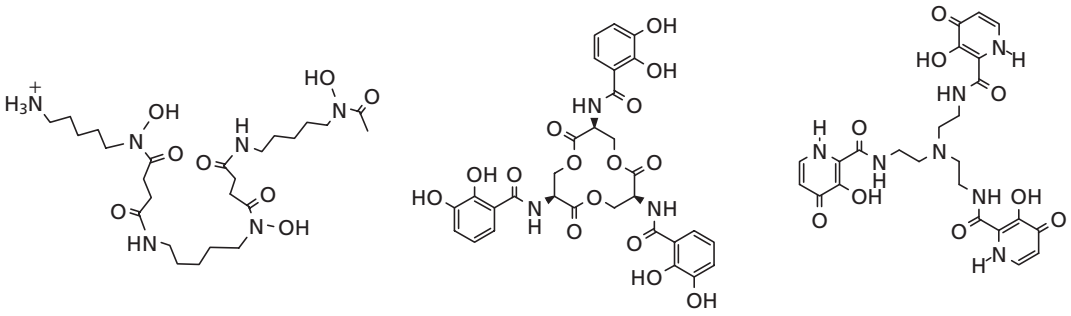
associated with the ring nitrogen atom. 3-Hydroxypyridin-4-ones form neutral 3 : 1 complexes with iron(III),[39] which are stable over a wide range of pH values. Although catechol derivatives possess higher β_3 values than that of 3-hydroxypyridin-4-one for iron(III), the corresponding pFe^{3+} values are lower (Table 1). This difference is due to the relatively higher affinity of catechol for protons. Indeed, among all dioxygen ligand classes investigated, 3-hydroxypyridin-4-ones possess the greatest affinity for iron(III) over the physiological pH range, as indicated by their respective pFe^{3+} values (Table 1). However, the pFe^{3+} value of deferiprone ($pFe^{3+} = 20$) is lower than that of natural hexadentate siderophores (e.g. DFO (**1**, $pFe^{3+} = 25$) and enterobactin (**2**, $pFe^{3+} = 35$)).[31] Not surprisingly, the pFe^{3+} values for hexadentate 3-hydroxypyridin-4-ones are higher than those of hexadentate hydroxamates, thus the pFe^{3+} value for **3** is 30.[40]

Aminocarboxylate ligands are excellent iron(III)-chelating agents. Several polycarboxylate ligands, such as ethylenediaminetetraacetic acid (EDTA) and diethylenetriaminepentaacetic acid (DTPA), have been widely investigated for their iron-chelating ability. However, the selectivity of these molecules for iron(III) is relatively poor. This lack of selectivity leads to zinc depletion in patients receiving aminocarboxylate-based ligands such as DTPA.[41] Indeed cereals (e.g. wheat) synthesise such molecules in order to scavenge both iron and zinc from the soil.[42,43] The secretion of these so-called phytosiderophores is activated when plants are grown in soils containing low levels of either zinc or iron. Aminocarboxylate-based polymers have been investigated for use as extractants in the remediation of soils contaminated with heavy metal.[44] Commercially available chelating resin Chelex100, a styrene-divinylbenzene resin containing iminodiacetic acid groups, is widely used for the removal of metal ions in solution.

Important properties of catechols, hydroxamates, hydroxypyridinones and aminocarboxylates are summarised in Table 2.

Design of Iron-Binding Macromolecules

A range of polymeric chelators and dendrimeric chelators have been synthesized. Most are based on bidentate ligands but some are based on hexadentate ligands.



1 2 3

Table 2 Comparative properties of catechols, hydroxamates, hydroxypyridinones and aminocarboxylates

	Hydroxypyridinones	Hydroxamates	Catechols	Aminocarboxylates
Stability of ligand under strong acid conditions	Stable	Unstable	Stable	Stable
Acid stability of iron complex	Stable	Stable	Unstable	Stable
O_2 sensitivity	Stable	Stable	Oxidised	Stable
Iron(III) selectivity	High	High	High	Low

Bidentate ligand-based macromolecular chelators

Hydroxypyridinones

Van der Does' group reported the synthesis of a series of HPO-based iron-binding resins. For instance, iron(III)-chelating beads (**4**) were synthesized by the copolymerization of 1-(*β*-acrylamidoethyl)-3-hydroxy-2-methyl-4-(1*H*)-pyridinone (AHMP) with 2-hydroxyethyl methacrylate, and ethyleneglycol dimethacrylate as the crosslinking agent, in the presence of an initiator 2,2'-azobisisobutyronitrile.[45] Iron(III)-chelating resins (**5**) were also synthesized by copolymerization of AHMP with *N,N*-dimethylacrylamide, and *N,N'*-ethylene-bis-acrylamide as a crosslinking agent, in the presence of an initiator ammonium persulfate.[46] Cohen *et al*. reported the synthesis of salicylate-, catecholate- and 3-hydroxypyridin-2-one functionalized dendrimers by attaching bidentate moieties to either poly(propyleneimine) or poly(amidoamine) dendrimers.[47] The ability of these dendritic chelators to bind large numbers of metal ions may lead to applications as metal sequestering agents for waste remediation and metal-separation technologies. These polydentate chelators may also be used as actinide-sequestering agents. Dendrimer (**6**) is an example of a 3-hydroxypyridin-2-one-based chelator.

Hydroxamates

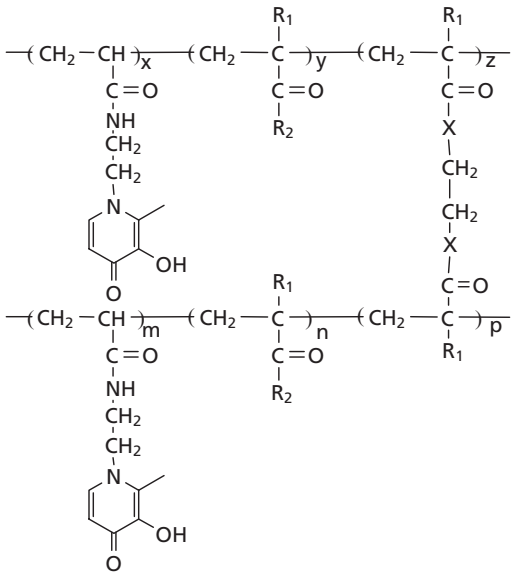
Winston *et al*.[48] reported the preparation of polymeric hydroxamic acid iron chelators by polymerization of activated ester of amino acid amide derivatives of acrylic or methacrylic acid in the presence of 2,2'-azobis(isobutyronitrile) (AIBN), followed by the conjugation of methyl hydroxamic acid with the polymer (an example is presented in Figure 3). These polymers were prepared for the purpose of developing new iron chelators for treating iron overload associated with thalassemia (Cooley's anaemia). Dhal synthesized polymeric hydroxamic acid hydrogels by copolymerization of acryloyl chloride (or acryloyl active ester, or 2-hydroxyethyl acrylate) and a cross-linking monomer such as divinylbenzene (DVB), in the presence of AIBN, followed by a reaction with hydroxylamine (Figure 3).[49]

Hexadentate ligand-based macromolecular chelators

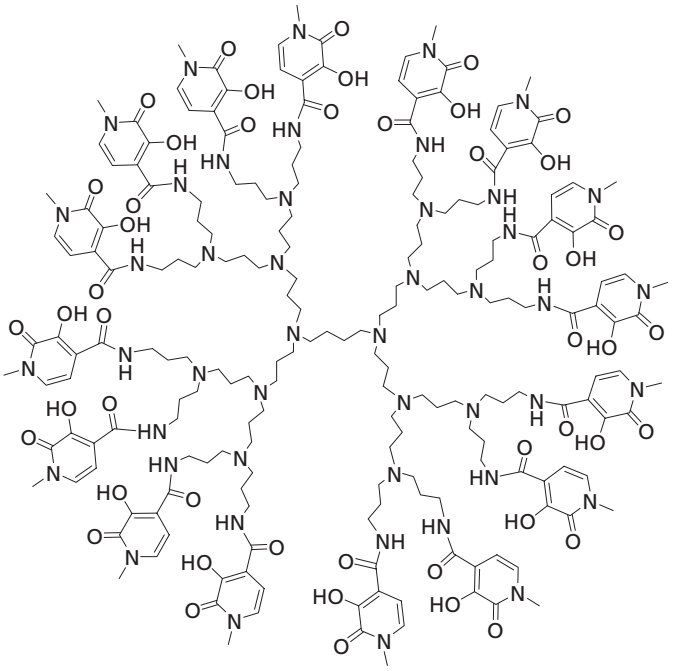
Hydroxamates

Some polymeric chelators have been prepared by immobilization of desferrioxamine (DFO) (**1**) on activated supports. For instance, Hallaway *et al*.[50] prepared a class of high-molecular-weight iron chelators by covalently attaching DFO, by its amino group, to a variety of biocompatible polymers such as dextran and hydroxyethyl starch. The iron-binding properties of DFO were found to be virtually unchanged after the attachment procedure, but the toxicity and circulatory half-life of the polymeric chelators were profoundly altered; toxicity decreased and half-life increased. Competitive iron-binding experiments indicate that the conjugates retain a high affinity for ferric iron. In addition, the derivatives inhibit iron-driven lipid peroxidation as effectively as the parent drug.[50] Margel prepared deferoxamine-conjugated agarose-polyacrolein microsphere beads, which could be used as the sorbent in a plasma/haemoperfusion system.[51] The advantages of this sorbent are minimal damage to plasma proteins during haemoperfusion, a high capacity and specificity for iron(III), and the possibility of reuse. Van der Does' group prepared iron(III) chelating polymers by immobilization of DFO onto Sepharose.[52] The products were found to possess a high affinity for iron(III) and were investigated for their ability to remove iron from milk, wine, whey and lactoferrin. However, the gels were not sufficiently stable for such application due to hydrolysis of the isourea bonds.

Takagai reported the synthesis of DFO-immobilized nylon 6,6 chelate fibre (**7**).[53] This chelate fibre possesses a high affinity for high-valence metal ions under highly acid condition. Kizhakkedathu *et al*.[13] prepared a novel class of high-molecular-weight iron chelators (**8**, **9**) based on DFO



4: R_1 = Me, R_2 = OCH_2CH_2OH, X = O
5: R_1 = H, R_2 = NMe_2, X = NH



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and polyethylene glycol methacrylate by reversible addition fragment chain transfer (RAFT) copolymerization with well-controlled molecular weight (27–127 kDa) and substitution of DFO (5–26 units per chain) along the copolymer. Biological assays showed that the cytotoxicity of these macromolecular chelators decreased more than 100 fold at identical concentrations of DFO. These macromolecular, blood-compatible and degradable conjugates are promising candidates as long-circulating, non-toxic iron chelators. Harmatz *et al*.[54] reported on starch-deferoxamine, which is synthesized by covalently attaching DFO to a modified starch polymer. This high-molecular-weight chelator retains

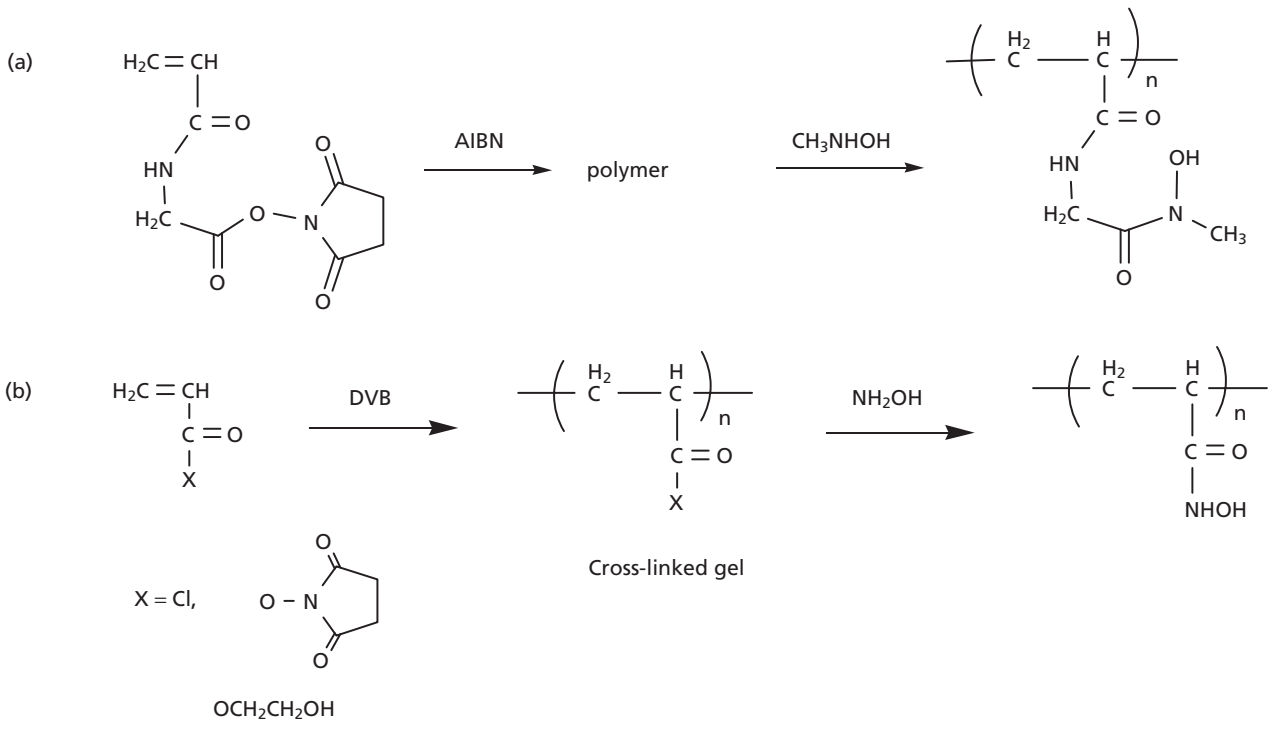
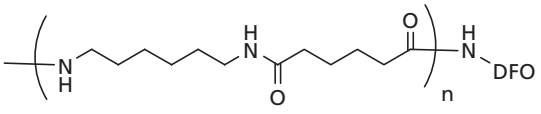


Figure 3 Synthesis of polymeric hydroxamates. (a) Linear polymers. (b) Cross-linked polymeric hydrogels.



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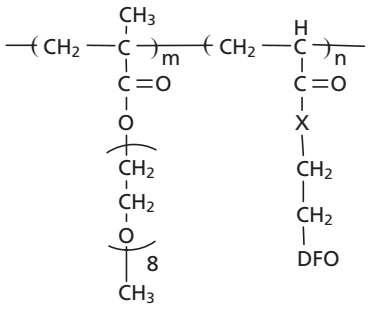


8: X = NH
9: X = O

the affinity and specificity of DFO for iron and has prolonged vascular retention.

Hydroxypyridinones

Apart from the polymers on which some natural hexadentate ligands (such as DFO) were immobilised, other hexadentate polymers have been rarely reported. However, the synthesis of 3-hydroxypyridin-4-one hexadentate ligand-containing copolymers by copolymerisation of a 3-hydroxypyridin-4-one hexadentate ligand with *N,N*-dimethylacrylamide (DMAA), and *N,N'*-ethylene-bis-acrylamide (EBAA) using $(NH_4)_2S_2O_8$ as the initiator has been achieved (Figure 4).[55] The copolymers possess a high selectivity and affinity for iron(III), and have potential as nonabsorbable iron-selective additives for the treatment of iron overload diseases associated with the hyperabsorption of iron (e.g. haemochromatosis).

Hexadentate ligands can be constructed by attaching three bidentate units to suitable molecular backbones. Theoretically, three 3-hydroxypyridin-4-one ligands with either the 2- or 5-substituents attached to a suitable tripodal molecule can form a high-affinity hexadentate ligand.[55] The synthesis of a range of 3-hydroxypyridin-4-one hexadentate-containing dendrimers, together with the evaluation of their iron-binding properties, has been reported. Using divergent and convergent synthetic strategies, first-generation and second-generation dendrimers (**10** and **11**) were prepared. These dendrimeric chelators were also found to possess a high selectivity and affinity for iron(III), and scavenge iron in intestine efficiently.[56] The first-generation dendrimer (**12**), which contains three hydroxypyridinone hexadentate moieties, has also been investigated.[57] Dendrimer **12** includes amide functions adjacent to the coordinating phenolates, which contributes to the stability of the iron complex via a hydrogen-bond effect.[58]

Comparison of Bidentate and Hexadentate-Based Macromolecules

Although bidentate ligand-containing polymeric chelators are easier to prepare than the corresponding hexadentate ligand-containing polymeric chelators, it is difficult for each bidentate ligand to form part of an ideal octahedral iron(III) coordination

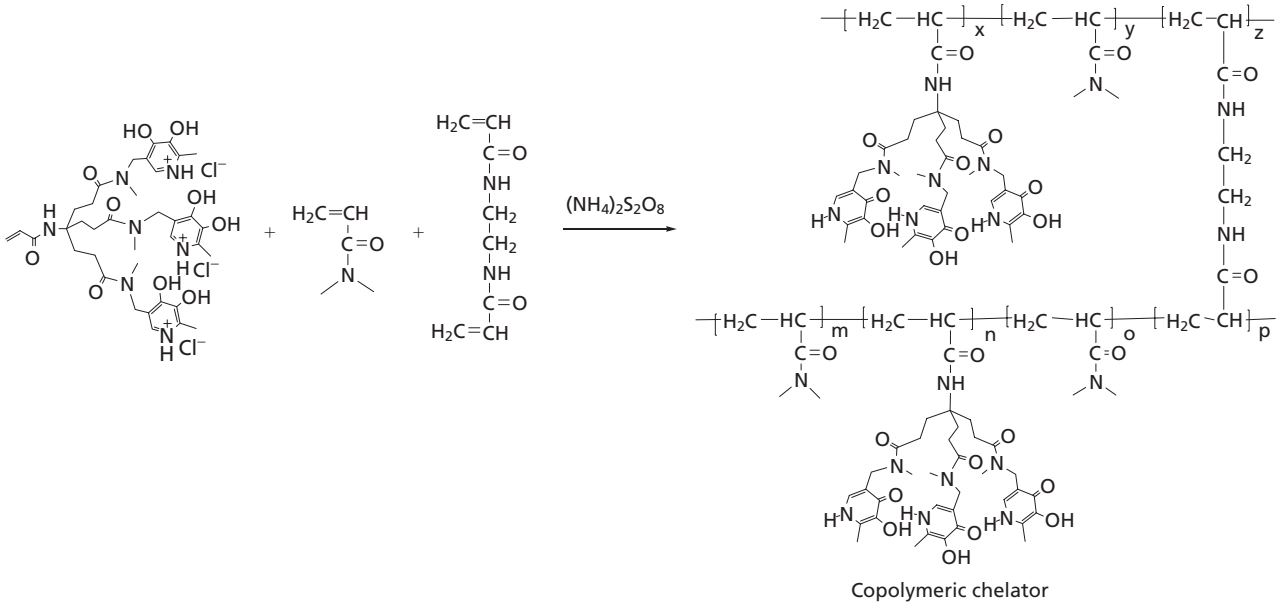
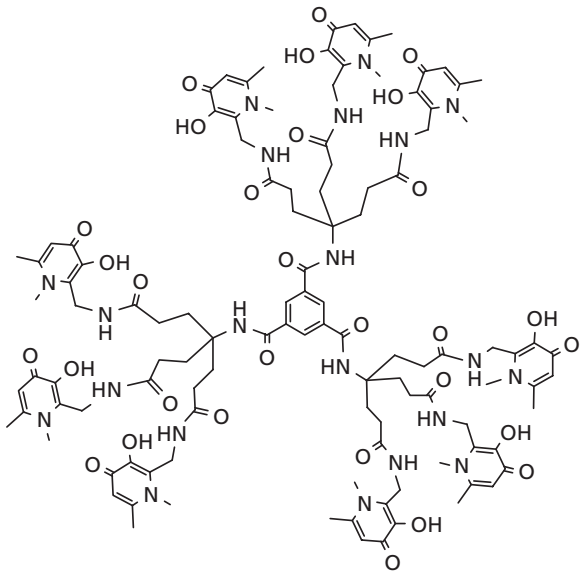


Figure 4 Synthesis of hexadentate 3-hydroxypyridin-4-one-containing copolymers.



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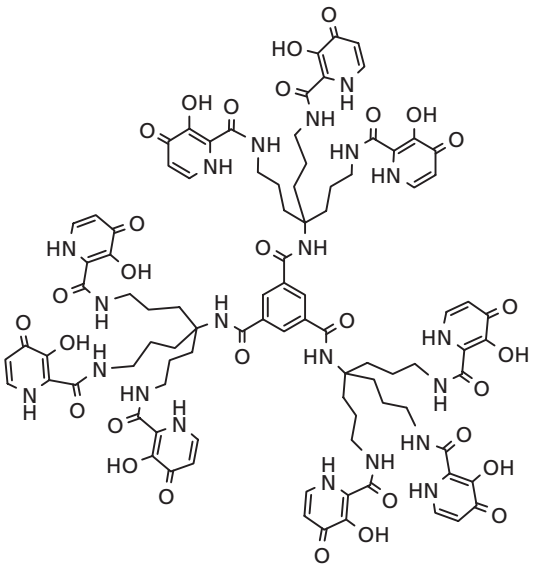

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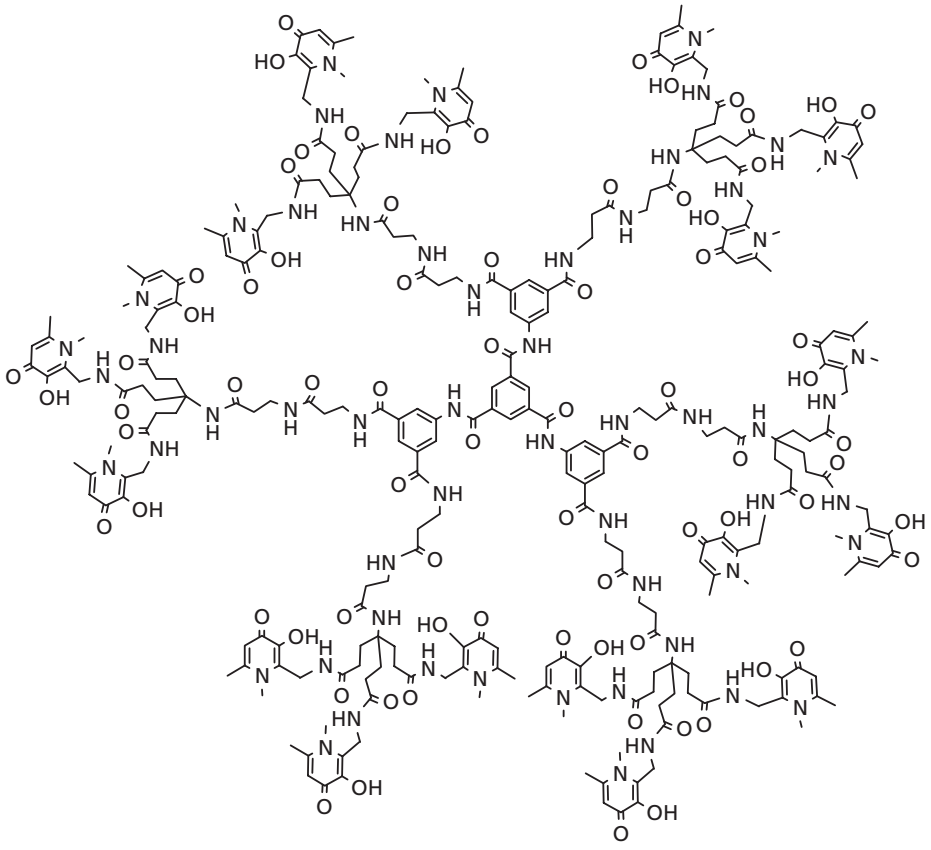

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site, thus the complexation of three bidentate ligands with iron will not be consistently strong, partial chelation of iron being likely (e.g. where only two bidentate ligands bind an iron atom) (Figure 5a). Such structures possess a markedly lower affinity for iron(III). In contrast, with hexadentate ligand-containing polymeric chelators, all the hexadentate moieties possess the ideal geometry to provide octahedral coordination sites for iron chelation and so form consistently stable iron complexes (Figure 5b). Such chelation will optimize the iron(III) affinity of the polymer. The iron chelation stoichiometry of the dendritic iron chelator **10**, which contains three hexadentate moieties, was studied by matrix-assisted laser desorption/

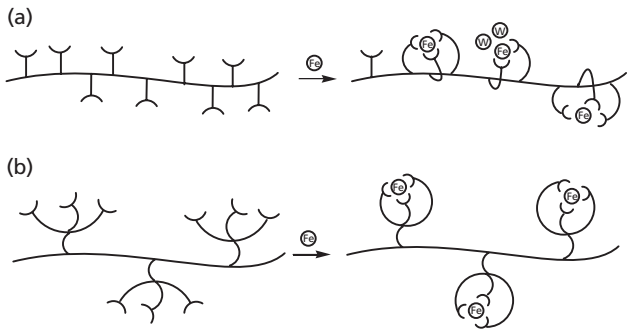


Figure 5 (a) Iron chelation by a bidentate ligand-containing polymeric chelator: three bidentate moieties bind one iron with ideal stereochemistry (left), only two bidentate moieties bind one iron and two ligand sites are occupied by water molecules (middle), three bidentate moieties bind one iron in a nonideal geometry (right). (b) Iron chelation by a hexadentate ligand-containing polymeric chelator: all the hexadentate moieties bind iron with an ideal stereochemistry.

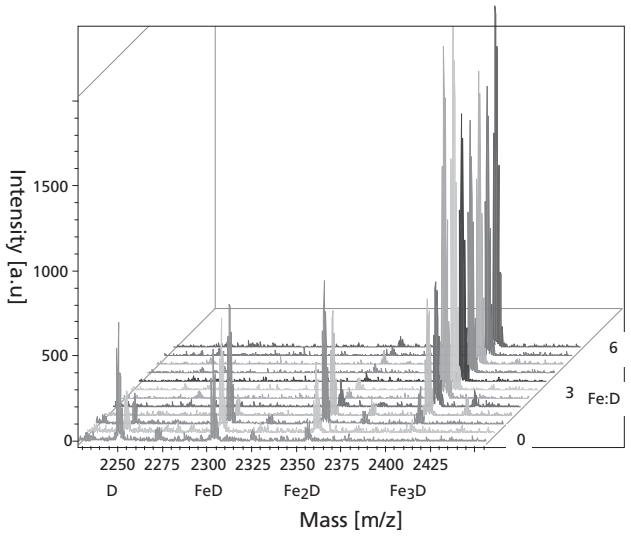


Figure 6 Stacked representation of all MALDI mass spectra of dendrimer **D** (14.28 μM) with varying iron(III) concentrations from 0 to 85.68 μM (iron : **D** ratio varying in the range 0–6 in axis Z).[59]

ionization time-of flight mass spectrometry (MALDI-TOF-MS).[59] When dendrimer **10** (**D**) is in large excess, almost no free iron is present – only free **D** and a small amount of FeD are identified corresponding to MALDI signals at 2249 and 2301 *m/z*. As the iron(III) concentration increases, partially saturated species are detected, with the profile gradually shifting toward the fully saturated species Fe_3D. After the iron : **D** ratio reaches 3, the fully saturated species Fe_3D dominates and partially saturated species, together with the peak of **D**, are no longer observed (Figure 6).

An important advantage of hexadentate-based macromolecular chelators over the corresponding bidentate-based macromolecular chelators is the extremely high selectivity for trivalent metal ions over bivalent metal ions. It is thus possible to create a polymer that is highly selective for iron in biological matrices.

Comparison of Polymeric and Dendrimeric Chelators

Generally speaking, polymers are much easier to synthesize and purify than dendrimers (especially high-generation dendrimers), leading to a relatively low cost for polymeric chelator preparation. However, dendrimers have the characteristic of precise molecular size and are thus ideal for efficient quality control. Divergent and convergent approaches are always employed for the synthesis of dendrimers.[60] For example, dendrimer **10** was synthesized by divergent strategy and easily obtained at a scale of 5–10 g in one batch. However, when preparing high-generation dendrimers, defect dendritic structures are frequently obtained when using divergent strategy, which renders it difficult for purification of products. Although the introduction of convergent synthetic strategy prevents the formation of the defect dendritic structures to some extent, purification is not easy for high-generation dendrimers.

Therapeutic Applications of Macromolecular Iron Chelators

Iron overload

Although iron is essential for all living cells, it is toxic when present in excess. In the presence of molecular oxygen, 'loosely-bound' iron is able to redox cycle between the most stable oxidation states iron(II) and iron(III), thereby generating oxygen-derived free radicals such as the hydroxyl radical.[61] The hydroxyl radical is highly reactive and capable of interacting with most types of biological molecules, including sugars, lipids, proteins and nucleic acids, resulting in peroxidative tissue damage.[62] The uncontrolled production of such a highly reactive species is undesirable and thus a number of protective strategies are adopted by cells to prevent their formation. One of the most important is the tight control of iron storage, transport and distribution. In fact iron metabolism in humans is highly conservative with the majority of iron being recycled within the body. Since humans lack a physiological mechanism for eliminating iron, iron homoeostasis is largely achieved by the regulation of iron absorption.[63] In the normal individual, iron levels are under extremely tight control and there is little opportunity for iron-catalysed free radical-generating reactions to occur. However, there are situations when the iron status can change, either locally as in ischaemic tissue, or systematically as with genetic haemochromatosis or transfusion-induced iron overload. In such circumstances, the elevated levels of iron ultimately lead to free radical-mediated tissue/organ damage and eventual death.[64] Although excess iron can be removed by venesection where adequate erythropoietic reserve exists (e.g. haemochromatosis), iron chelation is the only effective way to relieve iron overload in transfusion-dependent patients such as those suffering from β-thalassaemia.

For this purpose, the design of an orally active iron chelator has been a major objective resulting in a large number of iron chelators being synthesized.[65] The orally active chelators Deferiprone and Exjade have been subjected to extensive clinical investigation.[66–69] An alternative method of relieving iron overload is to reduce the efficiency of iron absorption from the intestine by administering iron chelators which bind iron irreversibly to form nontoxic kinetically inert complexes

that are not absorbed and are therefore excreted in the faeces. In principle, macromolecular chelators could find application as non-absorbable iron-selective additives. For instance, hydroxypyridinone-containing polymers have been demonstrated to significantly reduce iron absorption from the intestine. The result of in-vitro intestinal perfusion investigation with different ratios of copolymer and ^{58}Fe is presented in Figure 7.[55] Compared with the control groups (1826 pmol/cm tissue), the accumulated iron contents in the absorbates (the absorption of iron) was significantly reduced in the presence of polymeric chelator. In the case of ratios of copolymer and Fe of 1 : 1, 2 : 1 and 5 : 1, the accumulated iron content in the adsorbates was 399, 130 and 43 pmol per cm tissue, respectively, indicating that iron absorption can be reduced to a great extent by using polymeric iron chelators. Dendrimeric chelators have also been demonstrated to reduce iron absorption efficiently.[56] Thus iron-binding copolymers and dendrimers have clear potential in iron overload therapy by virtue of their ability to reduce iron absorption.

Antimicrobial iron chelators

Iron is essential for the growth of all bacteria and fungi, probably without exception. Consequently all microorganisms have developed efficient methods of absorbing iron from the environment. Many microorganisms secrete siderophores (e.g. desferioxamine (**1**) and enterobactin (**2**)) to scavenge iron.[70] Such methods of uptake can be circumvented by the introduction of high-affinity iron-selective chelating agents. The affinity for iron of these agents must be extraordinarily high, so that they can compete efficiently with siderophores. Recently research on the antimicrobial activity of chelators has become increasingly attractive.[71,72] However, most chelators investigated for this purpose have been bidentate ligands, which possess a relatively low affinity for iron(III) and thus a low antimicrobial activity.[73,74] A preliminary study indicated that 3-hydroxypyridin-4-one hexadentate ligands **3** and **13** inhibit the growth of various types of *Escherichia coli* and *Staphylococcus aureus* (Table 3). Thus using the iron complex of **3** or **13** as the only iron source, the growth of both *E. coli* and *S. aureus* was inhibited, indicating that these microorganisms do not recognise the iron complex of **3** and **13** and cannot transfer the coordinated iron into the cell. In most cases, microorganisms grow well in the presence of iron-siderophore complexes; for example, using the Fe-crocin complex as the only iron source, most types of *E. coli* and *S. aureus* grow well, with the exception of *E. coli* TonB, which lacks the specific protein for the transportation of Fe-crocin complex (Table 3).

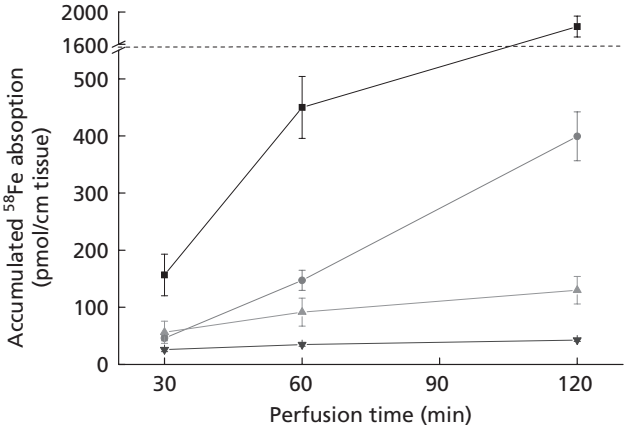
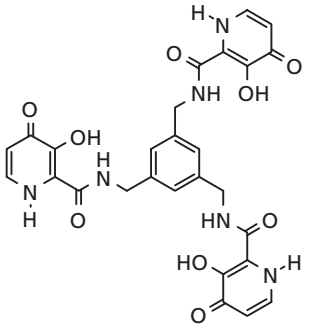


Figure 7 In-vitro intestinal perfusion investigation with different ratios of polymeric chelator and ^{58}Fe (■ control, ● copolymer: ^{58}Fe = 1:1, ▲ copolymer: ^{58}Fe = 2:1, ▼ copolymer: ^{58}Fe = 5:1). Initial concentration of ^{58}Fe of 50 μM, molar ratios presented.[55]



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Bacterial and fungal infection of wounds slows down and even prevents the healing process, particularly in the elderly. For instance, in superficial wounds, staphylococci and streptococci are the most commonly encountered pathogenic organisms; more unusual organisms exist in animal bite wounds; and pathogenic organisms cause surgical wound infection. The emergence of multi-drug resistant organisms, such as methicillin-resistant *S. aureus* (MRSA), render many of the present antibiotics useless in the treatment of wound

Table 3 Growth of bacterium in the presence of chelators

	3	**Fe-3**	**13**	**Fe-13**	**Fe-Crocin**	**Fe-Enterobactin**
E.coli *wt*	–	–	–	–	25	25
E.coli *fiu,cir*[a]	–	–	–	–	24	25
E.coli *fiu, cir, fepA*[a]	–	–	–	–	26	–
E.coli *TonB*[a]	–	–	–	–	–	–
S. aureus wt	–	–	–	–	27	12

[a]*fiu,cir* lacks ability to transport monocatechols; *fepA* lacks ability to transport Fe-enterobactin; *TonB* lacks ability to transport both Fe-enterobactin and Fe-crocin. 150 μM bipyridine and 150 μM ethylenediamine-*N*,*N*'-bis(2-hydroxyphenylacetic acid) (EDDHA) were added into the growth promotion biotests to bind ferrous and ferric iron present in the medium.[75]

infection. In principle, the topical application of a powerful iron chelator will greatly reduce such activity and thereby facilitate the healing process.[76–78] It can be anticipated that hexadentate ligand-based polymers and dendrimers will find promising applications in wound healing and other external infections associated with bacteria and fungi.

Conclusions

The design and synthesis of macromolecular iron chelators is an exciting field of chelation therapy. The discovery and development of new biologically active macromolecules will lead to novel human therapeutics. By careful consideration of both disease targets and their mechanisms of action, macromolecular iron chelators that exhibit pharmacological properties can, in principle, be developed into marketed products. Compared with many ligands, 3-hydroxypyridin-4-one and hexadentate-based macromolecular chelators have considerable potential for the development of new drugs for the treatment of iron overload and for the treatment of infection, by virtue of their high affinity for hard metal cations and the stability of their metal complexes over a wide range of pH values.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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