doi:10.1246/cl.2012.932
Published on the web September 1, 2012

Highly Selective and Low-swelling Phosphate-binding Polymer for Hyperphosphatemia Therapy

Atsushi Inoue,*[1] Satoshi Minakami,[1] Takami Kanno,[1] and Kazuharu Suyama[2]
[1]*Pharmaceutical Research Laboratories, Toray Industries, Inc., 10-1 Tebiro 6-chome, Kamakura, Kanagawa 248-8555*
[2]*Chemistry, Manufacturing and Controls Planning Dept., Toray Industries, Inc., 4845 Mishima, Shizuoka 411-8652*

(Received June 8, 2012; CL-120510; E-mail: Atsushi_Inoue@nts.toray.co.jp)

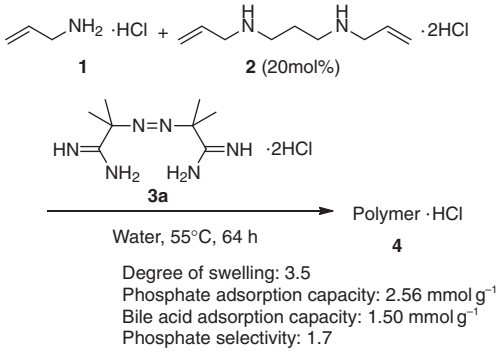
A crosslinked poly(allylamine) was prepared by copolymerization of allylammonium dihydrogen phosphate with *N*,*N*′-diallyl-1,3-diaminopropane bis(dihydrogen phosphate). This polymer has both a high phosphate adsorption capacity and a low degree of swelling. Thus, the polymer should be useful as a therapeutic agent for hyperphosphatemia, and compared with sevelamer hydrochloride, should have fewer side effects such as constipation.

Patients with renal failure often exhibit hyperphosphatemia due to decreased phosphate excretion. Even after starting dialysis, the disease state persists unless phosphate homeostasis is maintained. Thus, hyperphosphatemia therapy is indispensable for patients with renal failure. An oral phosphate binder, sevelamer hydrochloride (Renagel), is widely used for hyperphosphatemia therapy. However, sevelamer hydrochloride requires administration at a high pill burden in order to reduce phosphate absorption.[1] Further, sevelamer hydrochloride causes side effects including constipation, abdominal pain, and abdominal distension since it absorbs water in the gastrointestinal tract. Such side effects may lead to serious side effects such as intestinal perforation and intestinal obstruction.[2] Since sevelamer hydrochloride has relatively low affinity and selectivity for phosphate in the presence of bile acids,[3,4] there is the possibility of not only decreased phosphate adsorption capacity, but also inhibited uptake of fat-soluble vitamins as a consequence of bile acid adsorption in the intestine.[5] In the gastrointestinal tract, the adsorption of phosphate ion to the phosphate binder competes with the adsorption of bile acids. Therefore, development of an oral phosphate adsorption agent with higher phosphate selectivity in competition with bile acids is needed. Herein we report a novel phosphate-binding polymer with high selectivity and a low degree of swelling.

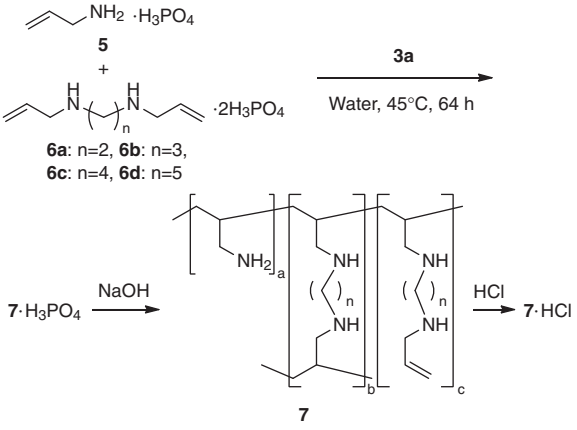
Sevelamer hydrochloride is synthesized by crosslinking poly(allylamine) homopolymer with epichlorohydrin.[6] In contrast, we chose crosslinking copolymerization of allylamine with a compound bearing two allylamine moieties as crosslinker.[7] To lower the degree of swelling and to increase phosphate selectivity, we used a much higher ratio of crosslinker than reported in the literature. We hypothesized that a polymer with high crosslinking density should be less swellable and should adsorb less bile acids, which are much larger than phosphate.

First, we synthesized a crosslinked polymer by using allylammonium chloride (**1**) and *N*,*N*′-diallyl-1,3-diaminopropane dihydrochloride (**2**) as crosslinker (20 mol %; Scheme 1). The degree of swelling was sufficiently low (3.5), but phosphate selectivity (1.7) and phosphate adsorption capacity (2.56 mmol g^{-1}) were unsatisfactory.

To improve the selectivity, we changed the counter ion of allylamine. Inspired by the molecular imprinting technique,[8,9]



Scheme 1. Copolymerization of allylammonium chloride.



Scheme 2. Copolymerization of allylamine phosphate.

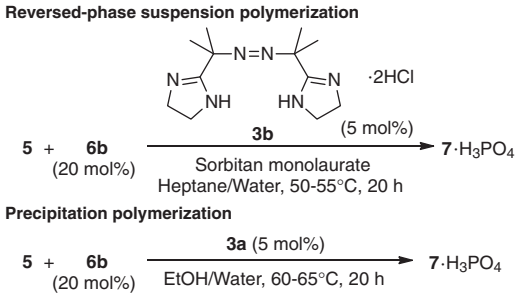
we attempted to polymerize allylammonium dihydrogen phosphate. Polymerization was performed as shown in Scheme 2. Under argon atmosphere, allylammonium dihydrogen phosphate (**5**, 40 mmol) and the bis(dihydrogen phosphate) salt of *N*,*N*′-diallyl-substituted alkylenediamine (**6**) were dissolved in water (4.0 mL) at 45 °C, and 2,2′-azobis(2-amidinopropane) hydrochloride (**3a**, 2 mmol) was added in one portion. The temperature was maintained at 45 °C for 64 h. During heating, the mixture became solid. The solid was crushed, washed successively with water and ethanol, and dried under vacuum to afford a phosphate polymer, which was then converted into the corresponding hydrochloride by successive treatment with aqueous sodium hydroxide solution and hydrochloric acid.

We investigated four crosslinkers with different alkyl chain lengths. The amount of crosslinker was varied in a range of 2 to 30 mol % with respect to allylammonium dihydrogen phosphate. The results are shown in Table 1. The phosphate adsorption capacity and bile acid adsorption capacity respectively indicate

Table 1. Assay results for **7**·HCl[a]

Entry	Crosslinker /mol %		Yield /%	Degree of swelling	Adsorption capacity /mmol g^{-1}		Selectivity
					Phosphate	Bile acid	
1	**6b**	2	74	8.0	3.26	3.10	1.1
2	**6b**	5	81	4.2	3.53	2.31	1.5
3	**6b**	10	81	3.6	3.71	1.36	2.7
4	**6b**	15	75	4.0	4.08	1.59	2.6
5	**6b**	20	82	3.2	4.23	1.57	2.7
6	**6b**	30	80	3.3	3.70	1.76	2.1
7	**6a**	20	29	4.9	2.96	2.19	1.4
8	**6c**	20	59	5.2	2.95	3.45	0.9
9	**6d**	20	46	7.6	1.79	2.61	0.7

[a]See the Supporting Information for detailed procedures.



Scheme 3. Reversed-phase suspension polymerization and precipitation polymerization.

the amount of phosphate and glycocholate removed by adsorption onto the polymer in a test solution (pH 6.8) containing phosphate (10 mmol L^{-1}) and glycocholate (10 mmol L^{-1}).[10] The degree of swelling is the weight of water-swelled polymer divided by its dry weight. The degree of swelling decreased and the phosphate selectivity improved as the amount of crosslinker **6b** ($n = 3$) was increased. The degree of swelling was found not to decrease even when the amount of the crosslinker was increased from 20 to 30 mol %. The use of the crosslinker **6a** ($n = 2$), **6c** ($n = 4$), or **6d** ($n = 5$) decreased phosphate selectivity and increased the degree of swelling. The best result was obtained when 20 mol % of crosslinker **2b** was used.[10] Using phosphate as the counter ion of the monomer improved the selectivity and adsorption capacity.

The polymer can also be prepared by reversed-phase suspension polymerization and precipitation polymerization, both of which are suitable for large-scale production (Scheme 3). The assay results for the polymers synthesized by those methods (Table 2) exhibit better phosphate selectivity than is shown in Table 1.

The effectiveness of this new polymer as an oral phosphate binder for hyperphosphatemia treatment was shown by comparison with sevelamer hydrochloride (Table 2). Renagel tablets were pulverized with a grinder, and the assay was performed. The results were corrected by the sevelamer hydrochloride content in the tablets (ca. 83%). The degree of swelling of sevelamer hydrochloride was 6.7. Its phosphate adsorption capacity was 3.36 mmol g^{-1} and the phosphate selectivity was 1.3. Our new polymer exhibited higher phosphate selectivity and a lower degree of swelling than sevelamer hydrochloride. The weight of our new polymer after swelling is less than half that of sevelamer hydrochloride, thus the side effects caused by swelling are likely to be less significant. Furthermore, the higher phosphate adsorption capacity should reduce a patient's pill burden.

Table 2. Assay results for polymers prepared by scalable methods and sevelamer hydrochloride[a]

Polymerization system	Yield /%	Degree of swelling	Adsorption capacity /mmol g^{-1}		Selectivity
			Phosphate	Bile acid	
suspension	97	3.1	4.03	0.50	8.1
precipitation	76	4.0	4.50	0.85	5.3
sevelamer HCl	—	6.7	3.36	2.51	1.3

[a]See the Supporting Information for detailed procedures.

In conclusion, we have developed a novel crosslinked poly(allylamine) with a high phosphate adsorption capacity and a low degree of swelling. Compared with sevelamer hydrochloride, the developed polymer has higher selectivity, higher absorption capacity, and a much lower degree of swelling. Therefore, the polymer shows promise as a pharmaceutical agent for treating hyperphosphatemia, and compared with sevelamer hydrochloride, should have fewer side effects such as constipation, abdominal pain, and abdominal distension.

References and Notes

1 S. M. Sprague, *Curr. Med. Res. Opin.* **2007**, *23*, 3167.
2 J. A. Daly, M. P. V. Mujica, *Expert Opin. Drug Saf.* **2006**, *5*, 675.
3 W. Braunlin, E. Zhorov, A. Guo, W. Apruzzese, Q. Xu, P. Hook, D. L. Smisek, W. H. Mandeville, S. R. Holmes-Farley, *Kidney Int.* **2002**, *62*, 611.
4 V. Autissier, S. J. P. Damment, R. A. Henderson, *J. Pharm. Sci.* **2007**, *96*, 2818.
5 O. Wrong, C. Harland, *Nephron Physiol.* **2007**, *107*, 17.
6 S. R. Holmes-Farley, W. H. Mandeville, III, G. M. Whitesides, PCT Int. Appl. WO 95 05184, **1995**.
7 T. Endo, Jpn. Kokai Tokkyo Koho 98 330,427, **1998**; T. Endo, *Chem. Abstr.* **1999**, *130*, 95992.
8 M. Komiyama, T. Takeuchi, T. Mukawa, H. Asanuma, *Molecular Imprinting: From Fundamentals to Applications*, Wiley-VCH, Weinheim, **2003**. doi:10.1002/352760202X.
9 X. Wu, K. Goswami, K. D. Shimizu, *J. Mol. Recognit.* **2008**, *21*, 410; A. Kugimiya, H. Takei, *Anal. Chim. Acta* **2008**, *606*, 252; A. Kugimiya, H. Takei, *Anal. Lett.* **2008**, *41*, 302; E. B. Özkütük, A. Ersöz, A. Denizli, R. Say, *J. Hazard. Mater.* **2008**, *157*, 130.
10 The adsorption capacity depends on the pH of the test solution. The adsorption capacity decreased below pH 4 or above pH 8.
11 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

