Title: PROCESS FOR PREPARING CROSSLESIKED ALLYLAMINES POLYMER

Abstract: The present invention relates to a cost effective and a commercially viable process for the preparation of crosslinked allylamine polymer. More specifically the present invention relates to a process for crosslinking of polyallylamine base with a crosslinking agent in an aqueous medium and isolating the crosslinked polyallylamine free base, which can be optionally converted to the desired salt.
RELATED APPLICATION

This application claims the benefit of Indian Patent Application No: 394/MUM/2010 filed on February 15, 2010 all of which is hereby incorporated by reference.

TECHNICAL FIELD

The present invention relates to a cost effective and a commercially viable process for the preparation of crosslinked allylamine polymer. More specifically the present invention relates to a process for crosslinking of polyallylamine base with a crosslinking agent in an aqueous medium and isolating the crosslinked polyallylamine free base which can be optionally converted to the desired salt. The crosslinked polyallylamine free base may also be converted to crosslinked poly(allylamine carbonate) with the use of carbon dioxide gas.

BACKGROUND OF THE INVENTION

The active ingredient in Renagel® tablets and capsules is sevelamer hydrochloride, a polymeric phosphate binder intended for oral administration. Sevelamer hydrochloride is poly(allylamine hydrochloride) crosslinked with epichlorohydrin in which forty percent of the amines are protonated. It is chemically known as poly(allylamine-co-N,N'-diallyl-1,3-diamino-2-hydroxypropane) hydrochloride. Sevelamer hydrochloride is hydrophilic, but insoluble in water. The other salt of sevelamer reported is sevelamer carbonate which is marketed as Renvela®. Because of the ability of these polymers to bind with phosphates and bile acids they are used in the treatment of hyperphosphatemia in patients with end stage renal disease who are on dialysis.

The structure of sevelamer hydrochloride is represented below:
The primary amine groups shown in the structure are derived directly from poly(allylamine hydrochloride). The crosslinking groups consist of two secondary amine groups derived from poly(allylamine hydrochloride) and one molecule of epichlorohydrin.

The process for preparing crosslinked polyallylamine comprises polymerizing the monomer viz. allylamine and then crosslinking with a crosslinking agent. The monomer allylamine does not polymerize readily as it undergoes degradative chain transfer. Allylamine is therefore generally converted into its hydrochloride salt with aqueous hydrochloric acid, concentrated by distilling out water and then polymerized in the presence of a free radical initiator to obtain poly(allylamine hydrochloride). The poly(allylamine hydrochloride) is isolated in a solid form by addition to an antisolvent. The poly(allylamine hydrochloride) is dissolved, the solution partly neutralized and then crosslinked using a wide range of crosslinking agents. The crosslinkers typically used include epichlorohydrin, 1,4-butanediol diglycidyl ether,
1,2-ethanediol diglycidyl ether, 1,3-dichloropropane, 1,2-dichloroethane, succinyl dichloride, dimethyl succinate and toluene diisocyanate. More specifically the partly neutralized polymer of allylamine hydrochloride is crosslinked using epichlorohydrin.

US 6,579,933 ('933 patent) discloses a process for preparing allylamine polymer and suggests their industrial utility as polymer flocculants, coating agents etc. The process comprises reacting equimolar quantities of monoallylamine with sulfuric acid to obtain an aqueous solution of monoallylamine sulfate salt, addition of 0.1 to 0.7 mol% (based on the monomer) of an azo based radical initiator and then polymerizing for 48 hours to obtain a solution poly(allylamine sulfate). Water was then added to the polymerization solution, neutralized with alkali followed by work up to obtain the monoallylamine polymer. The '933 patent discloses that the resultant polymer is a high molecular weight monoallylamine polymer having a weight average molecular weight in the range of 20,000 to 18000. However the '933 patent does not mention about crosslinking of the monoallylamine polymer thus obtained.

US Patents 6,083,495, 5,667,775, 5,496,545, 6,509,013 disclose a method of crosslinking poly(allylamine hydrochloride). The polymerization of hydrochloride salt of allylamine to obtain poly(allylamine hydrochloride) is described in these patents. For effective polymerization, the allylamine hydrochloride solution obtained by the addition of hydrochloric acid to allylamine needs to be concentrated by distilling out water under vacuum. Further long reaction times (~48 hours) are required for polymerization to obtain poly(allylamine hydrochloride). In all these patents poly(allylamine hydrochloride) is isolated in a solid form from the polymerization solution by addition of a water miscible antisolvent viz. methanol. The isolated solid poly(allylamine hydrochloride) is then re-dissolved in water, the solution obtained is then partly neutralized and then crosslinked using a wide range of crosslinking agents. More specifically, the partly neutralized polymer of allylamine hydrochloride is crosslinked using epichlorohydrin. Thus these patents disclose that
Cross linking is performed by dissolving poly(allylamine hydrochloride) in water and adjusting the pH to 10 with sodium hydroxide to form a solution and stirring the solution with epichlorohydrin for about 15 minutes to form a gel and allowing the gel to cure for 18 hours at room temperature. The gel is then fragmented into gel particles in a blender in the presence of isopropanol. The gel particles are then washed repeatedly with water and then suspended in isopropanol, filtered and dried under vacuum for 18 hours. At pH 10, the epichlorohydrin crosslinked polyallylamine polymer is partly in the form of a hydrochloride salt and is not completely in a free base form.

US Patent 4,605,701 discloses a method of crosslinking poly(allylamine hydrochloride). The method involves dispersing a poly(allylamine hydrochloride) in water and a water immiscible solvent followed by subjecting the polymer to crosslinking with epichlorohydrin. The liquid medium that is immiscible with the aqueous solvent is an organic solvent such as a halogenated or a non-halogenated aliphatic or an aromatic hydrocarbon. However, the use of chlorinated hydrocarbons is being discouraged in view of the environmental damage caused by the chlorinated hydrocarbons. Also high boiling points of solvents such as toluene, chlorobenzene and dichlorobenzene render the removal of solvents from the polymer difficult. Accordingly the present invention envisages the use of aqueous medium for the crosslinking reaction.

US Patent 6,525,113 discloses a process for preparing crosslinked poly(allylamine hydrochloride) in which an aqueous solution of poly(allylamine hydrochloride) is first partially neutralized by using an alkoxide or hydroxide. This is followed by adding a water miscible organic solvent such as acetonitrile. The crosslinking agent is then added to the reaction mixture and the suspension that is formed after crosslinking is filtered to obtain sevelamer hydrochloride.
WO 2006/097942 discloses a biphasic process for crosslinking partly neutralized aqueous poly(allylamine hydrochloride) using a crosslinking agent in a hydrocarbon solvent in presence of a dispersing agent to get a crosslinked polymer having a desired particle size range (60-100 mesh). The process is carried out in such a manner that the aqueous solution is partly neutralized with alkali, mixed with crosslinking agent and charged to an organic phase containing the dispersing agent. Crosslinking is carried out at a higher temperature and at a high speed of 800 to 1200 rpm. The crosslinked polymer is then isolated after a sequence of operations, i.e. filtration, washing with water to remove salts, washing with isopropyl alcohol (IPA) to remove water from the crosslinked polymer, and finally drying in a stationary tray dryer.

WO2010/041274 and WO2009/125433 disclose the process for preparation of crosslinked poly(allylamine carbonate) with chloride content of less than 0.1 to 0.01% or < 500 ppm by converting the crosslinked poly(allylamine hydrochloride) to crosslinked polyallylamine free base and reacting with a carbonate source.

None of the prior art processes disclose a totally solvent free process for preparing crosslinked polyallylamine or salts thereof. All the processes require an organic solvent either in the reaction step or in the isolation step. Also the prior art processes use a partially neutralized polyallylamine salt and do not isolate polyallylamine base for the crosslinking reaction. Further, all of the prior art processes isolate poly(allylamine hydrochloride) for the subsequent crosslinking reaction. The isolation of poly(allylamine hydrochloride) requires addition of a polymerized mass to a water miscible antisolvent such as methanol. For commercial scale operations these prior art processes have the following drawbacks:

> The allylamine hydrochloride solution obtained by the addition of hydrochloric acid to allylamine needs to be concentrated by distilling out water under vacuum. Further, long reaction times (~48 hours) are required for polymerization to obtain poly(allylamine hydrochloride). For
commercial scale manufacturing it means increased cycle times and energy requirements.

> The poly(allylamine hydrochloride) reaction mass is highly viscous at room temperature rendering difficulties of transferability.

> For proper dispersion and obtaining the poly(allylamine hydrochloride) in a powdery form, large volumes of water miscible antisolvent such as methanol are required. Further, the product requires to be leached with large volumes of water miscible solvent such as methanol in order to remove the unreacted monomer viz. allylamine hydrochloride. These operations render increased cost of production and energy utilization for solvent recoveries, besides reduced mass productivity.

> The poly(allylamine hydrochloride) which is isolated is an extremely hygroscopic material rendering difficulties in filtration and handling under humid conditions.

> The filtered poly(allylamine hydrochloride) needs to be dried to make it solvent free lest undesired impurities may generate during the crosslinking reaction, by reaction of the solvent traces with the crosslinking agent.

Hitherto there is no process reported which does not use organic solvent or any other agent like dispersing agent and isolates the crosslinked polyallylamine base in a particulate form. We have now developed a novel solvent free, efficient and commercially viable process for preparing crosslinked polyallylamine free base or salt thereof which overcomes the drawbacks mentioned *vide supra* of the prior art processes. The process of the present invention isolates from an aqueous alkaline medium the crosslinked polyallylamine in the form of a non-hygroscopic free base obtained by crosslinking polyallylamine base with a crosslinking agent in an aqueous medium. The obtained crosslinked polyallylamine free base can then be converted to the desired salt once again in aqueous medium.
SUMMARY OF THE INVENTION

The present invention provides a process for the preparation of a crosslinked polyallylamine free base or salt thereof,

comprising,

a. reacting polyallylamine base with a crosslinking agent;
b. adjusting the pH of the reaction mixture to above 11;
c. isolating the crosslinked polyallylamine free base from an aqueous alkaline medium;
d. optionally reacting the isolated crosslinked polyallylamine free base with an acid to obtain the salt of crosslinked polyallylamine free base;

or

e. optionally reacting the isolated crosslinked polyallylamine free base with carbon dioxide to obtain crosslinked poly(allylamine carbonate).

The present invention further provides for the process of preparation of polyallylamine base,

comprising,

a. polymerizing the hemisulfate salt of allylamine with a radical initiator to obtain poly(allylamine hemisulfate);
b. treating the poly(allylamine hemisulfate) with an aqueous alkali to obtain the polyallylamine base.

DESCRIPTION OF THE INVENTION

The present invention provides a process for the preparation of a crosslinked polyallylamine free base or salt thereof,
comprising,

a. reacting polyallylamine base with a crosslinking agent;

b. adjusting the pH of the reaction mixture to above 11;

c. isolating the crosslinked polyallylamine free base from an aqueous alkaline medium;

d. optionally reacting the isolated crosslinked polyallylamine free base with an acid to obtain the salt of crosslinked polyallylamine free base; or

e. optionally reacting the isolated crosslinked polyallylamine free base with carbon dioxide to obtain crosslinked poly(allylamine carbonate).

The present invention further provides for the process of preparation of polyallylamine base,

comprising,

a. polymerizing the hemisulfate salt of allylamine with a radical initiator to obtain poly(allylamine hemisulfate);

b. treating the poly(allylamine hemisulfate) with an aqueous alkali solution to obtain the polyallylamine base.

The term "crosslinked polyallylamine free base" means crosslinked polyallylamine in which all the amino groups are present in free form and are not protonated.

The reaction of polyallylamine base with a crosslinking agent may be carried out preferably in an aqueous medium.

The crosslinking agent may be selected from the group consisting of at least two functional groups which can react with the free amino groups of polyallylamine such as halogens, oxirane, isocyanates, carboxylic esters or acid halides.
The isolated crosslinked polyallylamine free base may be further converted to the salt of crosslinked polyallylamine free base by reacting with a suitable acid.

In another embodiment, the present invention provides a process for preparing the crosslinked polyallylamine free base or salt thereof comprising,

a. reacting polyallylamine base with a crosslinking agent;

b. adjusting the pH of the reaction mixture to above 11;

c. isolating the crosslinked polyallylamine free base from an aqueous alkaline medium.

In one embodiment, after crosslinking the polyallylamine, the pH of the medium is adjusted between 12 and 13 with an aqueous alkali hydroxide in order to completely convert the crosslinked polyallylamine to a free base prior to its isolation.

In another embodiment, the present invention provides a process for preparing the salt of crosslinked polyallylamine free base comprising,

a. reacting the isolated crosslinked polyallylamine free base with an acid to obtain the salt of crosslinked polyallylamine free base.

In yet another embodiment, the present invention provides a process for preparing the crosslinked poly(allylamine carbonate) comprising,

a. reacting the isolated crosslinked polyallylamine free base with carbon dioxide to obtain crosslinked poly(allylamine carbonate).

In yet another embodiment, the present invention provides a process for preparing the polyallylamine base comprising,
a. polymerizing the hemisulfate salt of allylamine with a radical initiator to obtain poly(allylamine hemisulfate)
b. treating the poly(allylamine hemisulfate) with an aqueous alkali solution to obtain the polyallylamine base.

The polymerization of the hemisulfate salt of allylamine maybe preferably carried out in aqueous medium.

The radical initiator is preferably a water soluble compound containing a functional group capable of forming salt and generating a free radical in aqueous medium.

The polyallylamine base can be obtained by treating the poly(allylamine hemisulfate) with an aqueous solution of an alkali selected from the group consisting of hydroxides or carbonates of an alkali metal.

The following examples serve to illustrate the invention without limiting the invention in its scope. The methods of preparing the crosslinked polyallylamine free base or its salt in the below examples are described as reference examples.

EXAMPLES

Example 1: Preparation of crosslinked polyallylamine base

To a solution of water (130ml) and sulfuric acid (100g) was carefully added allylamine (100g) while maintaining the temperature below 30°C. The solution was heated to 56 to 60°C and under stirring was added 2,2'-azobis(2-methyl propionamide) dihydrochloride (4.75g). The stirring was continued for 12hours and then the mass was cooled to 2-8°C. Sodium hydroxide solution (210g, 50% w/w) was cautiously added to the mixture at below 30°C. The alkaline mass was heated to 55°C and the unreacted allylamine was collected by distillation under vacuum. The mixture was cooled to 25°C, settled and the upper layer of polyallylamine base was collected.
Its pH was set to 10 to 11 with cone, hydrochloric acid to neutralize any alkali. Epichlorohydrin (8.3ml) was added and stirred until gelation ensued. The gel was allowed to stand for 12 hours; water was added and stirred vigorously until the solid mass was in particulate form. Sodium hydroxide solution (~100g, 50%w/w) was added to the suspension under stirring until the pH was between 12.0 to 13.0, and the crosslinked polyallylamine free base was filtered and washed with water to remove inorganics.

**Example 2: Formation of hydrochloride salt of the crosslinked polyallylamine base**

The crosslinked polyallylamine free base (40g, on dried basis), obtained as in Example 1 was suspended in water and the pH was adjusted to 7.7 with 6N hydrochloric acid. The mixture was stirred for 1 hour and solid was collected by filtration. The obtained crosslinked poly(allylamine hydrochloride), i.e. sevelamer hydrochloride, was dried under vacuum to obtain a brittle solid (45.7g).

**Example 3: Formation of carbonate salt of crosslinked polyallylamine free base**

The crosslinked polyallylamine free base (375g, on dried basis) was suspended in water and carbon dioxide gas was purged to the suspension until pH of suspension was 8.5. The mixture was stirred for 1 hour and solid was collected by filtration. The obtained crosslinked poly(allylamine carbonate), i.e. sevelamer carbonate, was dried under vacuum to obtain brittle solid (452g).
We Claim:

1. A process for the preparation of a crosslinked polyallylamine free base comprising,
   a. reacting polyallylamine base with a crosslinking agent;
   b. adjusting the pH of the reaction mixture to above 11;
   c. isolating the crosslinked polyallylamine free base from an aqueous alkaline medium.

2. The process as claimed in claim 1, comprising further reacting the isolated crosslinked polyallylamine free base with an acid to obtain the salt of crosslinked polyallylamine free base.

3. The process as claimed in claim 1, wherein the crosslinked polyallylamine free base is isolated from aqueous alkaline medium at pH in the range of 12 to 13.

4. The process as claimed in claim 1, wherein the crosslinking agent is epichlorohydrin.

5. The process as claimed in claim 1, wherein reaction medium for crosslinking of polyallylamine base is water.

6. The process as claimed in claim 1, wherein the crosslinked polyallylamine free base is sevelamer.

7. The process as claimed in claim 2, wherein the salt of crosslinked polyallylamine is crosslinked poly(allylamine hydrochloride).
8. The process as claimed in claim 2, wherein the salt is crosslinked poly(allylamine carbonate) or sevelamer carbonate formed by purging an aqueous suspension of the crosslinked polyallylamine free base with carbon dioxide.

9. A process for the preparation of polyallylamine base comprising
   a. polymerizing the hemisulfate salt of allylamine with a radical initiator to obtain poly(allylamine hemisulfate)
   b. treating the poly(allylamine hemisulfate) with an aqueous alkali solution to obtain the polyallylamine base.

10. The process as claimed in claim 9, wherein the radical initiator is a water soluble compound containing a functional group capable of forming salt and of generating a free radical in aqueous medium.

11. The process as claimed in claim 9, wherein the radical initiator is 2,2'-azobis-(2-amidinopropane)hydrochloride.